AUTONOMIC, BIOMETRIC AND OCULOMOTOR CORRELATES OF MYOPIA IN YOUNG ADULTS

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Summary

The principal work reported in this thesis is the examination of autonomic profile of ciliary muscle innervation as a risk factor in myopia development. Deficiency in sympathetic inhibitory control of accommodation has been proposed as a contributory factor in the development of late onset myopia (LOM). Complementary measurements of ocular biometry, oculomotor function and dynamic accommodation response were carried out on the same subject cohort, thus allowing cross-correlation of these factors with autonomic profile. Subjects were undergraduate and postgraduate students of Aston University.

A 2.5 year longitudinal study of refractive error progression in 40 subjects revealed the onset of LOM in 10, initially emmetropic, young adult subjects (age range 18-24 years) undertaking substantial amounts of near work. A controlled, double blind experimental protocol was conducted concurrently to measure post-task open-loop accommodative regression following distance (0 D) or near (3 D above baseline tonic accommodation) closed-loop tasks of short (10 second) or long (3 minute) duration. Closed-loop tasks consisted of observation of a high contrast Maltese cross target; open-loop conditions were imposed by observation of a 0.2 c/deg Difference of Gaussian target. Accommodation responses were recorded continuously at 42 Hz using a modified Shin-Nippon SRW-5000 open-view infra-red optometer. Blockade of the sympathetic branch of accommodative control was achieved by topical instillation of the non-selective β-adrenoceptor antagonist timolol maleate. Betaxolol hydrochloride (non-selective β_1-adrenoceptor antagonist) and normal saline were employed as control agents. Retarded open-loop accommodative regression under β_2 blockade following the 3 minute near task indicated the presence of sympathetic facility. Sympathetic inhibitory facility in accommodation control was found in similar proportions between LOM and stable emmetropic subjects. A cross-sectional study (N=60) of autonomic profile showed that sympathetic innervation of ciliary muscle is present in similar proportions between emmetropes, early-, and late-onset myopes. Sympathetic facility was identified in 27% of emmetropes, 21% of EOMs and 29% of LOMs.

In a cross-sectional study of ocular biometry in young adults, axial length was found to be the most significant structural correlate in myopia. Axial length to corneal curvature ratio showed significant correlation with refractive error (r^2=0.90). No significant difference in peripheral astigmatism was found between refractive groups. In all refractive groups, peripheral astigmatism was greatest in the temporal peripheral retina. Measurement of peripheral ocular dimensions revealed similar relative peripheral refractive error between emmetropic and late onset myopic eyes. Early onset myopic eyes exhibited a marked asymmetry between temporal and nasal peripheral retina; the temporal retina showing a greater tendency towards a prolate elliptical shape. Ocular volume was found to correlate with refractive error (r^2=0.70).

Examination of oculomotor function in the cross-sectional group showed that LOMs had higher AC/A ratios than other refractive groups. Lag of accommodation for a near task was also greatest in myopes. Tonic accommodation was highest in emmetropes and lowest in late onset myopes, and was not significantly affected by stability of refractive error. No statistically significant trends were observed in heterophoria between refractive error groups. Similarly, stability of refractive error had no effect on heterophoria. Cross-correlation between oculomotor function and autonomic profile failed to show any significant differences as a result of sympathetic deficit. Statistical testing failed to show significant effects of refractive error or refractive stability on oculomotor function.

Measurement of dynamic accommodation responses showed a reduction in accommodative accuracy as temporal frequency of the stimulus increased. Accuracy of the accommodation response was not significantly affected by the administration of autonomic drugs.

Myopes were found to be more susceptible to nearwork induced accommodative hysteresis, and to have less accurate steady state accommodative responses compared to emmetropes. The effect of cognitive demand on the accommodation response showed no distinct pattern between refractive groups.

This work has shown that the onset of myopia in young emmetropic adults is independent of sympathetic inhibitory facility in accommodative control. Axial elongation has been confirmed as the primary structural correlate in LOM. A programme of further work is suggested to investigate the ergonomic features of near work activity, and evaluate the effect of sympathetic facility on the dynamic accommodation response.

Key words: Myopia, accommodation, refractive error, ocular biometry, oculomotor function.

This thesis is dedicated to my Father

Mr Arthur James Mallen, IENG MIQA

1926-1998

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CHAPTER 1
ASPECTS OF ACCOMMODATION, MYOPIA AND NEAR WORK

GENERAL INTRODUCTION

The worldwide prevalence of myopia is on the increase (Fredrick, 2002). A recent large sample study has shown that the prevalence of myopia is approaching 80% in the young adult population in areas of the far-east (Wu *et al.*, 2001). From academic research and clinical optometric practice it can be seen that late onset myopia (i.e. myopia onset post 15 years of age) is an increasingly common problem. A population in which the prevalence of myopia is increasing is, as a consequence, placed at increased risk of associated pathologies, e.g. retinal detachment and glaucoma. Additionally, an increase in the myopic population reduces the pool of candidates for specific careers, e.g. certain branches of the armed forces and civil aviation. Contribution of the nearwork environment to the onset and progression of myopia has long been argued, with association between academic achievement and myopia being established (Sperduto, *et al.*, 1983; Rosenfield and Gilmartin, 1998). As many areas of work and leisure place an increasing demand on near vision, it is expedient to carry out a detailed study of a specific aspect of the near vision response; namely, the sympathetic branch of accommodative control and its effect on myopia development.

Practically, both the optometric profession and academic community has failed to agree on any prevention or treatment strategy for myopia, either early onset or late onset. With regard to late onset myopia, the facility exists to enable investigation and possibly identification of those individuals at risk. With further work it may be possible to introduce strategies to limit progression of, or prevent the onset of late onset myopia. These strategies may include a combination of optical, pharmacological and ergonomic interventions.

For many years near work has been postulated as a possible risk factor for myopia development. Many theories for the mechanism of myopigenesis related to near vision have been suggested, but as yet there has been no general agreement as to the exact processes involved (Rosenfield and Gilmartin, 1998). Clearly, further targeted work in this area is required to address an increasingly common problem.

FUNDAMENTAL ASPECTS OF ACCOMMODATION

1.1 Near Vision

The near vision response consists of accommodation, convergence and pupil miosis. A network of neural linkages coordinate this response to produce a clear, single binocular image of an object of regard at near. Cues to accommodation include retinal blur, retinal disparity and proximity (Ciuffreda, 1998). The neural pathway of this response can be briefly summarized as follows:

- Retinal blur signal is transmitted to the visual cortex (V1) via optic nerve, optic chiasm, optic tract, lateral geniculate nucleus and optic radiations.

- Fibres link V1 to the frontal eye field (involved in conjugate eye movements). Fibres then descend to the oculomotor nuclei in the midbrain.

- From the midbrain nuclei of the oculomotor nerve, fibres pass directly to the medial rectus muscles to bring about convergence.

- Fibres also synapse with the Edinger-Westphal nucleus of the oculomotor nerve, passing via the ciliary ganglion and short ciliary nerves to link with the ciliary muscle and sphincter pupillae to bring about accommodation and pupil constriction respectively (Davson, 1990; Saude, 1993; Snell and Lemp, 1989).

In recent years a number of models of the near vision response have been proposed. Such models vary in complexity, ranging from a simple model of accommodation or vergence control, to more complete models accounting for retinotopic, spatiotopic and proximal cues, with cross linkages modelling AC/A and CA/C ratios (Eadie and Carlin, 1995). Control of accommodation and vergence is based around a closed loop negative feedback system (Schor, 1992). A negative feedback system can be modelled as shown if figure 1.1.
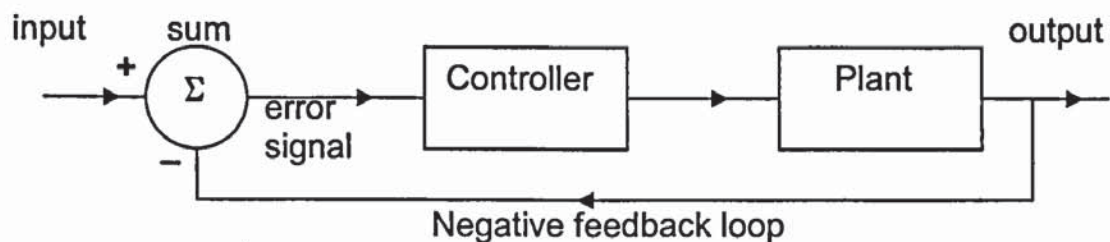
Figure 1.1. Model of a negative feedback, closed loop control system.

An input to the above system is sent via sum, control and plant components to produce an output. The output signal is fed back and subtracted (hence negative feedback) from the input signal, forming an error signal. This error signal is used to modify the output of the system. The process is repeated until the error signal is zero and a state of equilibrium is maintained until the input signal is altered.

A recent model of the accommodation and vergence control system by Hung and co-workers (1996) is shown in figure 1.2. The model takes into account the influence of target distance in terms of retinal blur signal and proximal cues, and the influence of retinal disparity as stimuli to the accommodation and vergence system. The model produces 2 output channels: the accommodative response (AR) mediated by ciliary muscle and crystalline lens (CM+CL), and vergence response (VR) mediated by the extraocular muscles (EOM). Interactions between the blur and disparity channels (convergent accommodation and accommodative convergence cross linkages) are shown. Tonic accommodation (TA) and tonic vergence (TV) inputs are shown at the second stage summing junctions (Σ). Adaptation factors of both accommodation (SAA, slow accommodative adaptation) and vergence (SVA, slow vergence adaptation) are included, together with accommodation and vergence gain control elements (G). Proximal drive to the near vision response is shown, mediated via perceived distance gain (PDG) and accommodative proximal gain (APG) and vergence proximal gain (VPG) elements. Tolerance in the accommodative and vergence systems due to depth of focus (DOF) and Panum's fusional area (PFA) are also included in the model. Negative feedback loops in the accommodation and vergence channels produces an error signal after the first summing junctions (Σ).

Figure 1.2 Model of accommodation and vergence control (Hung *et al.,* 1996; redrawn by Ciuffreda, 1998)

1.2 Parasympathetic system and accommodation control

The accommodative response is due to neural innervation of ciliary smooth muscle occurring as a result of stimulation of the parasympathetic branch of the autonomic nervous system (ANS) (Ruskell, 1990), and the consequent action of acetylcholine on muscarinic receptors (Kaufman, 1992). Parasympathetic innervation of ciliary muscle provides a fast, high magnitude contraction of muscle fibres. Thus, action of the parasympathetic system brings about a rapid accommodative response.

1.3 Sympathetic system and accommodation control

It has been shown that accommodation is chiefly controlled by the parasympathetic branch of the ANS (Tornqvist, 1967), however, there is strong evidence for the presence of

sympathetic control of accommodation (Cogan, 1937; Gilmartin, 1986, 1998). The actions of the sympathetic branch of the ANS on accommodation can be summarized as follows:

- It is inhibitory in nature, thus having an inhibitory effect with respect to the parasympathetic system (Gilmartin and Hogan, 1985a).

- It is mediated mainly by β_2 adrenoceptors on ciliary smooth muscle (Wax and Molinoff, 1987). The neurotransmitter substance is noradrenaline.

- The time course of action of the sympathetic branch is relatively slow compared to the parasympathetic branch. Maximal parasympathetic effect is realized in 1 to 2 seconds, compared to 10 to 40 seconds for the sympathetic system (Campbell and Westheimer, 1960; Törnqvist, 1966, 1967; Rosenfield and Gilmartin, 1989).

- Sympathetic inhibition of accommodation is augmented by concurrent parasympathetic activity. The magnitude of sympathetic activity is related to the magnitude of underlying parasympathetic activity (Gilmartin and Bullimore, 1987).

- The effect of sympathetic inhibition on accommodation is relatively small compared to the parasympathetic system. Maximal effect is in the region of –2 D (Gilmartin, 1998).

- Access to sympathetic inhibitory facility varies considerably between individuals (Gilmartin *et al.*, 2002b).

1.3.1 Anatomical investigation of the sympathetic system

Ruskell (1973) examined ciliary muscle samples from cynomolgous (*Macaca fascicularis*) and rhesus (*Macaca mulatta*) monkeys by electron microscopy. On average, 1% of receptors within the ciliary muscle samples were found to contain small granular vesicles. This histological feature had been shown to be specific to terminals of sympathetic nerve fibres. Superior cervical ganglionectomy was carried out in a sub-group of monkeys. In these subjects, an absence of sympathetic nerve fibre terminals in the ciliary muscle was noted. This finding supported the notion that sympathetic nerve fibres in the eye originate at the superior cervical ganglion, due to nerve fibre atrophy following superior cervical ganglionectomy.

Wax and Molinoff (1987) examined preparations of excised human irides and ciliary bodies by density gradient centrifugation and agonist/antagonist binding. The samples were treated with a variety of beta adrenoceptor agonists and antagonists. The affinity of

the receptors present in the tissue samples for the range of agents was graded. It was found that the adrenoceptors present in human ciliary muscle were predominantly of the β_2 subtype. A small number of β_1 receptors were found in isolated samples of ciliary muscle by microdissection.

Zetterstrom and Hahnenberger (1988) also examined excised strips of human ciliary muscle. The effect of a range of autonomic agents on the contraction of the ciliary muscle strips was measured using a tension gauge. Isoproterenol (non-selective β agonist) caused a relaxation of the muscle strip. This effect was inhibited by the use of timolol (non-selective β antagonist). Betaxolol (β_1 antagonist) had no effect on muscle tension, indicating an inhibitory effect mediated by β_2 receptors. Noradrenaline (non-selective α agonist) also caused relaxation of the muscle strip indicating the presence of an inhibitory branch mediated by α adrenoceptors. The α_1 antagonist prazosin caused partial blockade of the noradrenaline response, whilst the α_2 antagonist idazoxan had no effect. This finding suggested that the α inhibitory branch was mediated by the α_1 subclass of adrenoceptor.

1.3.2 Physiological investigation of the sympathetic system

Work by Törnqvist (1966) on monkey (*Macaca irus*) showed the effect on refractive state of direct electrical stimulation of the sympathetic cervical nerve while three levels of background parasympathetic activity were induced: normal cholinergic tone, increased cholinergic tone following the instillation of pilocarpine, and reduced cholinergic tone following the instillation of atropine. Direct electrical stimulation of the dissected preganglionic sympathetic nerve was carried out using a square wave function generator capable of 0.5 to 50 stimulus pulses per second. Refractive state of the eye was measured by a Thorner coincidence optometer (Giles, 1965). Törnqvist employed two pharmacological treatment states for this experimental work: alpha adrenoceptor antagonists (phentolamine and phenoxybenzamine) and beta adrenoceptor antagonist propranolol. The results can be summarized as follows. Under no drug conditions electrical stimulation of the sympathetic cervical nerve produced a relative hyperopic shift in refractive state. Magnitude of hyperopic shift was related to the rate of electrical nerve stimulation. Under increased parasympathetic tone (induced by pilocarpine) the magnitude of hyperopic shift was greater for a given level of electrical stimulation when compared to the response under normal parasympathetic tone. Under parasympathetic block (by atropine) the hyperopic shift induced by electrical stimulation was abolished. It was thus

demonstrated that end organ effects of sympathetic nerve stimulation were modulated by the concurrent level of parasympathetic activity. The next section of the work identified the class of adrenoceptor involved in the sympathetic response. Administration of the alpha-adrenoceptor antagonists phentolamine or phenoxybenzamine produced no attenuation of the hyperopic shift on sympathetic stimulation. In contrast, administration of the beta-adrenoceptor antagonist propranolol abolished the hyperopic shift. From this finding it was concluded that sympathetic inhibitory innervation of ciliary smooth muscle was mediated by beta-adrenoceptors.

Hurwitz and co-workers used pharmacological intervention to examine the effects of the beta sympathetic system on the accommodative responses of African green tail monkeys (*Cercopithecus ethiops*). The midbrain parasympathetic accommodative control centre was electrically stimulated to produce an accommodative response. The isoproterenol (beta agonist) injected subconjunctivally produced a significant reduction in accommodative response induced by electrical stimulation. A total attenuation of the accommodative response could not be produced, even with high doses of isoproterenol. Only instillation of atropine completely abolished the electrically induced accommodative response. Pre-treatment with propranolol (beta antagonist) prior to administration of isoproterenol attenuated the reduction in accommodative response observed under isoproterenol alone. It was concluded that beta sympathetic stimulation at the level of the ciliary muscle attenuates positive accommodation responses, and that parasympathetic blockade produced more significant levels of accommodative response attenuation than beta-sympathetic stimulation (Hurwitz *et al.*, 1972a).

An associated paper by Hurwitz *et al.* (1972b) concentrated specifically on the role of alpha adrenoceptors in the accommodation response. The study was once again based around the electrical stimulation of accommodation in monkey via the parasympathetic branch of the ANS. Subconjunctival injection of levarterenol (alpha agonist) produced a reduction in the accommodation response compared to the saline treated control eye. In subsequent trials one eye was pretreated with either phentolamine (alpha antagonist) or propranolol (beta antagonist). Eyes receiving phentolamine prior to levarterenol showed depression in the accommodation response. Eyes treated with propranolol prior to levarterenol showed an absence of the reduction in accommodation associated with levarterenol alone. It was suggested that the reduction in accommodation associated with

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levarterenol was due to the small beta agonist effects in addition to its predominant alpha agonist effects. Thus, sympathetic inhibition of accommodation is mediated by beta receptors at ciliary smooth muscle.

1.3.3 Pharmacological *in vivo* examination of the sympathetic system

Gilmartin and Hogan (1985b) observed that pharmacological intervention using the nonselective beta-adrenoceptor agonist isoprenaline sulphate could produce a significant hyperopia shift (i.e. outward shift) in the position of dark focus. Mean hyperopic shift in tonic accommodation (TA) for the ten subjects was 0.47 D. Additional trials with the antimuscarinic tropicamide produced a greater hyperopic shift in TA of 1.24 D. The study concluded that parasympathetic tone in ciliary muscle played a more significant role in determining the position of TA than the sympathetic system.

In their 1987 study, Gilmartin and Bullimore aimed to show that sympathetic innervation of ciliary smooth muscle was augmented by high levels of parasympathetic activity (Gilmartin and Bullimore, 1987). Dark focus was measured for 90 seconds by Canon R-1 infra-red optometer in 15 male emmetropic subjects before and subsequent to a 10 minute counting task. The counting task was carried out under timolol and saline conditions at accommodative demands of 0.3 D and 5.0 D. Examining data from the whole subject group showed a retardation of accommodative response decay to the tonic level following the 5 D task under timolol conditions. This finding failed to reach statistical significance following four factor analyses of variance. Analysis of the data with subjects in 2 groups (pre-task TA ≤ 0.55 D or > 0.55 D) failed to show a significant effect of timolol on the 5.0 D trial in the low TA group. Significance at the 4% level for timolol at 5.0 D was shown in the relatively high TA group. The study showed that sympathetic innervation of ciliary muscle is modulated by concurrent high levels of parasympathetic activity. Additionally, the effects of sympathetic blockade were more marked in subjects with high levels of tonic accommodation. A methodological limitation in this study was the use of saline as the pharmacological control against timolol. It could be argued that accommodative effects arising were due to the ocular hypotensive effects of timolol rather than β_2 blockade effects at the level of the ciliary muscle.

Gilmartin *et al* (1992) reviewed post-task open-loop accommodative regression responses in humans. The time course of regression of accommodation to the tonic level was

monitored using a continuous recording optometer. Figure 1.3 shows a schematic representation of three types of post-task regression response according to Gilmartin *et al* (1992).
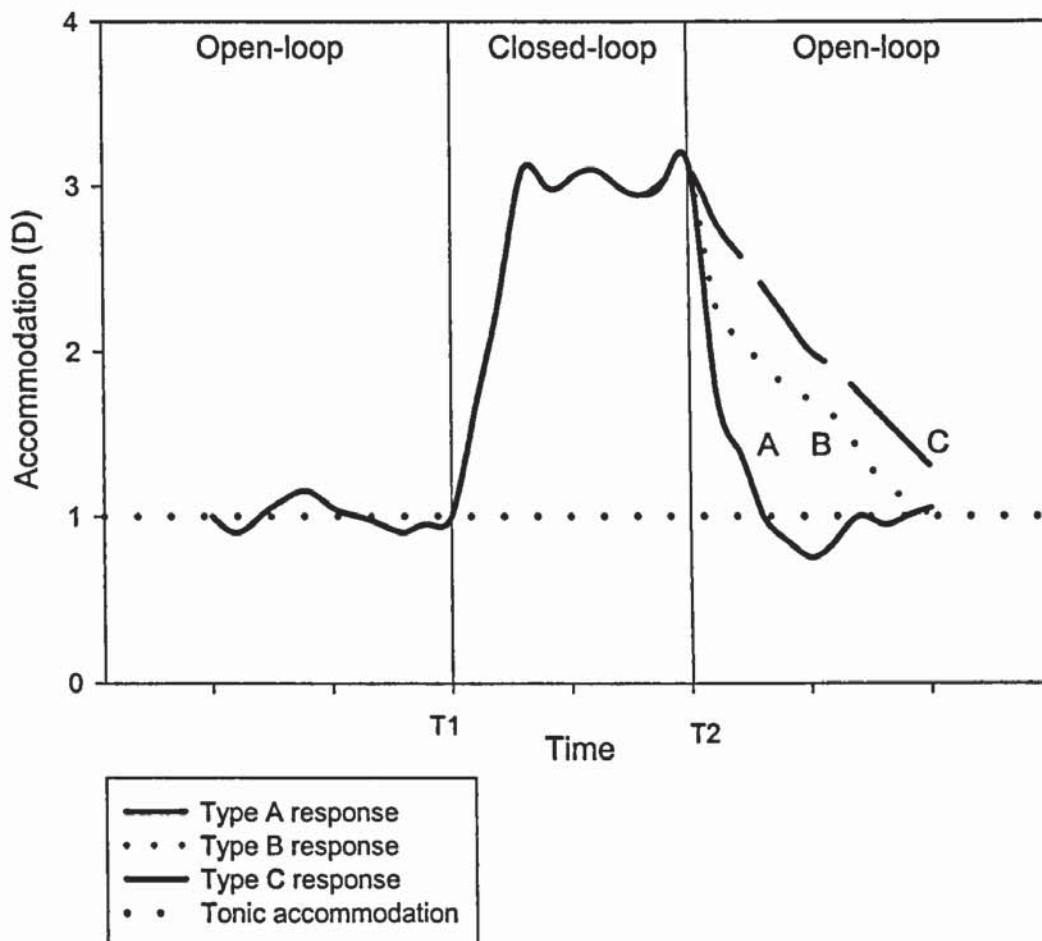
Figure 1.3. Post-task open-loop regression of accommodation (after Gilmartin *et al*, 1992)

The time points T1 and T2 indicate the commencement and cessation of a closed-loop near task respectively. The graph shows three different post task regression curves after the commencement of open-loop conditions. Type A response shows a rapid regression to the pre-task tonic level, with evidence of some overcompensation in the form of an overshoot (or counter-adaptation) of the pre-task tonic level. Time course for the type A response is typically of the order of 10 seconds. The rapid type A response suggests the presence of a sympathetic inhibitory branch in the accommodation control pathway. Type B response is slower, typically taking 20 to 40 seconds to return to the pre-task tonic level; this response suggests a deficiency in the sympathetic inhibitory pathway. The rationale behind many autonomic profiling studies has been an attempt to elicit this response in an individual following the instillation of timolol maleate. In a subject exhibiting a Type A response pre-

drug and subsequently exhibiting a Type B response post-drug following a sustained near task, it can be deduced that sympathetic inhibitory facility is present. A subject showing no pre- to post-drug change in response following a sustained near task can be assumed to have deficiency in sympathetic innervation of ciliary smooth muscle. Type C response shows an extremely retarded regression to the tonic level of several minutes duration, indicating absence of sympathetic inhibition of accommodation; this response is rarely observed.

Strang *et al.* (1994) examined inter-trial variation of post-task regression patterns in 10 emmetropes and 10 late onset myopes. A Canon R-1 infra-red optometer was used to measure the accommodative response for 90 seconds in darkroom conditions following completion of a 3 minute near task at 3 D above baseline TA. Three separate trials were carried out in order to assess repeatability. Analysis of variance showed no significant differences in the intra-subject regression profiles for the three trials, thus indicating the high repeatability of the technique. Regression of accommodation to the baseline TA level was slower in the late onset myopic group compared with the emmetropic group.

Gilmartin and Winfield (1995) also considered the possibility of differential accommodative regression patterns between emmetropes, and early- and late-onset myopes. Beta-adrenoceptor antagonist intervention was employed. This study is of interest because of the utilization of the β_1 selective adrenoceptor antagonist betaxolol hydrochloride as the control agent for timolol maleate trials. The rationale for the use of betaxolol as the control agent was that it would have minimal effect on the sympathetic innervation of ciliary muscle due to its β_1 selectivity, and it would have similar ocular hypotensive effects to timolol. Thus, any change in accommodative response will not be due to differential forces being applied to the lens/ciliary body complex as found in timolol versus saline designs. The study (N = 16: emmetropes N = 6, late onset myopes N = 5, early onset myopes N = 5) failed to show statistically significant differences between the refractive groups following 3 factor split plot analysis of variance on the % accommodative regression functions. It was thus deduced that a deficiency in sympathetic inhibition of accommodation was not a precursor to the development of late onset myopia. Owing to the small subject groups used in this study, it is necessary to repeat this work on a much larger subject cohort. This study forms the starting point for experimental work carried out in Chapter 3 of this thesis.

1.4 Receptors involved in the near response.

Van Alphen studied fresh human iris and ciliary muscle samples *in vitro* to determine the distribution of muscarinic and adrenergic receptor sub-types (van Alphen, 1976). Contraction force of the muscle samples was measured using a force transducer arrangement. Muscle contraction was assessed under adrenergic and muscarinic stimulation, both with and without adrenergic and muscarinic blockade. Table 1.1 (below) summarizes the findings of these studies of receptor distribution in humans.

Structure	*Receptor*	*Neurotransmitter*	*Function (on stimulation of receptor)*
Dilator pupillae	α_1 (sympathetic)	Noradrenaline	Pupil dilation
Constrictor pupillae	Muscarinic (parasympathetic)	Acetylcholine	Pupil constriction
Ciliary muscle	Muscarinic (parasympathetic) principally M_3	Acetylcholine	Stimulation of accommodation
Ciliary muscle	β_2 (sympathetic) α_1	Noradrenaline	Inhibition of accommodation
Ciliary body	β_1 (sympathetic)	Noradrenaline	Secretion of aqueous humour

Table 1.1. Receptors involved in the near response (van Alphen, 1976).

1.4.1 Adrenergic Receptors

Adrenergic receptors (adrenoceptors) are located in post-ganglionic nerve fibres of the sympathetic branch of the autonomic nervous system. A classification of adrenergic receptors into α and β categories was proposed by Ahlquist (1948). This classification system was based on whether a receptor has excitatory (α) or inhibitory (β) actions, but there are exceptions to this system, e.g. the heart. The neurotansmitter substances involved with adrenoceptors are catecholamines. This group of substances includes adrenaline, noradrenaline, dopamine and isopropyl noradrenaline (isoprenaline).

β adrenoceptors are the second major class of adrenergic receptor. β adrenoceptors can be further subdivided into β_1 and β_2 subclasses. β_1 receptors account for around 10% of the

total β receptor population in ciliary smooth muscle, thus β_2 receptors predominate (Wax and Molinoff, 1987).

1.4.2 Cholinergic receptors

Cholinergic receptors are involved in the mediation of parasympathetic control within the autonomic nervous system, and are located in both pre-ganglionic and post-ganglionic fibres. (Note that exceptions to this include sympathetic vasodilator fibres in skeletal muscle arteries, Hopkins and Pearson, 1998) This family of receptor can be further divided into two subclasses: nicotinic and muscarinic. Nicotinic receptors are found at autonomic synapses and within skeletal muscle. Muscarinic receptors are located at the autonomic ganglia (M_1), autonomic effector sites (M_2), and within ciliary smooth muscle (M_3). The neurotransmitter substance is acetylecholine.

1.5 Tonic Accommodation

Tonic accommodation (TA) is the resting point reached by the accommodative system in a stimulus free environment (Rosenfield et al., 1993). Tonic accommodation can be induced experimentally by opening the accommodative feedback loop. In experimental optometry a number of methods of opening the loop have been employed: total darkness, Ganzfeld (bright, featureless field), pinhole (eliminates retinal blur signal by increasing depth of focus) and a Difference-of-Gaussian function (DoG). Under genuine open loop conditions a change in the accommodation response has no effect on the retinal image quality, and therefore the closed loop of accommodative negative feedback control is disrupted. The accommodative response adopts a dioptric position proportional to the level of background ciliary muscle tone mediated by the autonomic nervous system. Tonic accommodation is a useful baseline for the measurement of post-task changes in the accommodation response (Gilmartin, 1998).

Leibowitz and Owens measured tonic accommodation in 220 college students using a laser optometer in dark room conditions. Mean tonic accommodation was found to be 1.52 D (SD 0.77) (Leibowitz and Owens, 1978). Hogan also used a similar helium neon laser optometer to measure tonic accommodation in 60 subjects, mean age 21.6 years. Mean tonic accommodation was 1.58 D (SD 1.11) (Hogan, 1985). Measurement of tonic accommodation by infrared optometer has been shown to produce lower estimates of tonic accommodation compared to laser optometers (Post et al., 1984). The higher values

recorded by laser optometer are thought to result from the cognitive effort required in judging the direction of laser speckle motion (Hogan and Gilmartin, 1984).

1.5.1 Tonic accommodation and refractive error

Tonic accommodation (TA) has been shown to vary according to refractive error. A variety of opinion exists. The majority of studies show highest levels of TA in hyperopes, followed by emmetropes and myopes. Conversely, other studies have shown highest TA in myopes. Studies have also attempted to show TA differences between early onset and late onset myopes. Other studies have failed to demonstrate significant differences in TA between refractive groups.

The study by Gawron (1981) found dark room measures of TA to be highest in myopes. Mean TA (±SD) for hyperopes (N = 65), emmetropes (N = 40) and myopes (N = 39) were 0.77 D (±0.55), 0.54 D (±0.54) and 0.87 D (±0.57) respectively.

McBrien and Millodot (1987a) measured TA (in darkness) using a Canon Autoref R-1 infra-red optometer. It was found that tonic accommodation was highest in hypermetropes and lowest in corrected late onset myopes. Table 1.2 summarizes their findings. The mean level of tonic accommodation for the whole subject group (N = 62) was 0.91 D (±0.53D).

Refractive group	N	Mean TA (D) (±SD)
LOM	15	0.49 (0.16)
EOM	15	0.92 (0.61)
EMM	17	0.89 (0.43)
HYP	15	1.33 (0.49)

Table 1.2. Tonic accommodation as a function of refractive error (McBrien and Millodot, 1987a)

Rosner and Rosner (1989) measured tonic accommodation as a function of refractive status in 113 subjects aged 6 to 14 years of age. Dynamic retinoscopy (Nott method) was carried out while the subject viewed a dimly illuminated 0.2 c/deg Difference of Gaussian target. Mean TA (±SD) was 1.52 D (0.48) range 0.61-2.35 D. One-way ANOVA showed these differences in TA between refractive groups to significant at the 2.5% level. Results were subdivided according to refractive error as shown in table 1.3.

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Group	N	TA (D)	SD	Range (D)
HYP	19	1.73	0.40	1.00-2.22
EMM	61	1.51	0.49	0.61-2.35
MYO	33	1.36	0.46	0.71-2.22

Table 1.3. TA as a function of refractive error in children.

Rosenfield and Gilmartin (1987) measured tonic accommodation (infrared optometer in darkroom conditions) prior to performance of a near vision task in late onset mypoes (LOM), early onset myopes (EOM) and emmetropes (EMM), (N = 17 for each group). Mean tonic accommodation found to be: LOM = 0.31 D, EOM = 0.46 D and EMM = 0.75 D.

Woung et al., (1993) measured tonic accommodation in EMMs (N = 18), EOMs (N = 18) and LOMs (N = 15) by infrared optometer (Nidek AR-1100) in a bright empty field (Ganzfeld). No statistically significant difference in TA was found between the refractive groups. Mean TA (±SD) for EMMs, EOMs and LOMs was: 0.79 D (±0.56), 0.65 D (±0.46) and 0.59 D (±0.55) respectively.

Tonic accommodation was measured in 28 subjects (EMM N = 9, EOM N = 9 and LOM N = 10) in a study by Morse and Smith (1993). Baseline TA measurements (pre-task) showed no significant difference between refractive groups.

Fisher et al (1987) classified refractive groups in terms of degree of refractive error rather than age of onset or age of ametropic stabilization. Baseline and post task adaptation of TA was measured by Hartinger coincidence optometer in low myopes (-0.75 to –4.00 D), high myopes (>4.00 D), emmetropes, and hyperopes. The study failed to demonstrate any statistically significant variation in baseline TA, or adaptation of TA between groups.

Open-loop accommodation responses were measured in 164 young adult subjects (63 emmetropes, 51 early onset myopes and 50 late onset myopes) by infra-red autorefractor in darkness, and using a 0.5 mm pinhole by Strang and co-workers (2000). Estimates of open-loop accommodation were significantly higher ($p < 0.001$) when induced by pinhole compared to dark room conditions. No significant difference in open-loop response was found between refractive groups. In a sub-set of subjects (20 emmetropes, 20 early onset

myopes and 20 late onset myopes) a comparison of open-loop accommodative response was made between bright empty field (Gantzfeld) and dark room conditions. No statistically significant difference was found in open-loop response level in terms of method of opening the loop (i.e. bright empty field versus dark room conditions), or between refractive error groups. Opening the negative feedback loop in the accommodative response by the pinhole method is likely to induce a significant proximal drive to accommodation (Strang *et al.*, 2000), resulting in higher estimates of tonic accommodation.

Limited agreement has been found in the above studies (e.g. TA lowest in myopes, particularly late onset myopes). The variability found in the absolute level of TA, inter-subject variability and variability between refractive error groups could be attributed to the measurement system employed and the method of opening the accommodative feedback loop.

1.5.2 Adaptation of tonic accommodation

It has been shown by Schor *et al.* (1984) that tonic accommodation is not fixed and is subject to adaptation effects following intense nearwork. The study showed a 0.5 D increase in tonic accommodation following a 30-minute 6 D near task. A short term (2-minute) near task failed to produce a significant change in tonic accommodation, thus indicating that there is a significant temporal aspect to the adaptation of tonic accommodation.

McBrien and Millodot (1988) measured differences in adaptation of tonic accommodation between refractive groups. Post task tonic accommodation was measured by Canon R-1 optometer before and after a 15-minute task. Observation distances of 6 m, pre-task tonic position, 37 cm and 20 cm were used. The LOM group exhibited a significant positive shift in TA following the 20 and 37 cm tasks (~0.4 D and ~0.3 D respectively). This effect was still evident 15 minutes post-task. The study suggested that autonomic innervation of ciliary muscle may be responsible for variation in TA adaptation between refractive groups.

The difference in adaptation of tonic accommodation following a near task between emmetropes and late onset myopes was examined by Gilmartin and Bullimore (1991). The

subject groups consisted of 15 emmetropes and 15 late onset myopes (myopia onset after 15 years of age). Regression of accommodation to the tonic (dark focus) level was measured following a cognitive task at 1, 3 and 5 D stimulus levels. Pre-task levels of tonic accommodation were found to be significantly lower in the late onset myopes. Analysis of post-task regression of accommodation showed that refractive group differences alone were not statistically significant. Interaction effects between time and refractive group did show significance, indicating that the rate of change to the pre-task tonic level was greater in the emmetropic group.

In contrast to the findings of McBrien and Millodot (1988), Morse and Smith (1993) found no significant differences in post-task adaptation of tonic accommodation between emmetropes, early onset myopes and late onset myopes.

The term *tonic accommodation* can be misleading. The term suggests that we are measuring the level of autonomic innervation of ciliary smooth muscle when the accommodative system is at rest. This is not the case since classical measurements on tonic accommodation are influenced by additional factors such as cognitive demand, proximal demand, vestibular inputs, method of measurement, etc (Rosenfield *et al.*, 1993). Alternative terms such as *dark accommodation, dark focus* and *resting state of accommodation* have been suggested.

1.6 Lag of accommodation

The amount of accommodation exerted by the oculomotor system (the accommodative response) rarely equals exactly the dioptric stimulus for accommodation. A small amount of accommodation is generally exerted during distance vision (lead of accommodation), i.e. accommodative stimuli below approximately 1.5 D. Conversely, the accommodative system tends to under accommodate progressively as near vision demand increases (lag of accommodation). This effect can be examined by plotting a stimulus/response curve for an individual. Figure 1.4 shows a typical stimulus response curve for a pre-presbyopic subject (Charman, 1982).
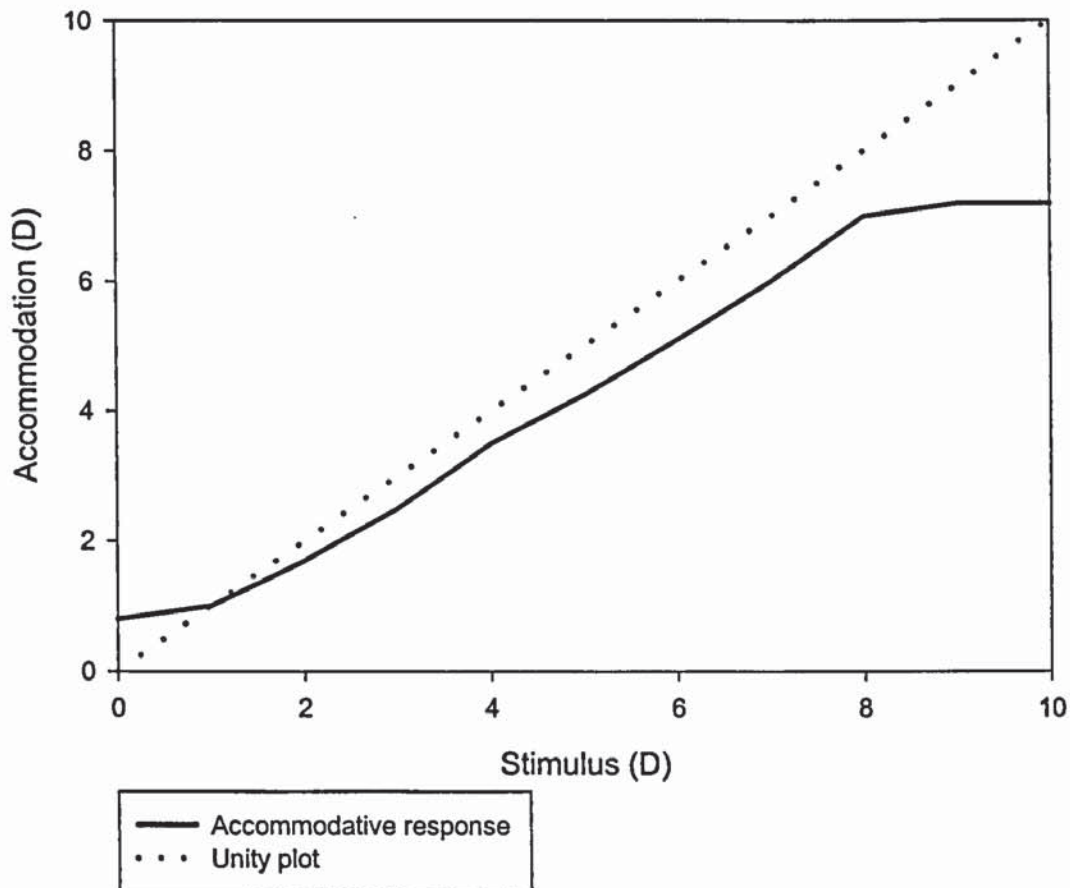
Figure 1.4. Stimulus response curve for a pre-prebyopic subject (after Charman, 1982).

It has been suggested that the crossover point (the intersection of the stimulus/response curve and dotted unity gain line) represents the dioptric position of tonic accommodation (Charman, 1982; Ramsdale and Charman, 1989). Conversely, other workers failed to find a strong correlation between the crossover point and tonic accommodation (Tan and O'Leary, 1988). Models of accommodation including accommodative error (lag of accommodation) at near as a risk factor in myopia will be discussed later.

1.7 Microfluctuations of accommodation

The steady state accommodative response is modulated by relatively small fluctuations (Charman and Heron, 1988; Winn et al., 1990). It is thought that the magnitude (root mean square) of these fluctuations is not greater than 0.25 D (Winn and Gilmartin, 1992; Collins et al., 1995). The generation and ultimate purpose of these fluctuations has been a point of debate for some time. It has been postulated that accommodative microfluctuations are generated within the accommodative system and are used to provide an odd-error cue to accommodation. An odd-error cue would provide both magnitude and direction

information in the form of a retinal blur signal, and would therefore enhance the accuracy of the closed-loop accommodative response. The fluctuations may be generated by some other system, but would still have efficacy by integrating with accommodation to provide an odd-error cue. Equally, the fluctuations may merely be a manifestation of biological noise within the accommodative plant (Charman and Heron, 1988).

Power spectrum waveform analysis by fast Fourier transform (Pugh, *et al.*, 1987) has shown that there are two dominant frequencies present in accommodative microfluctuations. A low frequency component of <0.6 Hz is thought to correlate with respiration, and a high frequency component (peak spectral response of 1.0 to 2.3 Hz) is thought to correlate with arterial pulse (Collins *et al.*, 1995; Winn *et al.*, 1990; Winn and Gilmartin, 1992). These findings provide evidence to support the notion that microfluctuations are generated by systems outside the accommodative apparatus. The degree to which these microfluctuations impact upon the overall accommodative response is still equivocal.

Evidence exists to show that the low frequency component may be predominant to the high frequency component in accommodative control. Gray *et al.* (1993) measured power spectra of microfluctuations concurrently with variations in artificial pupil size. High frequency components remained unchanged as pupil size was varied between 0.5 and 5 mm. Power of the low frequency component was constant in pupil sizes of greater than 2 mm, and increased with pupils of 2 mm diameter or less. Reducing pupil size produces an increase in depth of focus (Charman and Whitefoot, 1977). It follows that the increase in the low frequency component may be a reflex response to elevate the error signal derived from microfluctuations above the threshold imposed by increased depth of focus.

Recent advances in instrumentation for the continuous recording of accommodation responses (Mallen, *et al.*, 2001; Wolffsohn *et al.*, 2001) may allow new insight into the functions of microfluctuations. It may be possible to invert the microfluctuation signal and feed this into a dynamic accommodation stimulus out of phase, thus cancelling out the variation imposed on the steady state response. Monitoring the accommodative response to a range of stimuli with the microfluctuation signal effectively zero may produce interesting results.

1.8 The dynamic accommodation response

Dynamic accommodation describes the response of the accommodative system to a target moving in space, giving rise to a change in accommodative stimulus with respect to time.

1.8.1 Characteristics of sinusoidal accommodative responses

When evaluating the dynamic accommodative response to a moving target it is necessary to consider accommodative gain, accommodative lag and phase shift of the accommodative response. Accommodative gain can be calculated by dividing the amplitude of the response waveform by the amplitude of the stimulus waveform. Accommodative lag can be calculated by dividing the mean amplitude of the response waveform by the mean amplitude of the stimulus waveform. Phase shift can be calculated by measuring the amount of displacement (in degrees) between the peaks of the stimulus waveform and the peaks of the response waveform (Kruger and Pola, 1986). These three key features are represented in figure 1.5.

Point A (figure 1.5) indicates the phase lag of the accommodative response with respect to the dynamic stimulus. Point B indicates the amplitude of the accommodative stimulus. Point C indicates the amplitude of the accommodative response. Thus:

$$\text{Accommodative gain} = C/B$$
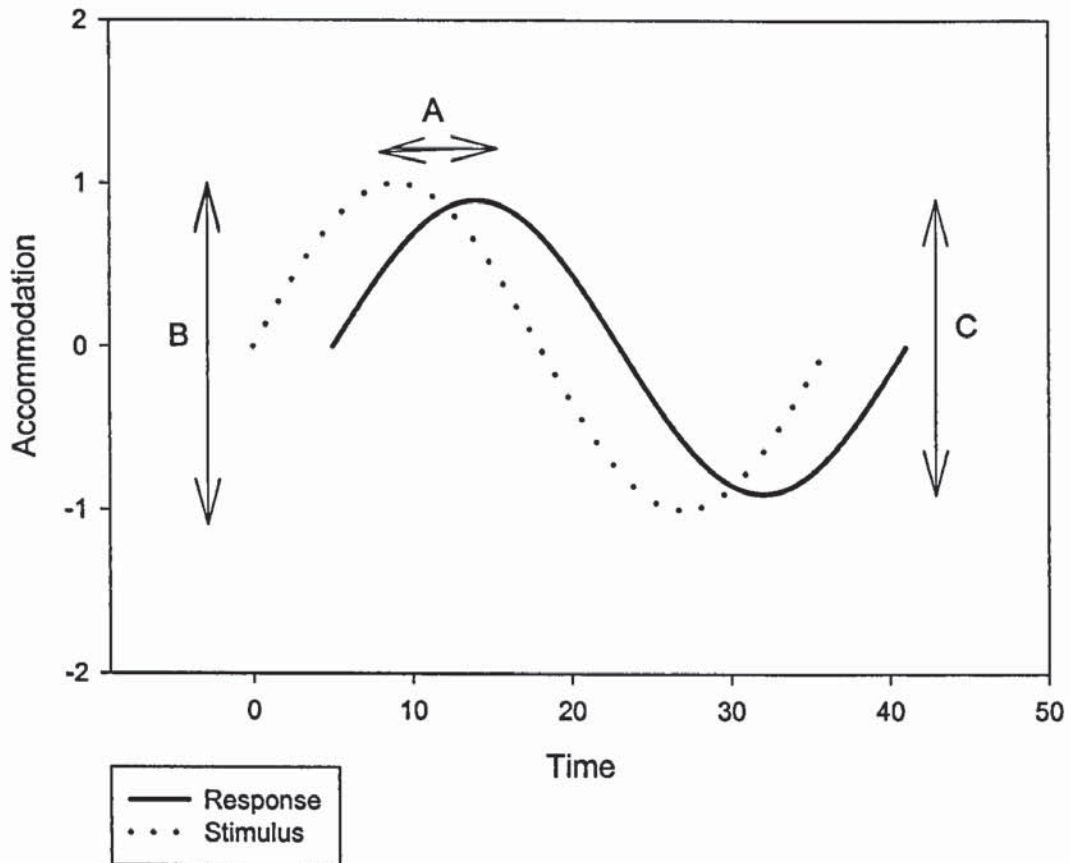
Figure 1.5. Characteristics of the dynamic accommodation response.

As the temporal frequency of the dynamic sinusoidal oscillation increases two notable effects on the accommodative response can be observed: A reduction in accommodative response gain and an increase in phase lag. Kruger and Pola (1986) measured accommodative response gain and phase lag to a dynamic sinusoidally oscillating target. Results for gain and phase lag for one subject from this study are redrawn in figures 1.6 and 1.7.
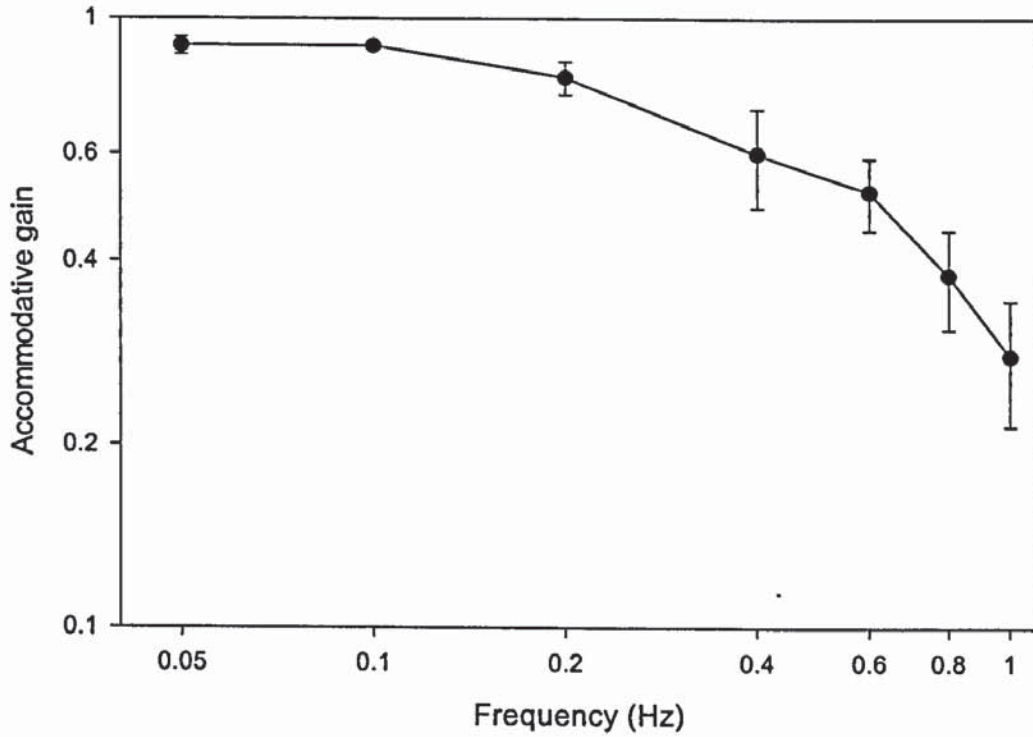
Figure 1.6. Accommodative gain versus temporal frequency. Redrawn from Kruger and Pola, 1986.
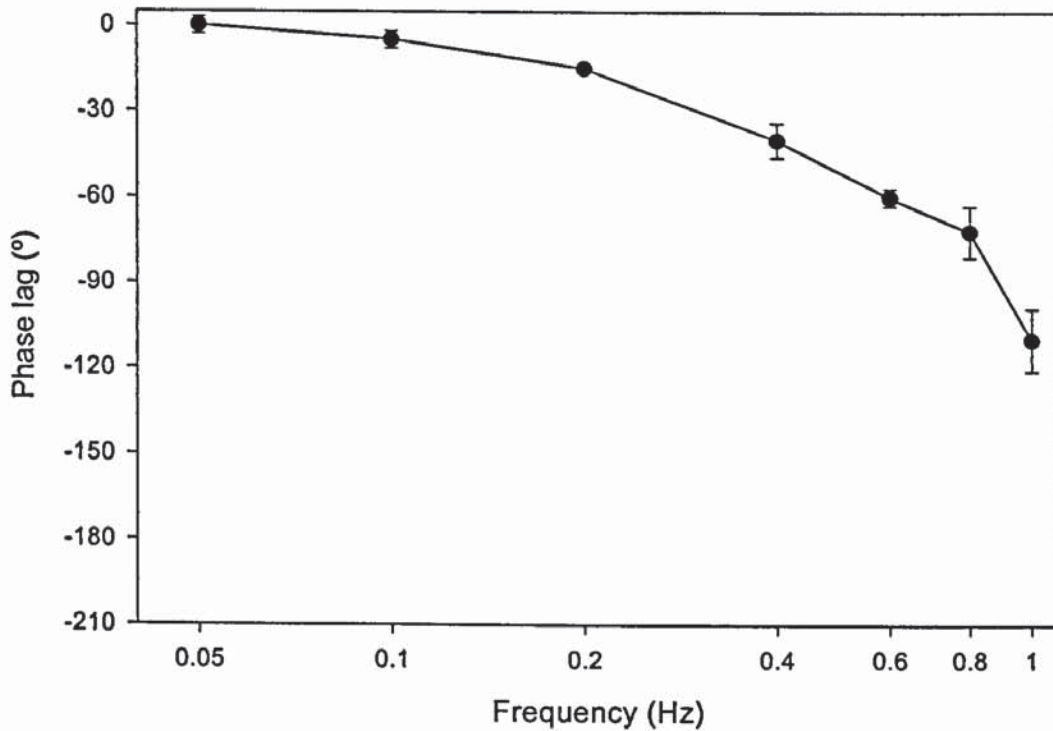
Figure 1.7. Phase lag versus temporal frequency. Redrawn from Kruger and Pola, 1986.

Recent work by Culhane *et al.* (1999) examined the dynamic accommodative response to a target sinusoidally oscillating at frequencies of 0.05, 0.1, 0.2, 0.3, 0.4 and 0.6 Hz. Findings

were in agreement with those of Kruger and Pola (1986). At frequencies of 0.05 and 0.1 Hz an accurate accommodation response is observed. At 0.3 Hz a reduction in accommodative gain and an increase in phase lag can be identified. At 0.6 Hz a breakdown in accommodative accuracy is seen, with the accommodation response adopting a mean position with low amplitude, out of phase sinusoidal modulation superimposed.

1.8.2 Characteristics of step accommodative responses

Responses to a step (square wave) changes in stimulus can be described in terms of the gain, the reaction time and the response time of the accommodative system. Reaction time is the time elapsed between the initial change in accommodative stimulus and the initial change in accommodative response. Response time is the interval between the initial change in accommodative response until stabilization of the accommodation response to the new stimulus level (Charman, 1983; Culhane and Winn, 1999).

Accommodative reaction times have been found to be similar, but response times more variable, over a range of stimulus step sizes. Heron and Winn (1989) measured accommodation responses to far-to-near and near-to-far stepwise stimulus changes of up to 4 D in magnitude. Reaction times were found to be in the order of 0.3 seconds for 1, 2, 3 and 4 D step sizes. Response time was found to increase as the magnitude of the stimulus step increased. Mean response times ranged from 0.76 seconds for the 1 D step, to 1.15 seconds for the 4 D step. Far-to-near accommodative responses were completed in a shorter time than near-to-far responses. Reaction time was similar for far-to-near and near-to-far steps, but response times were greater in the near-to-far direction. Vitreous force applied to the crystalline lens was suggested as a possible cause of the slower response times in the near-to-far direction. The authors found similar values for reaction and response times under monocular and binocular conditions.

Culhane and Winn (1999) measured accommodation responses to stepwise changes in stimulus vergence in 7 emmetropes, 7 early onset myopes and 7 late onset myopes. The stepwise changes in the stimulus were carried out from near-to-far (4 D to 2 D) and from far-to-near (2 D to 4 D) immediately following a period of sustained fixation. Subjects were exposed to steady state fixation periods of 10, 60 and 180 seconds. Accommodation response was recorded using a dynamic infra-red optometer. The late onset myopic group showed a significant increase in accommodative response time following the 180 second

fixation period. Response times were similar between the emmetropic and early onset myopic subjects. Reaction times were similar in all refractive groups. It was concluded that the adaptive elements of the accommodative system of late onset myopes differ from other refractive groups.

1.8.3 Effect of sympathetic intervention on sinusoidal dynamic responses

Winn and Culhane (1998) measured closed-loop accommodation responses to sinusoidal dynamic stimuli varying between 2 and 4 D at temporal frequencies of 0.05 to 0.6 Hz. Accommodation was recorded by dynamic infra-red optometer. Autonomic control of ciliary smooth muscle was modified at the level of the neuro-effector junction using the non-selective β adrenoceptor antagonist timolol maleate. Under timolol conditions the gain of dynamic accommodation responses to the sinusoidal stimulus was reduced at mid- to lower temporal frequencies (≤ 0.3 Hz). Timolol had no effect on the sinusoidal response at higher temporal frequencies (0.4 to 0.6 Hz). Closed-loop responses under saline (control) and betaxolol (control for the hypotensive effect of timolol) conditions revealed similar response profiles.

Using a similar experimental protocol to the above study, Culhane *et al.* (1999) measured the effect of sympathetic augmentation on closed-loop dynamic accommodation responses. The α_1 adrenoceptor agonist phenylephrine hydrochloride (2.5%) was instilled to augment the sympathetic branch of autonomic control against a saline control condition. Under both saline and phenylephrine conditions, a reduction in accommodative gain was observed as temporal frequency of sinusoidal oscillation increased. An increase in phase lag was also noted as temporal frequency increased. Statistical analysis (two-factor repeated measure ANOVA) of gain data showed a significant increase in accommodative gain at frequencies of 0.05, 0.1, 0.2 and 0.3 Hz under the phenylephrine condition when compared with the saline control. Phenylephrine failed to have a significant effect on phase lag. Increase in gain of the sinusoidal response profile at low to mid temporal frequencies seen with phenylephrine confirms the proposition that sympathetic input to the overall accommodation response is slow (Törnqvist, 1967).

1.8.4 Effect of sympathetic intervention on step dynamic responses

The effects of timolol on the amplitude and time constants of stepwise accommodative responses were investigated by Weber *et al.*, (1989). A reduction in crystalline lens

thickness, and consequently a reduction in accommodative response, was observed under closed-loop conditions at the far and near points, and under open-loop (dark focus) conditions. Timolol had no effect on the time course of accommodation responses in the near-to-far direction. Reduced time constants were observed in the far-to-near direction following the administration of timolol.

Culhane and Winn (1997) measured the time course and magnitude of closed-loop accommodation responses to stepwise stimuli under saline, timolol and betaxolol conditions. Stepwise changes in accommodation stimulus were made over 3 D to 5 D ('far-to-near'), and 5 D to 3 D ('near-to-far') vergence ranges. Steady-state fixation periods prior to the step change were 5, 10, 20, 60 and 180 seconds. Accommodation responses were monitored throughout using a continuous recording infra-red optometer. The results showed similar accommodation response profiles under saline control conditions, and following instillation of the β_1 adrenoceptor antagonist betaxolol. Under timolol (non-selective β antagonist) conditions, a delay in accommodative response time was found following a stepwise change occurring subsequent to a period of sustained fixation. The findings of this work are consistent with the characteristics of the sympathetic nervous system in accommodation control. Instillation of timolol causes blockade of β_2 receptors in ciliary smooth muscle, and thus impedes the sympathetic branch of accommodation control. As sympathetic facility is augmented by sustained accommodative effort (Gilmartin, 1986, 1998), a retardation of the accommodative response profile following β_2 blockade will only be manifest following a relatively prolonged accommodative task.

Further work by Culhane et al. (1999) examined the effect of sympathetic augmentation on the dynamics of stepwise accommodation responses. Response time to a 0.05 Hz, 2 to 4 D and 3 to 4 D stepwise dynamic stimulus was recorded by continuous recording optometer under saline and phenylephrine (2.5%) conditions. Sympathetic augmentation mediated by phenylephrine failed to have a significant effect on response time to stepwise dynamic stimulus changes. Average response times ranged from 0.72 to 0.87 seconds.

ASPECTS OF MYOPIA

1.9 Ametropia (component vs. correlation)

The formation of refractive error (ametropia) may be due to the parameters one or more of the optical components of the eye falling outside the range of values for emmetropia to be possible, e.g. high axial length. This is referred to as component ametropia and tends to produce high levels of refractive error. Refractive error can also be present in an eye where the optical components fall within the range of values for emmetropic eyes. In this case the ametropia is formed by a mismatch between the optical components, and is referred to as correlation ametropia. This aetiology of refractive error formation tends to produce lower levels of ametropia (Mutti and Zadnik, 1997).

The relationship between refractive components and refractive error in 408 eyes was examined by Sorsby et al. (1962b). For eyes with ocular refractions in the range +6.00 to - 4.00 D (it was not stated whether ocular refraction was measured in terms of absolute sphere or mean sphere) the refractive components measured (i.e. corneal power, crystalline lens power and axial length) all had values within the normal range for emmetropia. The formation of relatively low refractive error in these cases was due to the correlation between the refractive components being incorrect for ametropia. Low myopia was found in an eye with an axial length at the upper end of the normal range, but with corneal or lenticular power failing to weaken adequately to restore emmetropia. Conversely, low hypermetropia was found in a relatively short eye were the crystalline lens and/or cornea had failed to strengthen to the required value. Eyes expressing higher refractive error (greater than 4 D of myopia or 6 D of hyperopia) were shown to be a result of anomalous axial length. These high refractive errors were termed component ametropia.

Around the same time, Sorsby and co-workers examined the effects of optical components in cases on anisometropia (Sorsby et al., 1962a). Sixty-eight anisometropic subjects were examined. Anisometropia ranged from 2 to 15 D. Axial length was found to be the major factor in anisometropia. In only 7 cases did axial length account for less that 50% of the total anisometropia. Cornea and crystalline lens were found to contribute to the anisometropia in a total of 26 cases, and to counter the anisometropia in 10 cases and 1 case respectively.

A review and discussion of the major theories of refractive error development was carried out by McBrien and Barnes (1984). The *Biological – statistical theory* proposed by Steiger (1913; cited by McBrien and Barnes, 1984) suggested that all errors of refraction arose as a result of variation in associations of the individual components of refraction. However, the theory was questioned as the distribution of refractive status is not normal. The biological – statistical theory would predict considerably fewer eyes in the emmetropic portion of the distribution of refractive status than was shown by Sorsby *et al.,* (1960). The *Use-abuse theory* states that myopia incidence increases in a population carrying out considerable amounts of near work. This theory was proposed by Cohn who observed that the 'visual hygiene' of German schoolchildren was poor, i.e. inadequate lighting, incorrect posture when reading and low contrast print in textbooks (Cohn, 1886, cited by McBrien and Barnes, 1984). Cohn attributed the increasing prevalence and magnitude of myopia as children progressed through the education system to poor visual ergonomics. It was proposed that eyes engaged in intense nearwork developed myopia to reduce demand on the accommodative system. The *Emmetropization theory* is based on a coordination of growth of the ocular components to eliminate the formation of refractive error. Failure of this system leads to ametropia. At birth the human eye has a refractive error of around +2.00 DS (Cook and Glasscock, 1951), and grows towards emmetropia. Van Alphen (1961) proposed that ciliary muscle tone, intraocular pressure and scleral stretch were factors in the emmetropization process. A control system was envisaged which regulated axial length by varying tonus in the uveal tract, mediated by the autonomic nervous system. More recently, Medina and Fariza (1993) have used longitudinal refractive data to form a mathematical model of the emmetropization process. In human subjects, it was found that a closed-loop model with a feedback system was the best representation of the emmetropization mechanism.

1.9.1 Distribution of refractive error in the normal population

Sorsby and co-workers (Sorsby *et al.,* 1960) examined ocular refraction in 2066 male subjects aged 17 to 27 years. Figure 1.8 shows the distribution of ocular refraction found. The histogram shows that the distribution of refractive error is leptokurtotic in profile (peaked significantly more than a normal distribution), and skewed towards low hypermetropia.
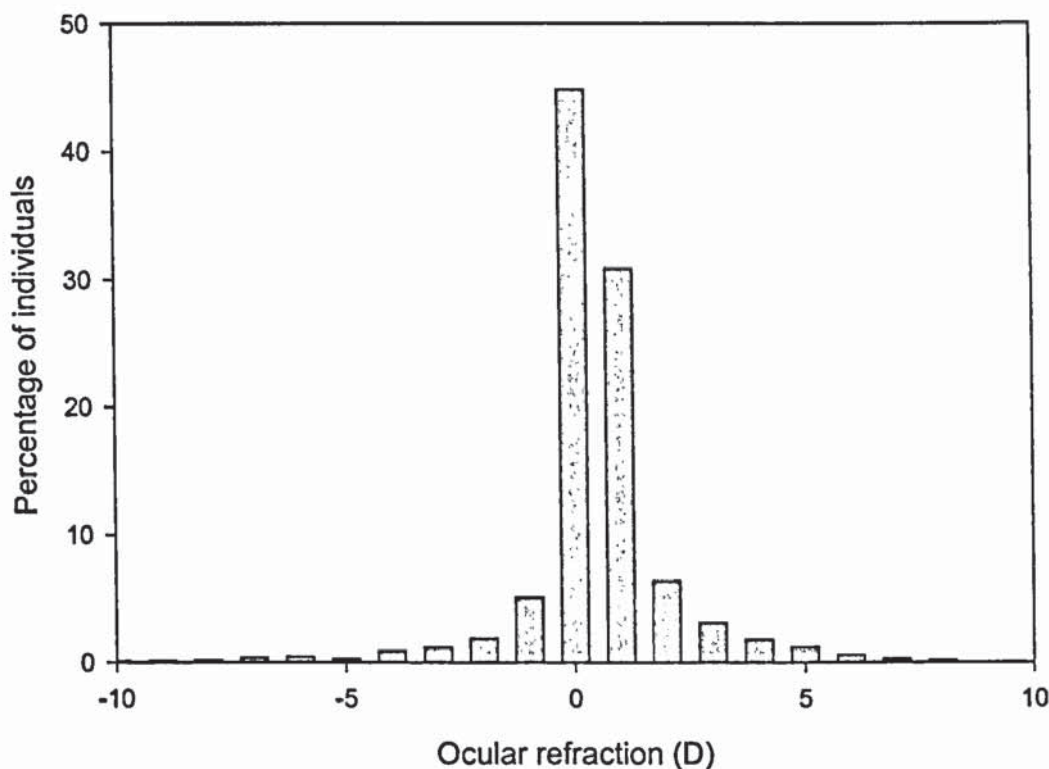
Figure 1.8. Distribution of ocular refraction in a population. (Redrawn from Sorsby *et al.*, 1960)

1.9.2 Myopia in childhood and adolescence

Onset and progression of myopia most commonly occurs in adolescence. Genetic and environmental factors are thought to trigger this phenomenon (Pacella *et al.*, 1999). A recent twin study by Hammond *et al.*, (2001) attributed 84% to 86% of the myopigenic model to genetic factors. Goss and Jackson (1996b) in their longitudinal study of clinical findings before the onset of myopia in youth, collated data on parental history of myopia. Prevalence of myopia as a function of family history of myopia in the N = 87 subject cohort was: neither parent myopic 6%, one parent myopic 37%, both parents myopic 57%. Gwiazda *et al* (1993b) also noted increased prevalence of myopia with family history: no parental myopia 8%, one myopic parent 23%, both parents myopic 42%. The precise genetic elements responsible for the familial aspects of myopia development are yet to be identified. Additionally, the question of environmental and hereditary linkage in populations where myopia prevalence is significantly increasing, such as the far-east, remains equivocal (Saw *et al.*, 1996). Wu and Edwards (1999) measured visual acuity and refractive error in 3131 Chinese children, and determined family history of myopia for a further two generations by questionnaire. Prevalence of myopia was seen to increase through the three generations (5.8%, 20.8% and 26.2% respectively). It was concluded that

the increase in myopia prevalence was due to an increase in environmental risk factors, as hereditary factors were relatively unchanged.

Recently, a three-year longitudinal study has examined the effect of reading and near-work on refractive error and ocular biometric factors in adolescent boys (Hepsen *et al.*, 2001). Subjects were grouped according to the amount of near-work carried out. The near-work group consisted of 67 subjects carrying out an average of 6 hours reading per day. The alternate group (N = 47) comprised apprentices working as skilled labourers. Within this classification system a further subdivision was applied dividing each group into subjects with baseline refractive error of ±0.50 D and ±1.00 D. A statistically significant myopic shift in refractive error was noted in 59.7% of subjects engaged in near-work. Mean myopic shift was –0.61 D. The labourers showed mean myopic shift of –0.12 D in 21.3% of the subject group. An interesting feature of this study is the close agreement between the mean age of subjects in the two main experimental groups (12.93 years and 12.96 years at the start of the study for the near-work and labourer groups respectively). The study indicates the possible risk factor of near-work as a precursor to the onset of myopia in secondary school aged children.

Goss and Winkler (1983) carried out analysis of clinical data from optometry practice records (N = 299) to determine the age of cessation of myopic progression. Four methods of analysis were employed: 1. Graphical (inspection), 2. Graphical (statistical), 3. Switched linear regression of refractive error in the horizontal meridian, 4. Switched linear regression of mean sphere. Figure 1.9 shows the results from method 2. The ascending broken line indicates the progression of myopic change as determined by linear regression. The horizontal broken line indicates stable refractive status. The intersection of the two broken lines indicates the point at which myopic progression ceases. Coincidence of this line is found at approximately 14 years on the age axis. The different statistical analyses of the data produced different estimates of myopia stabilization. The ages of cessation of myopia progression are shown in table 1.4 below.
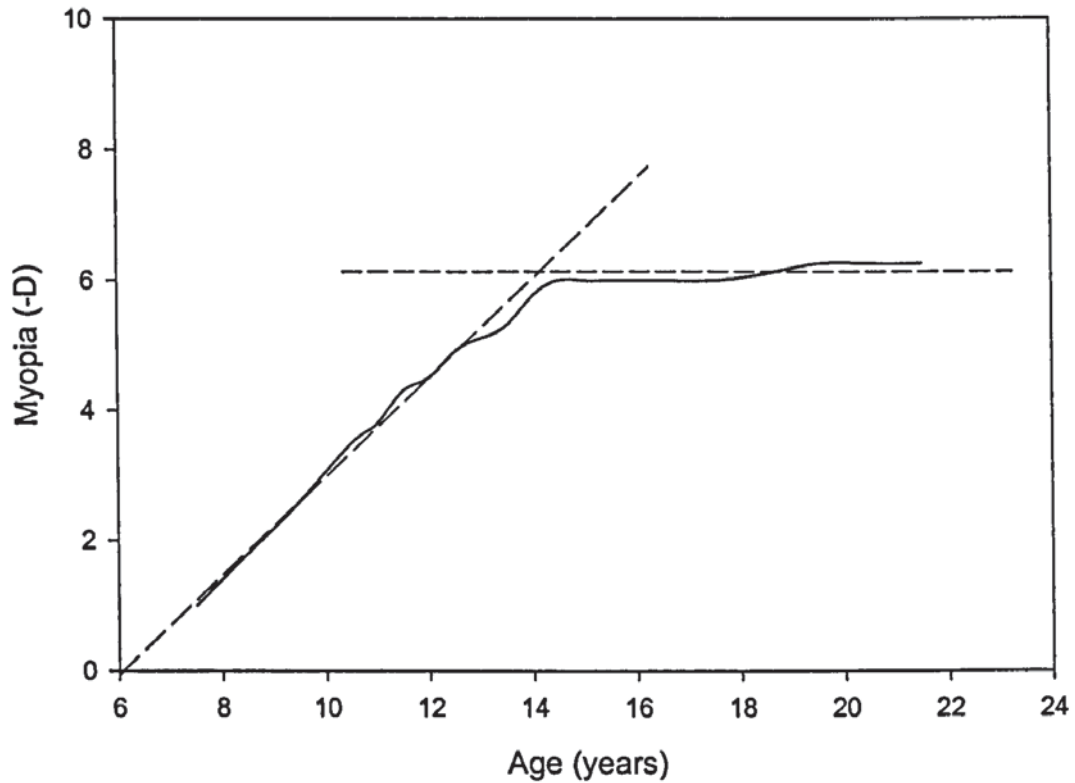
Figure 1.9. Mean progression of myopia against age. (Redrawn from Goss and Winkler, 1983.)

Method	Sex	N	Mean age	SD	t	p
1	M	59	16.53	2.11	3.21	0.0014
	F	56	15.28	2.04	3.21	0.0014
2	M	66	16.66	2.10	4.16	0.0001
	F	57	15.21	1.74	4.16	0.0001
3	M	59	15.01	2.01	1.34	0.18
	F	49	14.44	2.34	1.34	0.18
4	M	59	15.53	1.93	2.34	0.02
	F	45	14.57	2.18	2.34	0.02

Table 1.4. Age of cessation of myopia progression. (From Goss and Winkler, 1983)

Cessation of myopic progression occurred later in males than females, but the rate of myopic change per year was found to be higher in females. Table 1.5 shows mean rate of myopia progression (±SD) for male and female groups according to statistical methods 2, 3 and 4.

Gender	Method 2	Method 3	Method 4
Male	-0.45 (0.22)	-0.50 (0.26)	-0.46 (0.24)
Female	-0.50 (0.23)	-0.56 (0.30)	-0.54 (0.27)

Table 1.5. Mean rate of myopic progression per year. (Goss and Winkler, 1983)

Goss and Grosvenor (1990) reanalysed data from previous studies (Grosvenor *et al.*, 1987) measuring rate of myopic progression in childhood with single vision and bifocal correction modalities. The subject groups were additionally categorized in terms of near point heterophoria. Table 1.6 shows mean rates of myopia progression (D/year).

'phoria	Single vision group			Bifocal group		
	N	Mean	SD	N	Mean	SD
>6Δ exo	5	-0.50	0.26	6	-0.43	0.23
0-6Δ exo	20	-0.43	0.32	41	-0.42	0.27
eso	7	-0.51	0.22	18	-0.31	0.31

Table 1.6. Rates of childhood myopia progression as a function of method of correction and near point heterophoria. (Goss and Grosvenor, 1990)

The rate of myopic progression in groups with nearpoint orthophoria, or exophoria, were similar in single vision and bifocal correction modalities. Subjects exhibiting nearpoint esophoria who were corrected by bifocals showed a 0.20 D per year lower myopic progression rate when compared to the single vision correction group. This finding was close to statistical significance ($p < 0.10$). A reduction in rate of myopic progression in nearpoint esophorics wearing bifocals was also noted by Goss, (1986).

Fulk and Cyert (1996) agreed with the findings of previous studies (Goss, 1986 Goss and Grosvenor, 1990) that suggest a reduction in the rate of myopia progression in children with near point esophoria following the prescribing of bifocal spectacle lenses. The study measured refractive error and axial length in 28 subjects at 6 month intervals over a period of 18 months. Subjects were randomly assigned to either the single vision group (full myopic correction in the form of single vision lenses) or the bifocal group (a bifocal spectacle lens with full myopic correction for distance, and a near addition of +1.25 DS in a 28 mm flat top segment). Myopic progression was found to be significantly slower in the

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bifocal group during the last 6 months of the study (single vision 0.80 D/year, bifocal 0.37 D/year). It is interesting to note that the rate of myopic progression was significantly less in both subject groups during the second 6-month period of the study. This period was the summer vacation. The study concluded that bifocal lenses can slow myopia progression in children with near point esophoria, but the authors suggest a more in depth study to confirm this finding.

Variation in myopia progression rate during the course of an academic year has been examined recently by Tan et al. (2000). In the study, autorefraction was carried out on 168 children aged 7 to 12 years over a 10-month period. Information on the usual amount of near-work carried out by each child was also gained. The rate of myopia progression was found to increase in the period immediately following school examinations, suggesting a reflex change in myopia progression rate subsequent to a period of intense near-work.

A number of ongoing studies are currently attempting to show myopia progression control from the effects of a number of longitudinal treatment strategies (Saw et al., 2002). The Collaborative Assessment of Myopia Progression with Pirenzipine (CAMPP) Study is examining the potential myopia control effect of the M_1 antimuscarinic agent pirenzipine in myopic children aged 8 to 12 years (Bartlett, et al., 2000). Pirenzipine has been shown to regulate ocular growth in animal studies by a direct route at the level of the retina or choroid. Leech et al. (1995) showed a protective effect against axial elongation in form-deprived chicks pre-treated with pirenzipine. Tigges et al. (1999) has demonstrated that the administration of pirenzipine limits the amount of axial myopia induced by monocular occlusion against an untreated control group in newborn rhesus monkeys. It will be interesting to see if the encouraging results found in animal work can be replicated in human studies.

Work in Singapore entitled Atropine in the Treatment of Myopia (ATOM) is examining the effects of 1% atropine eye drops against an artificial tears placedo in a masked study of 400 myopic children between the ages of 6 to 12 years (Chua et al., 2002). The project is ongoing with no longitudinal results to date.

The Contact Lens and Myopia Progression (CLAMP) Study is a 3 year ongoing longitudinal study of the effects of rigid gas permeable (RGP) contact lenses in myopia

control. The subject cohort consists of 116 myopic children aged 8 to 11 years at the start of the study. Subjects were randomly assigned to wear RGP or soft contact lenses (Walline *et al.*, 2001).

The Hong Kong Progressive Lens Myopia Control Study has recently shown that the use of progressive addition spectacle lenses (+1.50 D near addition) in a mixed sex cohort of children failed to have a statistically significant effect on myopia progression rate compared to full distance single vision correction (Edwards *et al.* 2002). A similar study of the efficacy of progressive addition spectacle lenses, the Correction of Myopia Evaluation Trial (COMET), is an ongoing project in 469 myopic children aged 6 to 12 years (Hyman *et al.*, 2001).

1.9.3 Myopia in young adults

The onset of myopia in youth has been shown to be principally influenced by genetic factors (Hammond *et al.*, 2001). In contrast to this, it has been suggested that early adult onset (late onset) myopia is instigated by increased sensitivity to environmental elements such as prolonged near work (Rosenfield, 1998).

McBrien and Adams (1997) examined refractive and biometric changes over a 2-year period in a group of 166 clinical microscopists aged 21 to 63 years. Refractive error was measured without cycloplegia by autorefraction (Canon R-1) followed by subjective refraction. Of the 68 emmetropes (median age 30.83 years) at the start of the study, 39% became myopic ($\geq$-0.37 D) by the end of the 2-year period. Mean myopic shift was –0.58 (±0.04) D in this group. An increase in myopia of –0.37 D or more was found in 48% (108 eyes) of the initially myopic group. Mean myopic shift in this group was –0.77 (±0.04) D. The mean age of this group was 29.3 years. These progressing myopes exhibited a statistically significant myopic progression during the first 6 months of the study period. Myopia continued to progress during the remainder of the study, but at a slightly slower rate. Of the myopes exhibiting progression during the course of the study, 61% had evidence of stable refractive error prior to commencement of clinical microscopy duties. It was suggested that stable refractive error in these subjects had been triggered into further progression by conducting intense near-work.

Refractive error change was monitored in cadets at the United States Air Force Academy over a 2.5year period (O'Neal and Connon, 1987). The training course at USAFA included a significant amount of intense nearwork. Initial refraction data was taken from medical records of academy entry medical examinations for 672 subjects, aged 17 to 21 years. This data set was filtered to omit incomplete records and subjects with history of contact lens wear or near vision correction, leaving a valid data set on 497 subjects. Subjects' refractive status was re-examined 2.5 years later by subjective refraction under cycloplegia. On entry, the distribution of refractive status was as follows: 37.3% hyperopic, 18.5% emmetropic and 44.2% myopic. Mean spherical equivalent refraction (± SD) was –0.55 (±1.52) DS. Table 1. shows the distribution of myopic changes for the three refractive error groups. Significant myopic shifts occurred in all refractive groups. It was noted that the largest myopic shifts occurred in subjects with higher initial degrees of refractive error, both myopic and hypermetropic in nature. A previous study at the United States Military Academy, West Point, found that 15% of non-myopic entrants developed myopia during the course of academy training (Sutton and Ditmars, 1970).

	Hypermetropes	*Emmetropes*	*Myopes*
% showing myopic shift ≥0.25D	47.7	41.3	74.0
Mean group myopic shift (D)	-0.42	-0.52	-0.75

Table 1.7. Distribution of myopic changes (O'Neal and Connon, 1987)

Zadnik and Mutti (1987) assessed refractive error change in law students. Two separate studies were conducted: retrospective and longitudinal. The retrospective study compared previous spectacle prescription to current refractive error. 47.1% of the N = 87 sample had an increase in myopic correction of –0.50 DS or more in at least one eye. In the 6 month longitudinal study a myopic shift of at least –0.50 DS was observed in 37.5% of the N = 16 subject cohort. Refractive error was determined by subjective refraction under cycloplegia.

Midelfart and co-workers (Midelfart *et al.*, 1992) showed a strong correlation between magnitude of myopia and age of first correction in Norwegian medical students. Refractive error was measured using a Humphrey 500 autorefractor followed by subjective refraction. Of the cohort of 133 students, 67 (50.3%) were found to be myopic. 43.3% of the myopic subjects received first correction at or around 20 years of age, indicating a high incidence of adult onset myopia. It is interesting to compare this level of myopia in a population

exposed to intense near work to the incidence of myopia in the general population. Sperduto *et al.* (1983) found myopia prevalence of 24.2% in a sample aged 25 to 34 years.

A recent study by Saw *et al.* (2001) examined refractive error and ocular biometry (by A-scan ultrasonography) in 429 military conscripts. Past and current near-work activity, and educational attainment was assessed by interview and questionnaire. A significant correlation was found between age of myopia onset and near-work activity in childhood. Subjects undertaking high levels of near-work at seven years of age commenced myopic progression earlier than subjects engaged in less demanding near-work activity at that time. Although a correlation between near-work activity at age seven and myopia was found, near-work in later life failed to correlate with myopia. From this it may be argued that individuals are more sensitive to near-work as a myopia risk factor in early life. A strong correlation was observed between educational level and academic achievement, and final degree of myopia.

An ongoing study is attempting to quantify risk factors for myopic progression in adults (Reuter *et al.*, 2002). The 5-year study is currently at the 2-year follow-up stage, with a subject cohort of 153 subjects. Refraction, keratometry, ultrasonography, accommodative lag, heterophoria, response AC/A ratio and videophakometry are measured at 1-year intervals. Additionally, subjects are randomly questioned about their activities throughout the day to establish a profile of near-vision tasks for each individual. This study may show correlation between the amount of time spent conducting near-work and adult progression of myopia.

1.10 Structural correlates of myopia

Myopia results when the axial length of the eye is too long for its refractive power. Advances in ocular biometric techniques, e.g. ultrasonic, interferometric and keratoscopic methods, have increased the validity of associations between refractive error and structural parameters.

1.10.1 Vitreous chamber depth

An eye becomes myopic when the axial length of the globe exceeds its refractive power. The principal structural correlate of myopia is vitreous chamber depth (see Wildsoet, 1998 for review). During the process of emmetropization the natural increase in axial length due

to general body growth is counteracted by a thinning and flattening (and thus reduction in power) of the crystalline lens. A recent study has shown crystalline lens thinning causes a mean hyperopic shift of 3.33 D between the ages of 6 and 10 years. This hyperopic shift is sufficient to null myopic change as a result of axial growth (Zadnik et al.,, 1995). Studies have shown greater crystalline lens thinning in myopic groups (Zadnik et al., 1995; Fledelius, 1995), conversely, other studies have found no difference between refractive groups (McBrien and Millodot, 1987b; Bullimore et al., 1992).

McBrien and Millodot (1987b) measured ocular parameters in 30 emmetropes and 30 late onset myopes. Biometric parameters were measured by keratometry and A-scan ultrasonography under cycloplegia. It was found that differences in axial length, or more precisely vitreous chamber depth, accounted for the refractive error. Mean axial length was 0.82 mm greater in late onset myopes compared to emmetropes ($p < 0.05$). Vitreous chambers were 0.72 mm longer in the late onset group. It was noted that the late onset myopes had deeper anterior chambers and thinner crystalline lenses than the emmetropic group. The latter two parameters provided some compensation for the increase in axial length, thus reducing the manifest level of myopia. No significant difference in corneal radius was found between emmetropes and late onset myopes.

The report by Adams (1987) of adult onset myopia in a single subject gives longitudinal measurements of refraction and corneal curvature. An increase in myopia from –0.25 DS to –4.75 DS was recorded between the ages of 19 and 42 years. During this time the corneal radius was unchanged and within normal limits. A-scan ultrasonography carried out at the end of the study period found axial length to be 1.8mm longer than the population mean of 24.0 mm given by Stenstrom (1948). Adams concludes that in this case changes in corneal curvature were not a causal factor in myopia development. Adams indicates the need for a large sample longitudinal study of ocular component measurement in adult onset myopes.

Grosvenor and Scott (1993) reported the 3-year follow-up data from their longitudinal study (initial reporting of this study in Grosvenor and Scott, 1991). Longitudinal results were obtained from 53 subjects (20 youth onset myopes, 16 early adult onset myopes, and 17 emmetropes). Autorefraction, keratometry, and A-scan ultrasonography (for axial length, anterior chamber depth, lens thickness and vitreous chamber depth) were carried

out on all subjects. Cycloplegic agents were not administered. Group mean refractive changes were –0.26 D (±0.52) for youth onset myopes, -0.18 D (±0.40) for early adult onset myopes and –0.15 D (±0.87) for emmetropes. When subjects from youth onset and early adult onset myopic groups were matched for degree of refractive error, no significant difference in ocular refractive components was found. Both youth onset and early adult onset myopic eyes were found to have significantly longer vitreous chamber depths and axial lengths, and steeper corneas. There was no evidence of an onset of, or increase in existing myopia in eyes showing no increase in axial length. Thus, myopia onset and progression could not result from an increase in corneal or lenticular refractive power alone. It was concluded that all myopia must be a result of axial elongation.

Jiang and Woessner (1996) measured axial length, anterior chamber depth and crystalline lens thickness by A-scan ultrasonography in one subject. The subject was emmetropic at 19 years of age, but was prescribed a myopic correction 8 months later. Ocular biometric measurements were continued at 6 month intervals for a 3 year period. At the end of the 3 year period 3 D of myopia was manifest (RE –2.63 D, LE –3.00 D). During this period corneal curvature was relatively unchanged, but axial length was significantly greater. No significant changes in either lens thickness or anterior chamber depth were found, but a high correlation was found between increase in vitreous chamber depth and refractive error. Axial length increase was 0.83 mm (RE) and 0.90 mm (LE). Vitreous chamber increase was 0.81 mm (RE) and 0.98 mm (LE). These structural changes indicated that a 0.31mm increase in vitreous chamber depth produces a 1D increase in myopia.

In their longitudinal study of clinical microscopists, McBrien and Adams (1997) measured corneal curvature, anterior chamber depth, lens thickness and vitreous chamber depth over a 2-year period. It was found that increase in vitreous chamber depth was the most significant structural correlate of myopic change in the 'adult-onset myopic' group (N = 23), the 'changing emmetropic' group (N = 14) and the 'progressing myopic' group (N = 108). No significant difference was found in corneal curvature, anterior chamber depth or lens thickness between the refractive groups at the start of the study. Also there was no significant change in these parameters for the duration of the study.

The three year longitudinal study of 114 initially emmetropic boys, Hepsen et al. (2001) found significant myopic progression in 59.7% of subjects involved in intense near-work.

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Significant increase in axial length and reduction in corneal power were found, indicating that the cornea may have a small compensatory effect. It is interesting to note that an increase in both anterior chamber depth and vitreous chamber depth was found. An increase in anterior chamber depth of the order of 0.20 mm was found, compared to an increase of approximately 0.05 mm in this dimension in the adult study by Grosvenor and Scott (1993). No significant change in crystalline lens thickness was observed.

1.10.2 Axial length:corneal radius ratio

The ratio of axial length to corneal radius has been investigated as a risk factor in myopia development. Grosvenor suggested that high values of this ratio could predispose an emmetrope to myopia (Grosvenor, 1988). Further studies by Bullimore et al (1992), and Grosvenor and Scott (1991) found the axial length:corneal radius ratio (AL:CC) higher in myopes than emmetropes, and higher in early onset myopes than late onset myopes. AL:CC values from Grosvenor and Scott (1991) were 2.79, 3.09 and 3.21 for the emmetropic (N = 24), early adult onset myopic (N = 26) and youth onset myopic groups (N = 29) respectively. Statistical significance at the 0.1% level was achieved.

A cross-sectional study of biometric and refractive factors in 194 subjects was conducted by Grosvenor and Scott (1994). Axial length, vitreous chamber depth, crystalline lens thickness and anterior chamber depth were measured by A-scan ultrasonography. Corneal radius was assessed by automated keratometer and refractive error was measured by autorefraction. Crystalline lens power was calculated from refractive and biometric measures (Bennett and Rabbetts, 1998). Axial length to corneal radius (AL:CC) ratio was found to closely correlate with spherical equivalent refractive error (r = 0.915). Crystalline lens power was plotted against AL:CC ratio for hypermetropes and emmetropes, and for the myopic group. Linear regression showed that there was a negative correlation between lens power and AL:CC, i.e. as AL:CC increases, crystalline lens power reduces as a compensation. The regression plot for the myopic group is somewhat different. A shallower negative correlation is shown between lens power and AL:CC, indicating that in the myopic group an increase in AL:CC is accompanied by a smaller reduction in lens power. The work concluded that AL:CC ratio was the most significant factor in determining the refractive status of an eye. Also, by examining the AL:CC ratio and ocular refraction it was possible to deduce the amount of crystalline lens power reduction that had occurred in compensation for axial growth.

Goss and Jackson (1995) carried out a 3-year longitudinal study of ocular component parameters and refractive error change in 87 initially emmetropic school children. During the study period, 29 subjects became myopic (myopia defined as –0.25 D spherical equivalent in both eyes) and 58 subjects remained emmetropic (spherical equivalent refractive error between 0 and +1.25 D). Ocular parameters assessed during the study were: horizontal and vertical keratometry, AL:CC ratio (with respect to horizontal and vertical keratometric measures, anterior chamber depth, lens thickness, axial length, vitreous chamber depth and lens power. The most significant finding from the initial ocular measurements was the greater AL:CC ratio found in the 'became myopic' group compared to the 'remained emmetropic' group. Table 1.8 shows a summary of AL:CC values. Cut off values of AL:CC ratio for the prediction of myopia were found to be ≥ 3.00 with respect to horizontal keratometric measures and ≥ 3.02 with respect to vertical keratometric measures. Both values had equal sensitivity (0.88) as myopic predictors, but horizontal AL:CC had greater specificity (0.68) than vertical AL:CC (0.57).

	Became myopic			*Remained emmetropic*		
	N	*Mean*	*SD*	*N*	*Mean*	*SD*
Horizontal keratometry (males)	15	43.83 D	1.14	27	43.12 D	1.77
Horizontal keratometry(females)	14	44.63 D	1.76	31	43.85 D	1.56
Vertical keratometry (males)	15	44.36 D	1.31	27	43.42 D	1.83
Vertical keratometry (females)	14	45.22 D	1.52	31	44.39 D	1.78
Axial length (males)	14	23.56mm	0.51	25	23.40mm	0.70
Axial length (females)	10	23.00mm	0.84	31	22.88mm	0.70
AL:CC horizontal (males)	14	3.06	0.09	25	2.99	0.08
AL:CC horizontal (females)	10	3.03	0.05	31	2.97	0.05
AL:CC vertical (males)	14	3.09	0.09	25	3.01	0.09
AL:CC vertical (females)	10	3.07	0.05	31	3.01	0.07

Table 1.8. Biometric data from Goss and Jackson (1995).

In their longitudinal study, McBrien and Adams (1997) found that from the initially emmetropic subjects, no significant difference was found in axial length:corneal curvature

ratio between subjects that remained stable emmetropes (AL:CC = 3.01), remained emmetropic but changed in Rx (AL:CC = 3.00) or developed adult onset myopia (AL:CC = 3.02). The authors concluded that AL:CC ratio could not act as a predictor of myopia. Initially myopic subjects were divided into 'stable myopes' and 'progressing myopes' subgroups. No significant difference in AL:CC was found between these subgroups (stable myopes, 3.15; progressing myopes, 3.17). A significant difference in AL:CC ratio was found generally between myopic and emmetropic eyes (3.16 and 3.01 respectively) by virtue of the longer mean axial length in the myopic group.

1.10.3 Peripheral refraction

Peripheral refraction (also referred to as oblique or peripheral astigmatism) defines the type and magnitude of refractive error found at retinal locations off the visual axis. An increase in astigmatism with increasing retinal eccentricity has been demonstrated by a number of workers (Ferree *et al.*, 1931; Rempt *et al.*, 1971; Gustafsson *et al.*, 2001). The nature of the astigmatic imagery gives rise to two sets of line foci; tangential and sagittal. These line foci form image shells which straddle the retina in a typical human eye (Millodot, 1981). Ferree *et al.* (1931) found considerable variation of peripheral refraction among a population, but concluded that peripheral refraction could be divided into 2 discrete types. In type A eyes the tangential image shell shows increasing myopia, and the sagittal image shell exhibits increasing hyperopia as retinal eccentricity increases. Type B eyes show increasing hyperopia in both image shells as retinal eccentricity increases.

Rempt *et al.* (1971) measured peripheral refraction by streak retinoscopy in 442 subjects. Peripheral refraction was carried out in both temporal and nasal peripheral retina at eccentricities of 20, 40 and 60 degrees. Retinoscopy in the primary position was also carried out. The dioptric separation of sagittal and tangential image shells (the interval of Sturm) in the peripheral retinal was measured. The authors concluded that eyes could be classified into 5 groups according to the pattern of peripheral refraction, the additional 3 classes of peripheral refraction being intermediate subgroups to the major 2 classes proposed by Ferree *et al.* (1931).

It has been demonstrated experimentally (Millodot, 1981) and by ray trace modelling (Dunne, *et al.*, 1987) that oblique astigmatism differs according to central refractive state. Generally, in myopic eyes peripheral compound myopic astigmatism is found. Emmetropic

and hypermetropic eyes exhibit mixed, and compound hyperopic peripheral astigmatism respectively.

A recent study by Walker and Mutti (2002) has shown transient change in peripheral refraction during, and subsequent to, a sustained accommodative task. Relative peripheral refractive error (RPRE) was measured using a Canon R-1 device 30° from fixation in the nasal retina. During initial accommodation response a relative hyperopic shift in RPRE was observed, indicating a drift toward a more prolate retinal contour. As the task progressed, the prolate shift in retinal contour diminished to the pre-task baseline level. Cessation of the task caused an immediate hyperopic shift in RPRE with respect to the pre-task level, indicating a recoil response in retinal shape. These transient effects on retinal contour had diminished 45 minutes after cessation of the near task. Changes in choroidal tension during the accommodation response were suggested as possible factors in this phenomenon. It may prove fruitful to further explore this area of work. Degree of refractive error may influence transient shifts in retinal contour during near work, perhaps due to variation in scleral rigidity (see Chapter 9).

1.10.4 Peripheral refraction, eye shape and refractive error

The shape of the human eye, and variation with ametropia has received much attention in the literature (Cheng, *et al.* 1992; Millodot, 1981; Logan, 1997). Retinal contour has been measured by a variety of methods. These methods have included laser Doppler interferometry (LDI, Hitzenberger, 1991), magnetic resonance imaging (MRI, Cheng *et al.*, 1992), retinoscopy (Rempt *et al.*, 1971), X-ray tomography (Takei *et al.*, 2002) and computational methods (Dunne, 1995).

An MRI study of 8 hypermetropic, 8 emmetropic and 7 myopic eyes found that the myopic eyes were larger than the emmetropic and hypermetropic eyes. Eye enlargement in myopia was found to be relatively equal in the three major axes of the globe (i.e. axial length, vertical coronal, and horizontal coronal), indicating that the myopic eyes in the study were enlarged radially, rather than elongated in a prolate elliptical fashion. The study concluded that myopic, emmetropic and hypermetropic eyes possess a similar sphero-elliptical shape (Cheng *et al.*, 1992).

Love *et al.* (2000) measured peripheral refractive error in 40 young adult subjects (20 emmetropes and 20 myopes) and compared these values to central refractive error. Refractive measurements in the primary position, and at 35° in the nasal and temporal peripheral retina, were carried out by infra-red autorefraction. Myopic subjects showed greater relative peripheral hypermetropia compared to emmetropic subjects. Conversely, emmetropic subjects showed relative myopia in the peripheral retina. These findings were found to be statistically significant by ANOVA. These data are suggestive of a difference in retinal contour between emmetropic and myopic eyes. Emmetropic eyes tend to exhibit an oblate elliptical shape (a steepening ellipse), and myopic eyes tend to exhibit a prolate elliptical shape (a flattening ellipse). This finding is contrary to the findings of Cheng *et al.* (1992).

Peripheral refraction (30° nasally) was measured by Mutti *et al.* (1997) in children by infra-red autorefraction, and compared to central refraction. Peripheral refraction was found to become less myopic with age, indicating a change in ocular contour towards a more prolate shape. Myopes tended to express greater relative hyperopia in the peripheral retina than non-myopes. The authors concluded that a prolate ocular shape and axial elongation were both characteristic features of the myopic eye. General eye growth leads to a prolate shape change in the peripheral retina, indicating less restricted growth in the axial direction and restriction of growth equatorially. This differential growth is escalated in myopic eyes.

Examination of retinal contour by Logan (1997) also showed that the myopic eye had a prolate retinal shape. In a study of anisomyopes, it was found that the anterior segment dimensions were similar between right and left eyes. The principal structural correlate for the subject's anisomyopia was found to be the difference in vitreous chamber depth between the two eyes. Myopic eyes were found to have minimal expansion in equatorial (coronal) dimensions.

1.10.5 Mechanical forces applied to the posterior segment as myopigenic factors

The extraocular muscles are capable of exerting considerably greater force than the ciliary muscle. Peak force for the medial rectus muscle is approximately 150 g (Robinson, 1964) while peak contraction force of the ciliary muscle has been reported as 0.6 g (van Alphen, 1961). Greene has proposed that the actions of the superior and inferior oblique muscles produce localized stress and sheer forces within the sclera (Greene 1980, 1991). Greene

and McMahon (1979) observed that scleral creep (scleral stretching) rates in enucleated rabbit eyes increased following increases in temperature and simulated increases in intraocular pressure. Greene (1980) has also commented on the possibility of the lamina cribrosa acting as a weak point in the scleral tunic, perhaps leading to localized scleral stretch.

It is interesting to question whether there is a link between the localized forces applied to the temporal portion of the posterior sclera by the oblique muscles, and the formation of staphyloma which, if present, are usually located in this region of the globe (Curtin *et al*, 1979; Greene, 1991).

The sclera of the myopic eye has been show to be thinner in the horizontal plane than the sclera of the emmetropic or hypermetropic eye (Cheng *et al.* 1992). Mean scleral thickness of 0.8, 0.6 and 0.4 mm were found for hypermetropic, emmetropic and myopic groups respectively.

1.11 Heterophoria and myopia

Studies have shown a relationship between esophoria at near and myopia, and esophoria at near as a precursor to myopia. A mechanism for myopic onset in esophoric conditions at near has been proposed in the review by Goss and Rosenfield (1998), and can be summarized as follows:

1. Sustained nearwork induces an esophoric shift in vergence adaptation at near (Ehrlich, 1987).
2. Increased esophoria at near induces stress in binocular fusion. A negative shift in fusional vergence is required to counteract this stress. A reduction in convergent accommodation brings about the required negative shift in fusional vergence, but manifests an increase in lag of accommodation.
3. Increased lag of accommodation produces hyperopic defocus during near vision. Counteracting axial elongation is initiated. Permanent myopic shift in refraction is produced.

Goss (1991) found a statistically significant correlation between heterophoria and juvenile onset of myopia. Near point heterophoria data from optometric practice databases was assessed in a cohort of subjects aged 6 to 15 years. The myopic onset group (N = 61)

showed mean (±SEM) near heterophoria of 1.0(±0.8) Δ esophoria, compared with the stable emmetropic group (N = 61) who showed mean near heterophoria of 2.0(±0.8) Δ exophoria.

Goss and Jackson (1996a) carried out a prospective study of near dissociated heterophoria in emmetropic children. Measurements of near heterophoria were carried out at 6 month intervals over a 3 year period. It was postulated that a near point heterophoria outside the range of 3 Δ exophoria to 1 Δ esophoria could act as an additional risk factor to the onset of myopia in youth. Myopic subjects exhibited a generally more convergent near heterophoria than their emmetropic counterparts.

1.12 Accommodation and myopia
1.12.1 Lag of accommodation and myopia
The accommodative response tends to be over-exerted when viewing distant objects and under-exerted when viewing near objects. These occurrences are termed lead of accommodation and lag of accommodation respectively. Lag of accommodation when viewing a near object produces hyperopic defocus at the retina. A study of 60 young adult subjects (30 emmetropes and 30 myopes, mean age 24 years) by Subbaram and Bullimore (2002) measured accommodation responses to distance and near targets. A reduced Bailey-Lovie chart (Bailey and Lovie, 1976) was viewed monocularly via a +6.50 D Badal system. The Badal system was adjusted to produce accommodative stimuli of 0, 2, and 4 dioptres. Accommodation responses were measured by Canon R-1 infra-red autorefractor. Mean measurements of logMAR visual acuity and pupil diameter were carried out. Average accommodation responses (all subjects) for the stimulus levels of 0, 2 and 4 D were: 0.22 ± 0.28 D, 1.83 ± 0.23 D and 3.71 ± 0.27 D respectively, indicating a lead of accommodation when the accommodative stimulus was low and a lag of accommodation at higher stimulus levels. Similar results were found when data from the two refractive groups were analysed separately. Repeated measures ANOVA showed no significant difference in lag of accommodation between emmetropic and myopic subjects. The study does not offer any information with regard to the age of onset or stability of refractive error in the myopic group, which has been shown to have ramifications on the accommodative response (Abbott et al. 1998).

Abbott *et al.* (1998) measured stimulus response (S-R) curves in 33 adult subjects by 3 methods: decreasing target distance series (DDS), negative lens series (NLS) and positive lens series (PLS). The subject cohort consisted of 10 emmetropes, 11 early onset myopes (5 stable, 5 progressing, and 1 subject omitted from analysis) and 12 late onset myopes (5 stable and 7 progressing). From a methodological point of view, the highest levels of accommodative lag at near were found when measuring S-R curves by the negative lens series. When classifying refractive error in terms of emmetropia, early onset myopia and late onset myopia, no statistically significant difference in accommodative lag was found between the groups. However, categorization of refractive error in terms of stability of refraction revealed higher lags of accommodation (i.e. depression of the S-R curve) in the progressing myopes. This finding agreed with previous studies by Gwiazda and co-workers in children (Gwiazda *et al.* 1993a; Gwiazda *et al.* 1995). It appears then that this shows that there is an inherent difference in the near response between the emmetropic or stable myopic eye and the progressing myopic eye.

Considerable amounts of experimental work have been carried out to determine whether lag of accommodation at near is a precursor to, or a consequence of, the onset of myopia. Portello *et al.* (1997) measured lag of accommodation in a cohort of emmetropic subjects. A significantly greater lag of accommodation was found in subjects who later became myopic compared to subjects that remained emmetropic. Goss (1991) also found an increase in lag of accommodation preceding the onset of myopia. Binocular cross-cylinder results were found to be significantly higher (by ANOVA) in the subject group subsequently developing myopia.

Rosenfield and Gilmartin (1999) investigated error in the accommodation response and accommodative adaptation to a near task in 18 young adult subjects. The subject cohort consisted of 8 emmetropes and 10 myopes. The within task accommodation response to a sustained, 3 D accommodative demand, cognitive task was measured by infra-red optometer. Post-task open-loop responses (dark focus) were measured for a further 10 minutes. The experiment identified 11 subjects demonstrating accommodative adaptation to the near task. The 7 non-adaptors showed relatively consistent lags of accommodation during the near task, and rapid decay of accommodation post-task under open loop conditions. The adaptive group showed a steady reduction in lag of accommodation during the first 3 minutes of the near task, and a more accurate accommodation response (i.e.

accommodative response dioptrically closer to accommodative demand) for the remaining 7 minutes. However, under open-loop conditions, the adaptive group exhibited a delayed relaxation of the accommodation response to the pre-task dark focus level.

The reduction in lag of accommodation found in adaptive subjects is thought to be due to input from the slow, blur-driven accommodative response (Schor *et al*, 1986). Considerable evidence exists to show that the slow blur-driven accommodative response is likely to be mediated by the parasympathetic and sympathetic branches of accommodative control (Gilmartin, 1986; Gilmartin 1998), while the fast blur-driven system is mediated only by the parasympathetic system (Gilmartin and Winfield, 1995). Subjects exhibiting accommodative adaptation facility will thus experience lower levels of retinal blur than a non-adaptive subject during a near task. Non-adaptive subjects may experience sustained hyperopic retinal defocus during a near task. This hyperopic defocus (Flitcroft, 1999) may be sufficient to trigger a corrective mechanism in the form of axial elongation of the eye (Flitcroft, 1998). Following the near task, however, the adaptive subject may experience transient blur at distance. This blur would be myopic in nature. The non-adaptive subject would rapidly return to a state of clear distance vision.

Rosenfield and Abraham-Cohen (1999) have shown that myopes are subjectively less sensitive to retinal blur than emmetropes. A bipartite target, one half fixed and one half moveable, was imaged within a Badal optical system. The cyclopleged subject viewed both halves of the target via a near correcting lens and 2 mm artificial pupil. The moveable half of the target was moved to and fro within the Badal system until the point of first noticeable blur was detected. In this study comprising 12 myopes (8 early onset, 4 late onset) and 12 emmetropes, mean subjective blur detection thresholds were 0.11 ± 0.01 D for the emmetropic group, and 0.19 ± 0.02 D for the myopic group. The measured difference in blur sensitivity threshold was statistically significant. It was noted that the blur sensitivity values were more variable in the myopes. Additionally, no significant difference was found in dioptric blur threshold when the target was moved towards, or away from the subject. This may indicate that subjects are equally sensitive to relative myopic and hyperopic retinal defocus. These findings support the hypothesis that the increased lag of accommodation at near in myopic individuals is due to a deficit in blur recognition, and thus a reduced accommodative drive, rather than a deficit in the actual accommodation response.

Jiang and Morse (1999) compared perceptual depth of focus (referred to as 'effective threshold', ET) in young adult emmetropes (N = 8) and late onset myopes (N = 10). Five subjects in the late onset group had stable refractive error and thus were designated as 'stable myopes', the remaining 5 late onset myopes were designated as 'progressing myopes'. The progressing myopes were found to have significantly higher effective threshold values (mean, 0.79 D) than emmetropes or stable myopes, indicating that progressing myopes were less sensitive to the perceptual detection of blur. The difference in ET between emmetropes and stable myopes was not statistically significant. This study is further indication of change in the oculomotor system occurring during the progression of myopia (Abbott, *et al.*, 1998).

Recent analysis of data from the Orinda Longitudinal Study of Myopia (Mutti *et al.*, 2002) has shown that in 903 children an increase in lag of accommodation was not present prior to the onset of myopia. Following myopia onset, lag of accommodation was significantly associated with magnitude of myopia. The work concluded that increased lag of accommodation to near targets was a symptom of, rather than a cause of, myopia in children.

A model of optical and oculomotor factors and contributory elements in the emmetropization process and myopigenesis was produced by Flitcroft (1998). The model is based on computational schematics of the accommodation and vergence systems, and takes into account the effect of tonic accommodation, tonic vergence (heterophoria), accommodative and vergence gain, AC/A and CA/A ratios, depth of focus, accommodative demand and task duration. The model highlights near work as a significant factor in myopia development. Of particular note are the models showing greater predicted myopia as near working distance decreases (i.e. dioptric demand increases), and duration of near work increases.

The role of retinal defocus as a trigger for the development of myopia has received considerable attention from workers in the field of animal myopia (see Smith, 1998 for a full review). A great number of experiments have taken place to test the hypothesis that artificially induced retinal blur, spatial restriction of visual experience, or form deprivation can lead to the induction of permanent myopia. Young noted significant degrees of

permanent myopia induced in monkey following restriction of the visual space to approximately 20 inches. The myopia was permanent, and axial in origin. Various age groups of monkey were used in this work; the most significant degrees of myopia being induced in the younger (11 to 24 months old) subjects (Young; 1961, 1963). Recently, Smith and co-workers (Smith *et al.*, 1999) have shown that form deprivation can cause axial myopia in monkeys between the ages of 3.7 and 5 years. This age group in monkey is equivalent to 15 to 20 years of age in humans. This study has demonstrated form deprivation myopia in older animals than previous studies, indicating that degraded retinal imagery can cause myopia beyond the normal age of ocular development.

Form deprivation has been shown to produce permanent myopia change due to an increase in axial length (Wiesel and Raviola, 1979). Studies of form deprivation have traditionally entailed lid suturing of one eye, with the fellow eye being left open to act as a control. Gottlieb *et al.* (1987) reported localized globe expansion following restriction of corresponding areas of the visual field in chick eyes, indicating that differential adaptation to degraded retinal imagery is possible.

Of particular interest with regard to this thesis is the phenomenon of myopia induced in animals by optical defocus methods. Optical defocus methods have a significant advantage over traditional form deprivation techniques in that optical methods have both a magnitude and directional component (i.e. hyperopic or myopic). These studies have a clear analogy with the hyperopic defocus induced by lag accommodation during near work, and the myopic defocus following a near task due to accommodative adaptation, although these effects are smaller. Eyes of young chicks have been shown to fully compensate for artificial refractive errors induced by spectacle lenses (Schaeffel and Howland, 1991). Irving *et al.* (1991) fitted +10 DS and −10 DS rigid contact lenses in a goggle arrangement to newly hatched chicks. After 1 week the chick eyes had compensated for the induced hyperopic and myopia in the appropriate direction, i.e. application of a positive lens induced an amount of myopic retinal defocus which was compensated by a reduction in axial length; application of a negative lens induced hyperopic defocus which led to compensatory axial elongation. A subsequent study by Irving *et al.* (1992) found that newly hatched chick eyes could accurately compensate for defocus induced refractive error between −10 DS and +15 DS. Outside this range the compensatory ocular growth was less accurate. Change in the optical defocus to opposite sign after 1 week resulted in an

adaptation to this new refractive state, but only to 80% of the new error. It was also noted that hyperopic shifts in refractive state occurred more quickly than myopic shifts, indicating asymmetry in the compensatory responses to induced myopia and hyperopia.

In contrast to the directionally accurate compensations to optical defocus found in the chicken, Ni and Smith (1989) found that both positive and negative spherical lenses induced axial myopia in kitten eyes. This finding suggests that the cat eye is unable to detect the direction of optically induced retinal defocus.

1.12.2 Amplitude of accommodation and myopia

McBrien and Millodot (1986a) measured amplitude of accommodation in EOM, LOM, EMM and HYP refractive groups. The results of this study are summarized in table 1.9.

REFRACTIVE ERROR	EOM	LOM	EMM	HYP
Mean amplitude of accommodation (D±SD)	9.87±0.96	10.77±1.17	9.28±0.77	8.63±0.54
Mean age (Years)	19.89	19.75	19.72	19.91
Pupil diameter (mm)	4.57	4.31	4.20	4.01
Range of Rx (D)	-0.625 to −9.875	-0.375 to −2.875	-0.25 to +0.75	+0.75 to +4.75

Table 1.9. Amplitude of accommodation as a function of refractive group. (McBrien and Millodot, 1986a)

The results showed higher amplitude of accommodation in LOM compared to other refractive groups of similar age. Hyperopes exhibited the lowest amplitude of accommodation. The differences found in amplitude of accommodation between refractive groups were statistically significant at the 5% level. Conversely, Fisher et al. (1987) failed to show significant differences in amplitude of ocular accommodation between high myopes, low myopes, emmetropes and hyperopes. It is noted that this study classified myopia in terms of absolute magnitude, rather than age of stabilisation. Fong (1997) measured refractive error and amplitude of accommodation in 696 subjects. Subjects were matched for age, racial background and occupation. Myopic subjects were found to have significantly lower amplitudes of accommodation than non-myopes ($p = 0.03$).

The role of the amplitude of accommodation in early onset or late onset myopia seems insignificant, as the level of accommodation exerted during normal near vision tasks is

well within the maximum level of accommodative effort (Rosenfield, 1998). Taking the example of the McBrien and Millodot (1986a) study of subjects in the age range of late onset myopia, less than one third of the amplitude of accommodation would need to be exerted during a near task at 40 cm in all refractive groups.

1.13 Aspects of intraocular pressure related to accommodation and myopia
1.13.1 Intraocular pressure and accommodation

The effect of intraocular pressure (IOP) on axial length has been proposed by several workers as a possible mechanism for myopic change (Pruett, 1988). It has been proposed that the sclera of the myopic eye is deficient in terms of rigidity, thus scleral stretch (causing axial elongation) occurs with relatively normal values of IOP. Conversely, it has been suggested that normal scleral function combined with elevated IOP leads to axial elongation.

Armaly and Burian (1958) were first to demonstrate a fall in IOP following sustained accommodation in a group of 7 young adult subjects. Tonometry was carried out using a Mueller electronic tonometer while the fellow eye observed a Landolt ring target at 25 cm. Accommodative demand was varied by the addition of a +4.00 DS lens; with the lens in place accommodative demand was zero D, without the lens demand rose to 4 D. A mean reduction in IOP of approximately 3.5 mmHg was found across the subject group. Statistical analysis by ANOVA of the last 2 trials revealed significance of the reduction in IOP following sustained accommodation. An increase in aqueous outflow facility, reduction in aqueous formation or reduction in intraocular blood volume during accommodation were suggested as possible mechanisms for this hypotensive effect.

Further work by Armaly and Rubin (1961) examined change in IOP during accommodation in two age groups; group 1 age range 20 to 25 years, group 2 age range 45 to 55 years. IOP measurement was made by Goldmann applanation tonometry. The study used a similar accommodative stimulus arrangement to that utilized in the previous study (Armaly and Burian, 1958). Combined results for both age groups showed a statistically significant mean fall in IOP of 3.58 mmHg during a 4 D steady-state accommodative task. Separate analysis of data for the two age groups showed larger reduction in IOP on accommodation in the younger group (group mean IOP fall 4.5±1.0 mmHg and 2.3±0.78 mmHg for the younger and older groups respectively). Time course for the maximum fall

in IOP to occur was greatest in the older age group (2.7 minutes versus 4 minutes for the older group).

A later study also based on Goldmann applanation tonometry by Mauger *et al.* (1984) confirmed a reduction in IOP on accommodation. It is interesting to note that similar reductions in IOP were noted for 1.50 D demand and 4.00 D demand tasks. A mean decrease in IOP of 2.38 mmHg was noted following 3.5 minutes of a 4.00 D task, with the majority of the fall in IOP occurring in the first 30 seconds of the trial.

The three studies mentioned do not measure the actual accommodative response to the stimulus. New facilities for the continuous recording of accommodation (see Chapter 2) could be included in a design to measure accommodative response to a near target and IOP simultaneously. A study of any differences in IOP change between emmetropes, and early and late onset myopes could produce interesting results. Also, a similar design applied to progressing and stable myopes could also prove fruitful.

Coleman and Trokel (1969) measured IOP directly by manometry in a single subject with underlying ocular disease. Significant increases in IOP were demonstrated with lid closure (5mmHg), blinking (5-10 mmHg), levoversion (5-10 mmHg) and attempted accommodation during cycloplegia (2-4 mmHg). Lid squeezing produced an increase in IOP in excess of 70 mmHg. It was suggested that the considerable IOP increase from this type of lid pressure may be an important factor in progression rate in uncorrected myopes. The increase in IOP on attempted accommodation is opposite to the findings of other studies (Armaly and Burian, 1958; Mauger *et al.*, 1984).

It has proposed that the extraocular muscles may have an effect on IOP during eye movements and convergence, due to indentation of the sclera (Greene, 1991). Collins *et al.* (1967) observed IOP increase in the cat following increase in extraocular muscle force. It could be the case that in the human eye IOP varies according to gaze direction. This may be a factor in myopia if IOP is increased significantly above the baseline level when conducting a visual task for long periods. Further work in this area may prove fruitful.

1.13.2 Intra-ocular pressure as a function of refractive error

Myopes tend to exhibit higher intraocular pressures (Ong and Ciuffreda, 1997). Abdalla and Hamdi (1970) compared IOP (by Goldmann applanation tonometry) in emmetropes (±2 DS), low myopes (-2 to –6 DS) and high myopes (>-6 DS). Results were further categorized according to age. The myopic groups exhibit higher IOP than the emmetropic groups in all age categories. Table 1.10 shows a summary of mean IOP against subject age and refractive group.

Age (years)	Refractive group	N	Mean IOP (±SD) mmHg
11-20	Emmetropia	75	14.05(2.24)
	Low myopia	39	15.73(1.92)
	High myopia	18	14.61(2.58)
21-30	Emmetropia	90	13.72(2.40)
	Low myopia	19	14.53(1.44)
	High myopia	25	14.48(2.62)
31-40	Emmetropia	148	14.19(2.01)
	Low myopia	19	14.70(2.14)
	High myopia	28	16.58(2.32)
41-50	Emmetropia	144	14.39(2.22)
	Low myopia	11	16.05(2.83)
	High myopia	34	15.33(2.69)
>50	Emmetropia	78	14.87(1.88)
	Low myopia	17	16.03(2.50)
	High myopia	15	16.00(1.34)

Table 1.10. Intraocular pressure as a function of age and refractive error (Abdalla and Hamdi, 1970)

Edwards *et al* (1993) conducted a cross sectional study of IOP in Chinese children. Myopic subjects had higher mean IOP than emmetropic or hyperopic subjects. Subjects with myopic parents also exhibited higher IOP than children with non-myopic parents. Mean IOP for the emmetropic/hyperopic group (N = 93) was 13.96 (SD 2.38) mmHg, mean IOP for the myopic group (N = 13) was 15.36 (SD 3.15) mmHg. However, no correlation was found between IOP and degree of myopia. Mean IOP for the subjects with non-myopic parents (N = 61) was 13.44 (SD 2.42) mmHg, subjects with one myopic parent (N = 43)

mean IOP = 14.70 (SD 2.62) mmHg, subjects with two myopic parents (N = 16) mean IOP = 14.58 (SD 2.45) mmHg.

Edwards and Brown (1996) measured IOP in Chinese children (N = 106) at yearly intervals (over a 2-year period) by non-contact tonometry. Subjects were 7 years of age at the commencement of the study. In the 13 subjects who became myopic, a mean increase in IOP of 1.19mmHg was observed (p = 0.028). This increase in IOP was observed after, rather than before, the onset of myopic change. No significant change in IOP was found in the subjects remaining emmetropic (N = 82). A reduction in IOP was found in subjects with pre-existing myopia (N = 10).

Tomlinson and Phillips (1970) examined the relationship of IOP to refractive error and axial length. Subjects were categorized according to refractive error. Table 1.11 is a summary of the findings of this work.

Refractive group	Mean IOP (SD) mmHg	Mean axial length (SD) mm
Myopia	15.49 (2.81)	24.61 (1.00)
Emmetropia	14.74 (2.42)	23.40 (1.38)
Hyperopia	13.91 (2.28)	22.53 (1.02)

Table 1.11. Refractive error, intraocular pressure and axial length (Tomlinson and Phillips, 1970).

Tomlinson and Phillips (1972) measured IOP, axial length and refractive error in 13 anisometropes. Subjects were aged 8-16 years. Highest IOP was found in the longer of the two eyes. Mean IOP for the longer and shorter eyes was 14.15 and 13.15 mmHg respectively. This difference was statistically significant (p <0.05). There was a tendency for the more myopic of the two eyes to have the highest IOP, but this finding failed to achieve statistical significance (p <0.13).

David *et al.* (1985) examined IOP as a function of refractive error in 2403 subjects in a glaucoma screening programme. Subjects were aged 40 years and over. Results once again showed higher IOP in myopic eyes. Statistical significance by ANOVA at the 1% level was found. Results are summarized in table 1.12.

Refractive status	N	Mean IOP mmHg	SD
HYP >+2DS	487	14.19	3.44
EMM –2 to +2DS	3695	14.87	3.70
MYO –2 to –5DS	465	15.10	4.99
MYO >-5DS	174	16.00	6.35

Table 1.12. Intraocular pressure versus refractive status (David *et al.*, 1985).

Recently, Goss and Caffey (1999) measured IOP over a 3-year period at 6-month intervals in a cohort of 87 initially emmetropic children. Twenty-nine subjects developed myopia during this period. No significant difference was found in IOP before the onset of myopia. A small, but statistically insignificant increase in IOP was observed after the onset of myopia.

1.14.1 Nearwork induced transient myopia (NITM)

Nearwork induced transient myopia (NITM) is a short-term myopic shift in distance refraction following a near task. A comprehensive review of the numerous studies in this area was carried out by Ong and Ciuffreda (1995). When discussing NITM the following factors need consideration:

1. Dioptric magnitude of the near task.
2. Duration of the near task.
3. Proximal effects of the near task.
4. Effect of the near task on oculomotor balance.
5. Cognitive demand of the task.

Experimentation has examined the following features of NITM:

1. Magnitude of NITM in an experimental group.
2. Magnitude of NITM in refractive subgroups.
3. Time constant of NITM decay.

NITM has been assessed by post-task changes in visual acuity, contrast sensitivity and far point refraction. Of these methods, change in far point refraction offers the most sensitive measure (Ong and Ciuffreda, 1995). Measurement of far point refraction by objective infra-red optometer has been utilized by numerous studies [Rosenfield *et al.*, 1992a; Ehrlich, 1987; Ong *et al*, 1995).

NITM was initially studied by Lancaster and Williams (1914). The study found myopic shifts of up to 1.30 D following a 45 minute near task. Decay of NITM to the pre-task level was complete in 15 minutes. Pre- and post-task far point refraction was measured subjectively. It was postulated that NITM may be of lenticular origin. This study shows the highest level of transient myopia in all the studies demonstrating NITM. This may be due to the subjective nature of the pre- and post-task refraction assessments and variability of results due to subject fatigue.

More recent studies have utilized objective measurements of refraction in the calculation of NITM. Ostberg (1980) examined NITM by laser optometer in air traffic controllers (N = 9) and general office workers (N = 20). Air traffic controllers spent long periods viewing radar screens. General office workers conducted less intense near tasks with opportunity for rest periods. The air traffic controllers group showed a post task myopic shift of 0.25 D and a reduction in slope of the stimulus/response curve. Decay of NITM was greater than 20 minutes in some cases. The general office workers did not exhibit these changes. The findings of this study were limited by the lack of standardization of near task and stimulus type, and that standard time intervals were not set between refraction points.

Ehrlich (1987) measured far point refraction, near point heterophoria and near point fixation disparity in 15 subjects (mean age 22 ± 2.4 years) using a Dioptron II infrared optometer before, and following a continuous 2 hour visual search task at 5 D. A highly significant ($p < 0.05$) mean post-task myopic shift of 0.29 D ± 0.19 D was found. Recovery from this shift was incomplete 1 hour post-task. Ehrlich suggested that the magnitude of post-task myopic shift was related to the pre-task level of tonic accommodation, i.e. subjects with higher pre-task dark focus show higher levels of induced myopia post-task.

Owens and Wolf-Kelly (1987) made pre- and post-task measurements of monocular far point, stimulus/response function and tonic accommodation. Text reading (VDT or paper hard copy) was carried out binocularly for 1 hour at 20 cm. Average post task myopic shift of 0.43 D and upward bias of stimulus/response curve of 0.30 D was found.

Fisher *et al.* (1987) attempted to find differences in NITM between emmetropes (±0.75D), hyperopes (>+0.75 D), low myopes (>-0.75 D, ≤-4 D) and high myopes (>-4 D). Mean NITM for all subjects following the 10 minute near point task was 0.20 D. No significant

myopic shift was found in any refractive subgroup, perhaps accounted for by the small subgroup size of 12 subjects.

Miwa and Tokoro (1993) also investigated NITM in 11 low (classified as <2D) and 8 high (greater than 2 D) myopes. Pre-task refraction was measured in light and dark conditions using a Nidek AR 1600 autorefractor. A 15 minute binocular reading task was carried out at a distance of 0.3m. The subjects wore additional –3.00 DS lenses over their normal distance correction, giving a stimulus to accommodation of 6 D. Immediately following the task the refractive error was measured in light and dark room conditions. Similar levels of NITM were found in the low and high myopic groups (low myopes –0.23 ± 0.31 D, high myopes –0.20 ± 0.30 D) in light conditions, thus failing to show a statistically significant difference between refractive groups. A significant difference in dark focus shift was found between the refractive groups, however, with a mean change in dark focus (pre-task to post-task) for the low myopes of +0.13 ± 0.42 D and –0.31 ± 0.42 D for the high myopes.

Rosenfield *et al.* (1992a) examined the effect of vergence on NITM following a 20 minute, 5 D visual search and hand-eye coordination task. Vergence was manipulated by the use of base-in and base-out prism, or no prism. Prism power was equivalent to 1/3 of the range of fusional vergence. Mean myopic shift of 0.12 D was found. NITM decay was complete within 30-50 s post-task. No significant difference was found in magnitude or decay of NITM for any of the vergence conditions.

Rosenfield *et al.* (1992b) investigated the effects of blur, proximity and task duration on NITM. Effect of blur and proximity: Subjects performed a monocular 25 cm near task through distance refractive correction (full blur), pinhole (no blur), +2 D near add (50% blur reduction), +4 D add (100% blur reduction). The +4 D add condition did not show significant NITM. Significant NITM was found following the pinhole condition, perhaps indicating that proximity has an input to NITM. To assess the effect of task duration, separate 25 cm near tasks were performed for 40 minutes, or four 10 minute periods punctuated by 5 minute rests. Similar post task myopic shifts of 0.20 D were found with both protocols.

Ong *et al.* (1995) also assessed the effect of proximity on NITM in 15 subjects (age range 22-39 years). A near task was preformed under two conditions: at 6 m through a –5 D lens,

and at 20 cm. Both conditions induced 5 D of accommodative stimulus: the former providing blur only, the later providing blur and proximal drive. Mean post-task NITM was 0.36 D. The magnitude of NITM was similar for both blur only, and blur with proximity groups suggesting that NITM is dependent on the overall accommodative drive.

Additional work by Ong *et al.* (1995) investigated the combined effects of blur, disparity and proximity on NITM. Blur, disparity and proximity factors were manipulated using spherical lenses, ophthalmic prisms and variable target distance. Significant NITM of 0.1-0.39 D was found. The results suggested that stimulus blur was the chief factor in NITM (Ong *et al.*, 1994).

In a study of 11 adult onset myopes, 13 early onset myopes, 11 emmetropes and 9 hypermetropes, Ciuffreda and Wallis (1998) measured distance refractive state before, and subsequent to, a 5 D 10-minute cognitive task. Myopic subjects showed significantly greater near work after effects (myopic shift in distance refraction) compared to emmetropic and hypermetropic subjects. Mean post-task shifts in distance refraction were –0.34 D, -0.36 D, +0.09 D and –0.01 D for the early onset myopic, late onset myopic, emmetropic and hypermetropic subject groups respectively. Decay of near work induced after effects was slower in the late onset myopic group compared to early onset myopes. Mean decay time constants were 35 seconds for the early onset myopes and 63 seconds for the late onset myopes. The results of this study correlate well with the suggestion that late onset myopes have a deficiency in inhibitory sympathetic facility at the level of the ciliary muscle (Gilmartin, 1998). Of particular interest is the increased time course of post-task accommodative hysteresis in late onset myopes. Had this study have included an autonomic profiling protocol, it may have been possible to establish a direct link between age of myopia onset, NITM and inhibitory sympathetic innervation of ciliary smooth muscle.

1.14.2 Suggested mechanisms for the manifestation of NITM

A number of workers have formulated theories as to the manifestation of NITM. These theories include transient change in axial length, and anatomical, neurological or pharmacological effects within the ciliary muscle and crystalline lens (Ong and Ciuffreda, 1997).

With regard to axial length change as a cause of NITM, studies have shown both increases (in the region of 0.1 mm) and decreases (0.08 mm) in axial length following a sustained near task. Measurement of axial length was carried out by A-scan ultrasonography (Ong and Ciuffreda, 1997). It is interesting to note that the magnitude of axial length change found is of the same order as the accuracy of ultrasound (approximately ± 0.1 mm, Storey, 1982). Drexler et al. (1998) employed a partial coherence interferometric technique to observe axial elongation during sustained accommodation. It is interesting to note that greater elongation was evident in emmetropic eyes. Improved experimental work in this area will be possible with the introduction of the *Zeiss IOLMaster* (see Chapter 2), by virtue if its higher resolution compared to ultrasonic techniques (Santodomingo-Rubido et al., 2002). See proposals for future work (Chapter 9).

Other proposed therories for the mechanism of NITM have centred around the crystalline lens and ciliary body. The theories have been discussed in anatomical, pharmacological and neurological terms. In the physical domain, hysteresis of the forces applied to the lens by the capsule during accommodation have been suggested as a possible cause of NITM (Ong and Ciuffreda, 1997). Kikkawa and Sato (1963) examined the effects of external physical forces on rabbit and cat crystalline lenses. Resultant deformation of the lens surface was slow to decay. From a pharmacological viewpoint, it is known that sustained near vision triggers a sympathetic inhibitory input to the combined accommodative response in certain individuals (Gilmartin, 1986; Gilmartin et al., 2002b). Central to the thrust of this thesis is the delay in relaxation of accommodation noted in certain individuals following an intense near task. Combining an autonomic profiling protocol and a battery of NITM trials in the same cohort of subjects may further our understanding of this area (see Chapters 3, and 8).

1.15 Aims and scope of thesis

The aim of this thesis is to examine the profile of autonomic control of accommodation, ocular biometry and oculomotor factors against longitudinal change in refraction in a large sample of subjects. Specifically, the presence of an inhibitory sympathetic branch of accommodative control, and biometric and oculomotor precursors to late onset myopia will be investigated on an individual level. Previous reports have suggested that individuals with a deficit of the inhibitory sympathetic branch of accommodative control may be at increased risk of developing late onset myopia (Gilmartin, 1998). Established experimental

protocols will be employed throughout to determine the presence or otherwise of sympathetic facility in accommodation control. Subjects used in the study are considered at risk of myopia development and progression due to their considerable near vision demands.

The thesis addresses the above issues as follows:

1. A 2.5 year longitudinal study of refractive error development and progression combined with a double masked autonomic profiling paradigm. Further examinations concerning oculomotor status (heterophoria, tonic accommodation, lag of accommodation, amplitude of accommodation and AC/A ratio) and ocular biometry (corneal curvature, anterior chamber depth, axial length and axial length to corneal curvature ratio) were carried out.

2. A broad cross sectional investigation of autonomic, biometric and oculomotor profile in a large sample of subjects with known refractive status. An attempt to establish a distribution of autonomic profile as a function of refractive error in the largest sample of subjects to date.

3. Measurement of biometric factors using novel instrumentation to correlate structural change with myopic progression in a 12-month longitudinal study.

4. Detailed examination of the effects of sustained near vision (pre-adaptation) on the accuracy of dynamic accommodation responses.

5. Examination of the effects of a range of topical autonomic agents on the dynamic accommodation response. This work investigates these effects in a larger sample than previous studies.

6. Examination of the effect of cognitive demand on nearwork induced transient myopia in emmetropes, early onset myopes and late onset myopes.

Much of the research takes advantage of new measurement techniques for the continuous recording of accommodation responses and ocular biometry. The use of this apparatus allows *in vivo* investigation of systems to a greater level of precision than previously possible. The thesis provides a full account of the modification of the apparatus to enable continuous recording of accommodation.

The instrumentation, methodologies and subject group sizes used in this work provide a firm basis for the investigation of deficiency in sympathetic inhibition of accommodation

as a risk factor in development of late onset myopia. Work to date has shown a theoretical foundation for the link between sympathetic deficiency and LOM development, but results of experimental work in this area have been equivocal. This study aims to answer this long standing question.

CHAPTER 2
INSTRUMENTATION AND APPARATUS

This chapter describes the apparatus utilized in the experimental work. Commercially available devices are discussed; modification and evaluation of these devices is described. Also included is a description of a range of novel instruments purpose built for use within the bounds of this thesis. Diagrams and digital images are included where appropriate. A further range of devices constructed by the author for use in related research projects can be found in Appendices.

2.1 Review of apparatus for the continuous recording of accommodation

The Canon Autoref R-1 device is an open view infra-red autorefactor. The device has been used extensively in accommodation research. Continuous recording modifications by Pugh and Winn produced a useful tool for accommodation research (Pugh & Winn, 1988). The Canon R-1 utilizes three sets of infra-red emitters and detectors arranged at orientations of 30°, 150° and 270°. A motorized lens system is used to focus light returning from the eye to achieve maximum voltage output of the IR detectors. The output voltages from the detectors are analysed and combined to produce a sphero-cylindrical estimate of refraction for the eye under examination (McBrien & Millodot, 1985; Davis *et al.*, 1993). Modifications for the continuous recording of accommodation involves the disabling of the motorized lens system to allow manual focusing of the returning IR light. The voltage signal form one IR detector is extracted and fed to a storage oscilloscope (Pugh & Winn, 1989). The voltage output from the detector is proportional to the accommodation response of the eye.

Limitations of this system are the need for calibration prior to each session of measurements and the limited dynamic range of measurements (up to 2 D). Disabling the motor drive system to enable continuous recording of accommodation means that is not possible to take simultaneous static measurements of refractive error. Also, the Canon R-1 is reliant on a fairly complex opto-mechanical arrangement, which can cause reliability problems. The Canon R-1 is no longer in production and existing machines are approaching the end of their useful lives. Therefore, an alternative continuous recording system was required.

2.2 The Shin-Nippon SRW-5000 open view infrared autorefractor; description and clinical evaluation

The Shin-Nippon SRW-5000 open view infrared autorefractor is a relatively new device for the objective measurement of refractive error. The open view design, similar to that of the Canon R-1, makes the device particularly useful in accommodation research.

2.2.1 Features of the SRW-5000.

- Measurement range +22.00 DS to –22.00 DS, +10.00 DC to –10.00 DC.
- Cylinder axis expressed to 1°.
- Precision of 0.12 D or 0.25 D selectable.
- Back vertex correction of 0, 10, 12, 13.5, 15 and 16.5 mm selectable.
- Measurement of refractive error complete in approximately 1 second (in static mode).
- Automatic averaging of multiple measurements (expressed in sphero-cylindrical form).
- Automatic measurement of inter-pupilliary distance.
- Built in thermal printer for hard copy of refraction results.
- Built in cathode ray tube display for optical alignment of the instrument head with the eye under examination, and display of refraction results.
- Open view arrangement and design of instrument head allows measurement of peripheral refraction up to 40° nasal and temporal.

In standard format the device takes single shot measurements of refractive error (referred to as static mode). The measurement procedure can be summarized as follows:

- Subject was set up on the instrument chin rest. Instruction was given on appropriate fixation.
- The instrument head was aligned with the eye under examination using the joystick.
- The measurement button on the joystick was depressed.
- A ring of infrared light (wavelength 850 nm) was momentarily imaged on the subject's retina. Presentation time is 250 ms.

- This light was reflected from the retina and collected be the semi-reflecting mirror in the instrument head.
- A motorized lens system brings this light into approximate focus on a CCD camera.
- Multi-meridional image analysis of the video output of the CCD camera was carried out internally.
- From the multi-meridional assessment of ring diameter an estimate of refractive error is produced in sphero-cylindrical form. Ring diameter is relatively larger in myopia, smaller in hyperopia and distorted into an oval shape in astigmatism.

2.2.2 Clinical evaluation of the SRW-5000

It was necessary to evaluate the performance of the SRW-5000 against standard clinical techniques with regard to validity and repeatability.

Method

Retinoscopy and standard non-cycloplegic subjective refraction was carried out on 100 subjects (200 eyes) by a UK trained optometrist. Astigmatic correction was determined by crossed-cylinder test. Spherical correction was binocularly balanced with the fellow eye fogged. The endpoint of refraction was the most plus (or least minus) spherical lens giving best visual acuity. Mean age of subjects was 24.4 ± 8.0 years, with 74% of subjects being aged 26 years or less. Gender bias was 54/46 male/female. Informed consent was given by all subjects under the terms of the Declaration of Helsinki.

Autorefraction of subjects was carried out by a second optometrist. Subjects were instructed to observe a single letter approximately equal to their unaided vision on a standard 90% contrast internally illuminated Snellen chart at 6 m. Seven autorefractor readings were taken in quick succession. The mean of 6 readings was calculated in sphero-cylindrical form. Repeatability of autorefraction was assessed by re-measuring 50 eyes on a subsequent occasion, by the same Optometrist. Both Optometrists were masked from each other's refraction results.

Data and statistical analysis

Results were collated in a spreadsheet. Standard clinical notation for refractive error (i.e. +1.25/-0.50 x 75) is not convenient for mathematical averaging and statistical analysis

(Bullimore, *et al.*,1998). Major problems occur when attempting to compare, for example, the cylindrical components of the following prescriptions: -6.50/-0.50 x 175 and –6.25/-0.50 x 5. To overcome this problem all prescriptions were converted into a vector representation according to Thibos *et al.* (1997). The standard notation of Sph/Cyl x Axis is converted into three dioptric vector quantities, MSE, J_0 and J_{45}. The following formulae are used for conversion:

- MSE = Sph + (Cyl / 2). *This quantity is the mean spherical error in Dioptres.*
- J_0 = - (Cyl / 2) cos (2 x Axis). *Cylinder at axis 0° with power J_0 in Dioptres.*
- J_{45} = - (Cyl / 2) sin (2 x Axis). *Cylinder at axis 0° with power J_{45} in Dioptres.*

Statistical analysis between measures was carried out by paired two-tailed *t*-tests. Bias and 95% confidence limits were calculated and plotted graphically according to established methods for the comparison of clinical measurements (Bland and Altman, 1986).

Results

Validity. The autorefractor results were found to be more positive than the subjective results. Mean difference in MSE was +0.16 ± 0.44 D ($p < 0.001$) over the prescription range +6.50 to –15.00 D. Mean difference found in spherical component was also slightly more plus than the subjective result (+0.15 ± 0.46 D ($p < 0.001$). Cylindrical vectors by autorefraction were found to be more negative than subjective results: -0.10 ± 0.19 D, $p <$ 0.001 for J_0; -0.10 ± 0.15 D, $p < 0.001$ for J_{45}. Comparison of cylinder power from the raw data showed no significant difference between SRW-5000 and subjective refraction. Average cylinder powers were: - 0.74 ± 0.81 DC by autorefraction, and - 0.75 ± 0.83 DC by subjective refraction ($p = 0.76$). The following figure (2.1 – 2.4) show Bland-Altman (1986) plots for validity of the SRW-5000 in terms of sphere, cylinder and mean sphere power, and vector components J_0 and J_{45}. Key to graphs: Solid line on the graphs indicates mean difference between SRW-5000 and subjective result, dashed line indicated upper and lower 95% confidence limits.
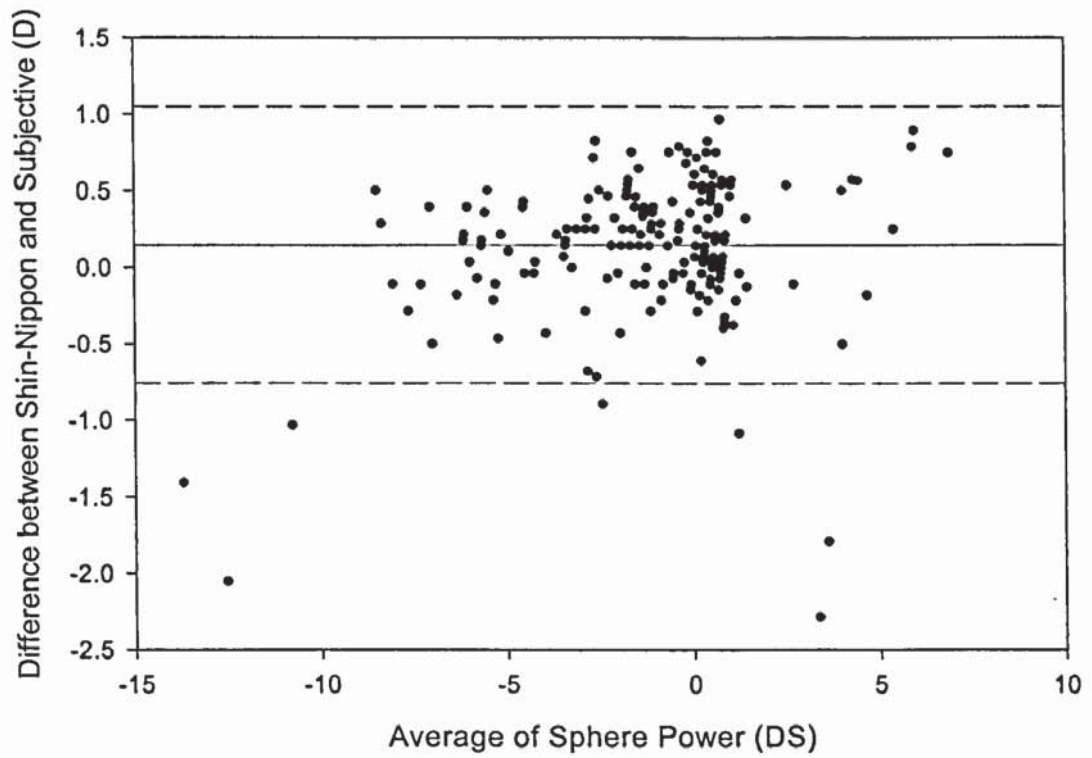
Figure 2.1. Difference in sphere power between SRW-5000 and subjective
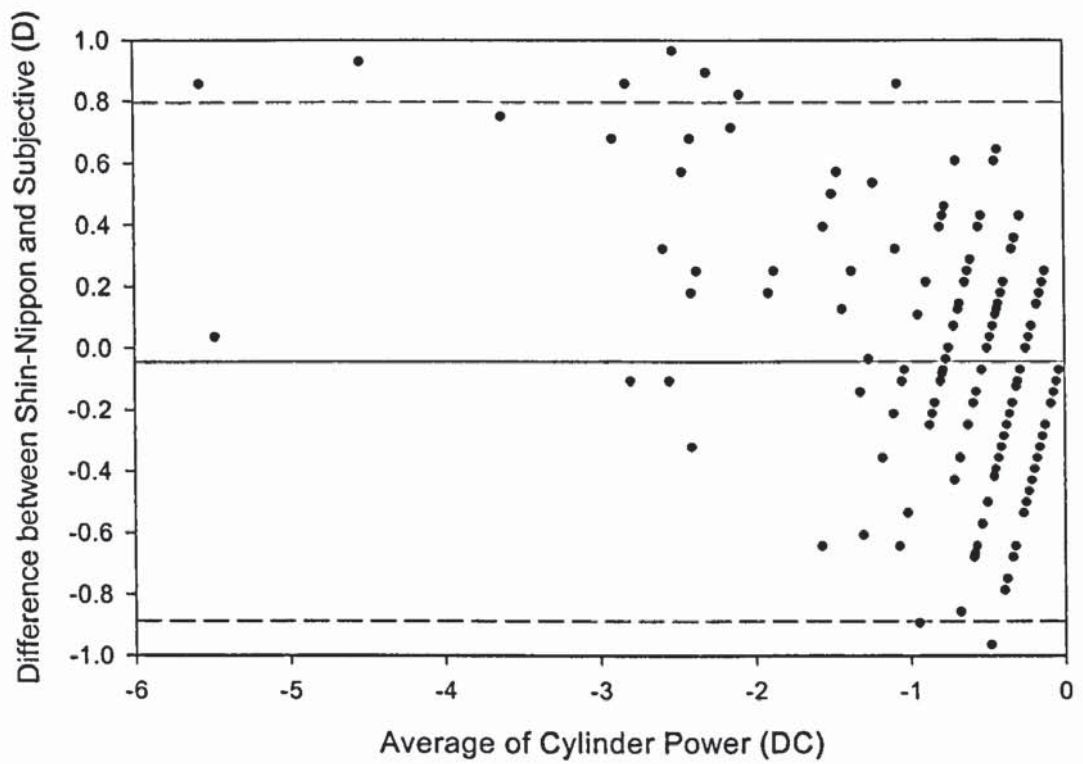
Figure 2.2. Difference in cylinder power between SRW-5000 and subjective
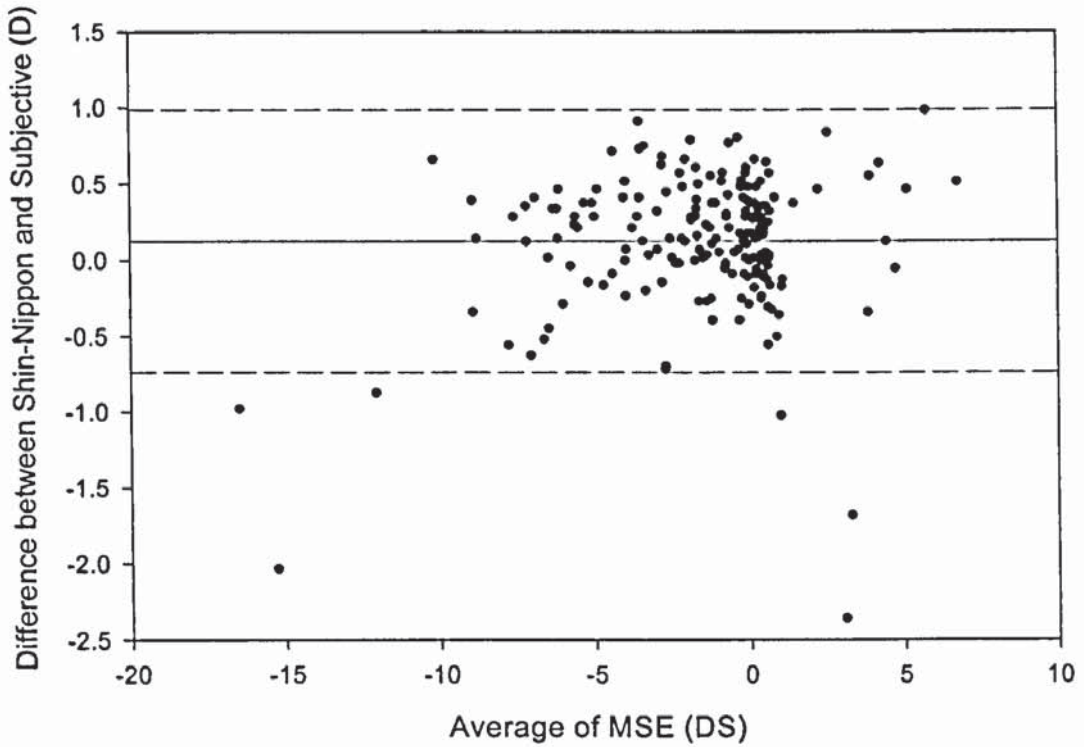
Figure 2.3. Difference in MSE between SRW-5000 and subjective
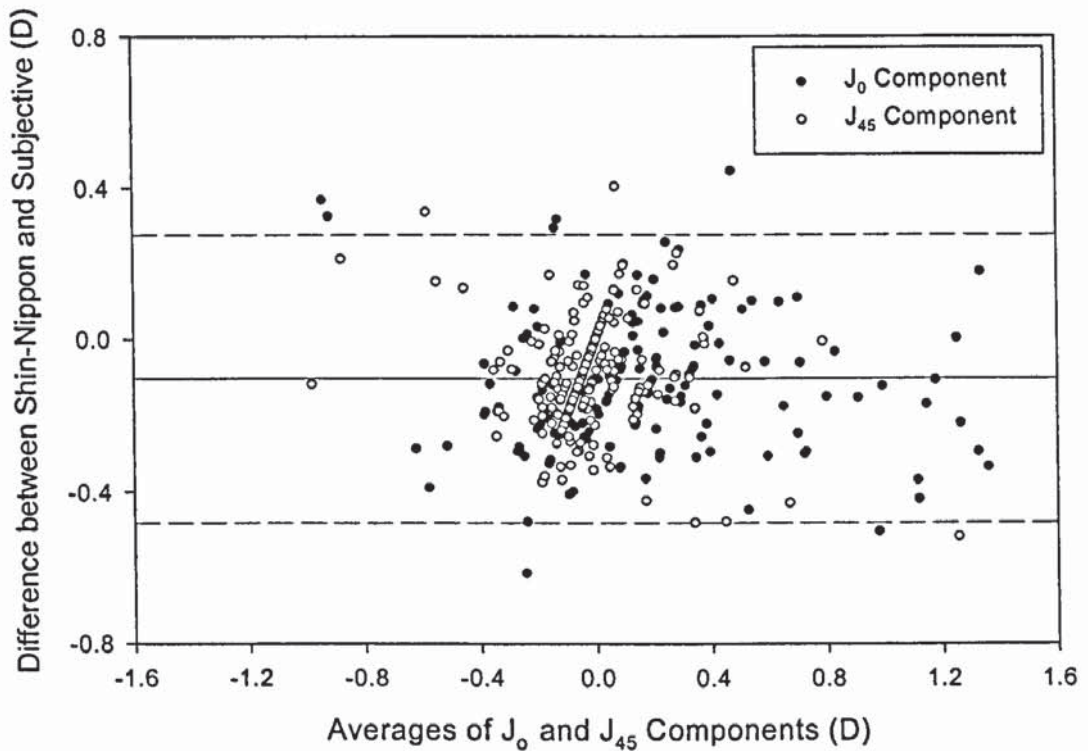
Figure 2.4. Difference in vectors J_0 and J_{45} between SRW-5000 and subjective

Repeatability. Repeatability was assessed in two ways. Firstly the difference between the first reading and the subsequent 6 readings at the first measurement session was analysed.

Mean difference of spherical component and cylindrical component was 0.14 DS and 0.16 DC respectively. Variation in vector components MSE, J_0 and J_{45} were found to be 0.13 D, 0.08 D and 0.07 D respectively.

Secondly, the repeatability of autorefractor result was assessed between sessions. The seven individual readings from each session were converted into vector components and averaged. Table 2.1 below shows mean difference and standard deviation for MSE, J_0 and J_{45} vector components, and sphere and cylinder power. Additionally for MSE, sphere and cylinder power a figure is given showing the percentage agreement of values within standard clinical increments for lens power.

	Sphere	*Cylinder*	*MSE*	*J_0*	*J_{45}*
Mean difference (D)	-0.02	-0.03	0.04	0.01	-0.02
SD of difference (D)	0.24	0.24	0.22	0.12	0.12
95% confidence limits	0.47	0.47	0.43	0.24	0.24
% within ± 0.25 D	67	65	74	-	-
% within ± 0.50 D	89	97	97	-	-
% within ± 1.00 D	100	100	100	-	-

Table 2.1. Inter-session repeatability of the SRW-5000

The use of variable size artificial pupils demonstrated the validity of measurements in eyes with pupils greater than 2.9 mm. Pupils smaller than 2.9 mm obscure part of the measurement ring, and a 'retry' message is displayed.

Conclusions

From the results it can be seen that the SRW-5000 device produces results which are valid when compared to standard clinical procedures, and repeatable. The device is capable of producing results of equal or better validity and repeatability than instruments used previously in this area of study, (e.g. the Canon Autoref R-1). The ergonomics of the instrument, and particularly the open view design, make it ideal for accommodation research applications See supporting publication, Mallen, *et al.,* (2001) for a full account of this work.

2.3 Modification of the Shin-Nippon SRW-5000 as a continuously recording optometer

In standard format the Shin-Nippon SRW-5000 is capable of taking 45 static measurements of refractive error per minute. This in itself is impressive, but a higher degree of temporal resolution is required when examining the dynamics of the accommodation response. The operating principles of the SRW-5000 make the device amenable to modification to enable the continuous measurement and recording of the accommodation response and pupil size. Modification of the SRW-5000 was carried out. Validity and repeatability of the continuous recording system was carried out on model and real eyes. Figure 2.5 shows the instrument layout for continuous recording of accommodation.
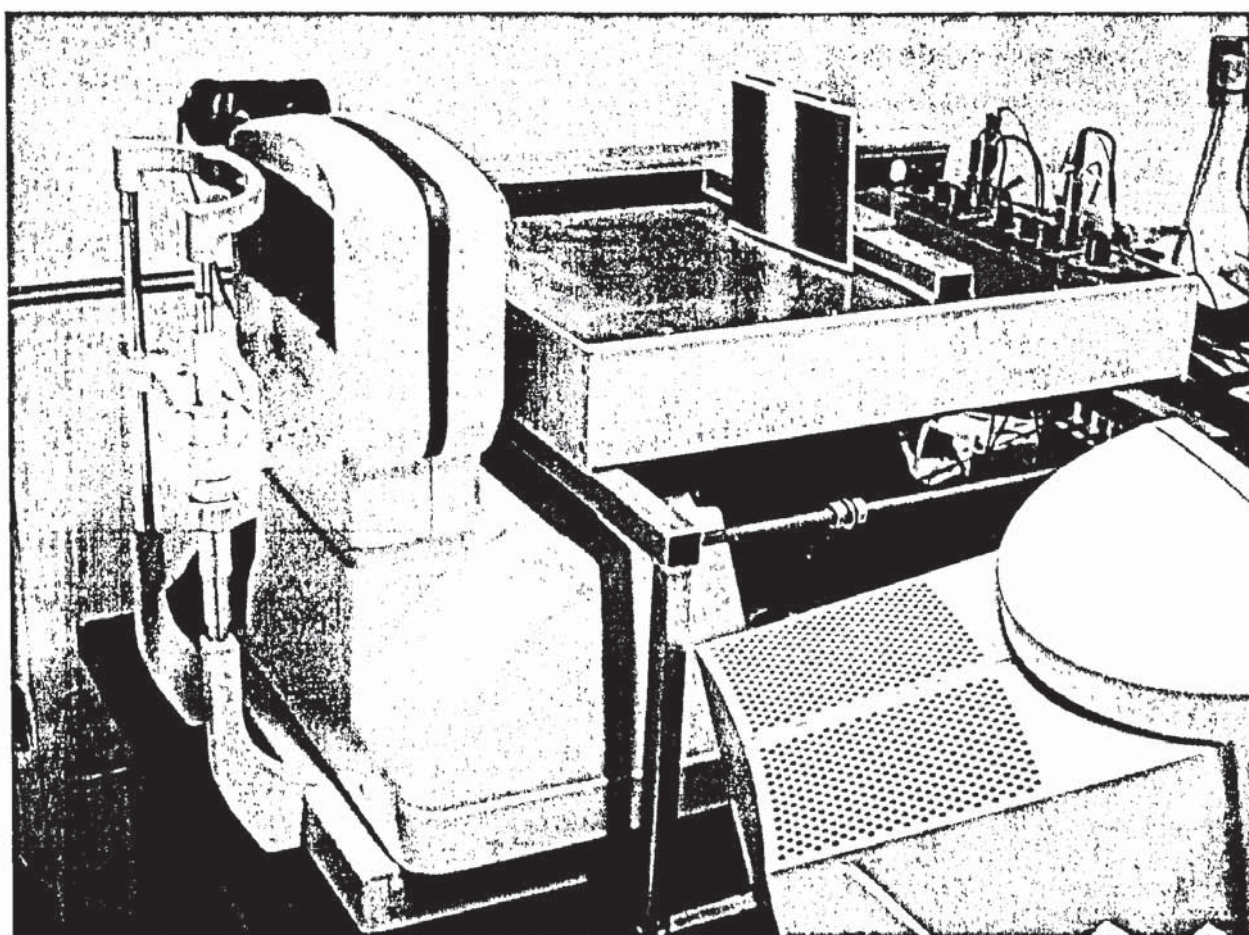
Figure 2.5. Shin-Nippon continuous recording optometer and X-Y plotter.

2.3.1 Method

In normal static mode of operation the infrared measurement ring of the SRW-5000 is momentarily illuminated. For continuous recording of accommodation it is necessary to

have constant illumination of the ring. This was achieved by entering the 'sales mode' menu of the device and altering the 'Ref.Led' status from 'Auto' to 'On'.

The video output of the SRW-5000 was connected to a National Instruments PCI-1408 image acquisition card (see section 2.4). Image analysis programming within *LabView* (see section 2.4) was used to isolate the image of the measurement ring from the additional information within the video output. Sub-pixel analysis of the measurement ring diameter in the horzontal meridian was carried out by *LabView* programming. During initial trials of this system, the output signal of the CCD (charged coupled device) detecting the image of the measurement ring was intercepted on the main printed circuit board of the SRW-5000. This signal contained only an image of the ring, i.e. prior to the addition of alignment and prescription data elements to the video signal. Collecting the video signal in this way made the ring edge detection process more robust. Due to video signal impedance difficulties (i.e. the degradation of signal quality induced when a single signal source is fed to more than one device) a buffer circuit was required. Figure 2.6 shows the circuit designed for this purpose.
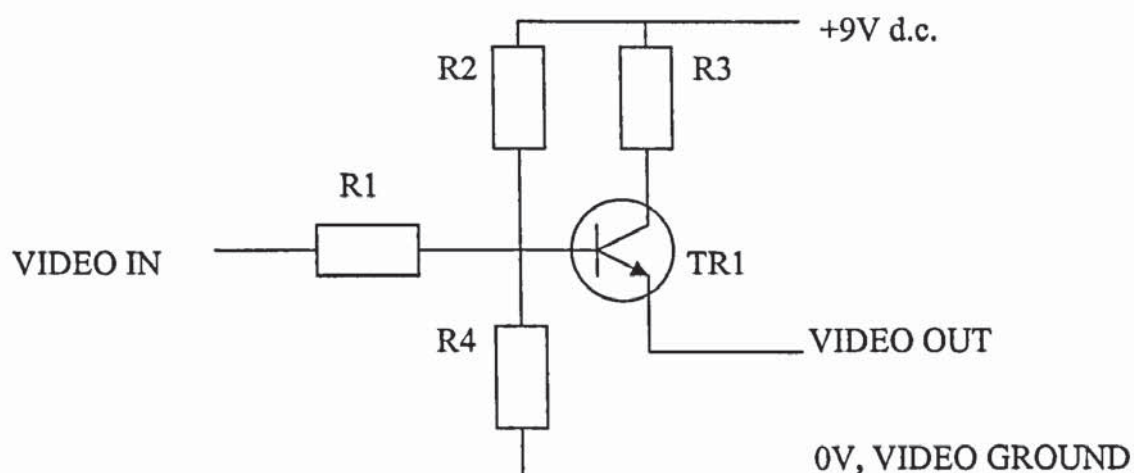
Figure 2.6. Diagram of video buffer circuit. Key to symbols: TR1 = BC108C NPN transistor, R1 = 1kΩ 0.5W resistor, R2 = 10kΩ 0.5W resistor, R3 = 100Ω 0.5W resistor, R4 = 4.7kΩ 0.5W resistor.

Continuous measurement of pupil size was achieved by alteration of the *LabView* programming to detect the largest dark image particle within the video signal. Small, bright particles were sequentially removed from the main image until only the pupil image remained.

Model eye. The mean refraction results over time from the horizontal meridian in continuous recording mode were compared with refraction results taken by static mode. This was carried out over a 6.50 D range of ametropia settings on the model eye. Focusing tolerance of the system was tested by taking 50 dynamic readings with the instrument up to 5 mm forward and backward of optimum focus. Measurement errors due to eccentric fixation were assessed by continuous recording with the model eye rotated up to 25° (in 5° steps) from the optical axis of the instrument.

Human eye. The dynamic accommodative response of a human eye (subject age 27 years) to a moving, 90% contrast, Maltese cross target was recorded. The target was subject to sinusoidal oscillation over a dioptric range of 2 to 3.7 D at a temporal frequency of 0.2 Hz, and viewed via a +5 D Badal system (Atchison *et al.*, 1995). The output of the dynamic stimulus generator was fed to an analogue input channel of a National Instruments BNC 2090 device to allow the simultaneous recording of accommodative stimulus and accommodative response.

Alteration of the *LabView* program was carried out to allow the continuous measurement of pupil size. Real time recording of pupil size variation in a human eye was carried out while observing the dynamic stimulus.

2.3.2 Results

Model eye. Continuous measurements of refractive error were made while the axial length of the model eye was changed. Figure 2.7 shows measurement ring diameter against 'refractive error' for the model eye. The continuous recording system showed a linear relationship between 'refractive error' and measurement ring image size. This relationship was demonstrated over a 6.5 D range. The ability of the apparatus to take static and dynamic measurements simultaneously allows for easy calibration of the system. Movement of the instrument away from the position of optimum focus had less than 0.1 D effect on the dioptric equivalent of ring diameter. Consequently, the use of a bite-bar arrangement is not necessary with this system; this feature offers considerable advancement in terms of subject fatigue reduction during lengthy experimental protocols. Rotation of the eye with respect to the optical axis of the instrument produced a measurement error of less than 0.25 D for eccentricities up to 10°. Maximum eccentric error was less than 0.50 D for the 0° to 25° range tested. Attempted measurements with a

pupil smaller that 2.9mm results in the obscuring of part of the measurement ring, and simultaneous edge detection at both sides of the measurement ring is not possible. Consequently, no measure of ring diameter is obtained.
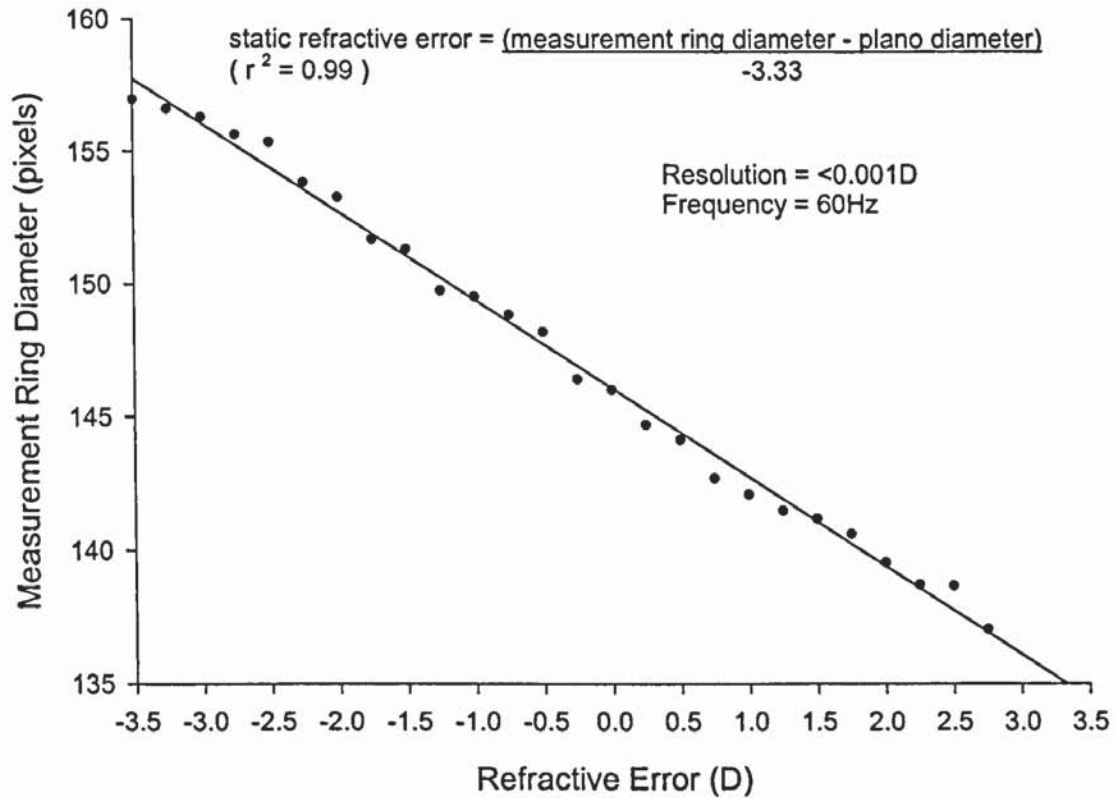
Figure 2.7. Measurement ring diameter against refractive error in a model eye.

Human eye. The apparatus was capable of recording the dynamic accommodative response to a moving target. Stimulus to accommodation varied simusoidally from 2.0 D to 3.7 D at a temporal frequency of 0.2 Hz. Accommodative gain, response phase shift and accommodative microfluctuations could clearly be demonstrated. Initial experimental trial results are illustrated in figure 2.8. Figure 2.9 shows variation in pupil size found while the human observer tracked the same dynamic accommodative target.

The high dioptric and temporal resolution of the continuous recording system allows the measurement of microfluctuations of accommodation. See supporting publication, Wolffsohn *et al.*, (2001) for a full account of this work.
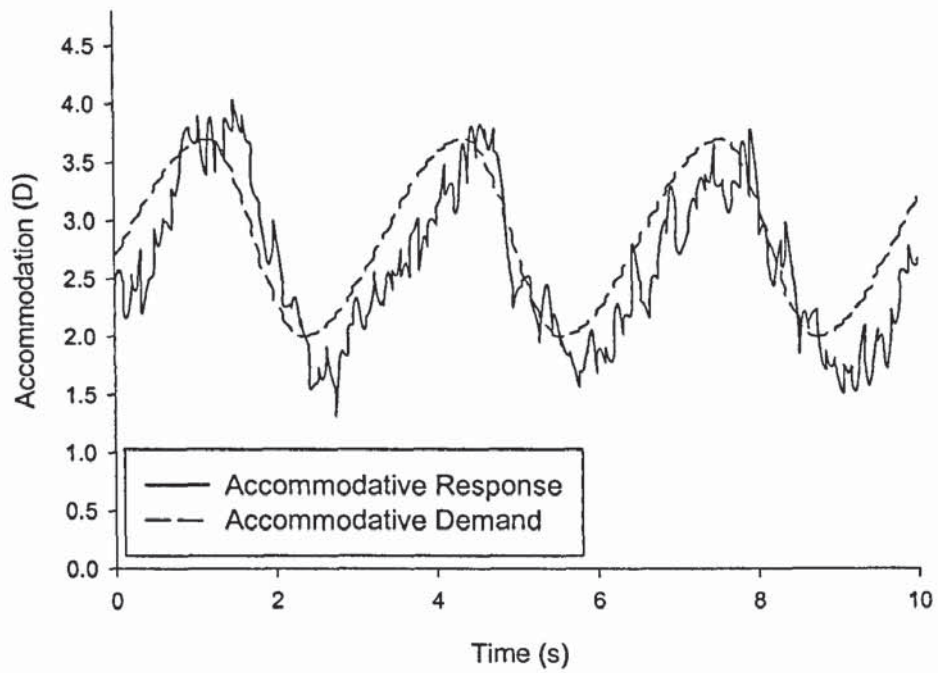
Figure 2.8. Continuous recording of dynamic accommodation response of a human eye.
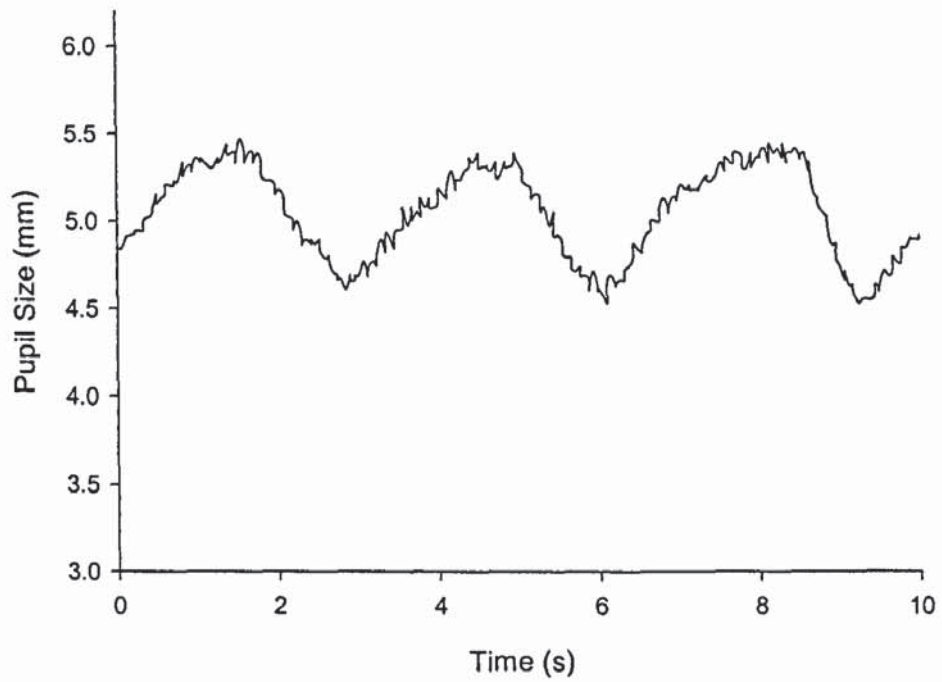
Figure 2.9. Continuous recording of pupil size during a dynamic accommodative task.

2.4 National Instruments *LabView* software and associated hardware

2.4.1 Software

LabView is a commercially available test, measurement and automation package. The system operates well within a Windows environment. Programming in *LabView* is carried out diagrammatically. Controls and indicators are programmed onto a 'control panel' window. Behind this window is the 'diagram' for the program. This contains all processing, conversion and storage components to the program in addition to inputs and outputs to control panel indicators and controls. The functions available within *LabView* are too numerous to discuss fully here, but a brief description of the continuous recording program is given below.

The NTSC (National Television Systems Committee) video output signal from the Shin-Nippon is acquired from the PCI 1408 (see below) and converted into a digital (binary) image. This image is filtered to remove elements in ascending order of size. Filtering is controlled from the control panel. To increase filtering the 'number of erosions' control is increased. Correct setting of the filter should leave only the measurement ring in the binary image. Brightness of the ring image can be adjusted in two ways: Firstly, by altering the black and white signal levels within the Measurement and Automation software controlling the PCI 1408. The aim being to produce a high contrast image of the ring with fairly well defined edges. This makes the edge detection threshold setting (see later) less critical. Secondly, by altering the 'intensity' control within *LabView*. This controls the overall intensity of the binary image. The image of the measurement ring is placed in a window. The coordinates of the ring can be plotted. Along the horizontal axis of the ring 2 points are identified and marked; the outer edge on the left hand side and the inner edge on the right hand side. The distance between the markers in pixels is recorded as ring diameter. Pixel diameter of the ring is converted into a dioptric value of accommodation response. For this method to be accurate, baseline values of residual refractive error and ring diameter at infinity must be included in the equation. These values are determined prior to recording, and inputted via the control panel. As it is possible to take static and dynamic measurements of refractive error or accommodation simultaneously, the calibration of the system can be checked at any time during experimental trials. The final stage of the program is storage of data. Accommodation response, time, ring dimension (in pixels), and signals from accommodative stimulus apparatus are saved to an *Excel* spreadsheet file.

2.4.2 Hardware

The National Instruments boards were installed in a PC equipped with an Intel Pentium 3 processor. The first device used was a PCI 1408 video input board. This device fits into a standard PCI slot in the motherboard of the PC. It allows capture and analysis of up to 4 composite video signals within *LabView*. If multiple input signals are to be used, a common time base (Genlock) for the signals in required. The primary function of this device was to capture the video signal from the Shin-Nippon SRW-5000 for continuous recording of accommodation.

The second piece of hardware was a PCI 6024E card and BNC 2090 16 channel analogue and digital input/output device. The device consists of a 1U 19" rack case with 16 assignable input and output channels connected to the PCI 6024E card via a multiway cable. Considerable flexibility is possible with this device. Channels can be configured as analogue inputs to monitor, store and analyse signals from a wide range of external transducers. Channels can be configured as outputs to control external devices. The main function of this device for the purpose of this project was to monitor the signal driving an X-Y plotter (section 2.8) during dynamic accommodation experiments. This facility allowed the real time monitoring of dynamic accommodation stimulus/response functions.

The expertise and technical advice given by Dr S. Tsujimura (Leverhulme Research Fellow) for continuous recording modifications is gratefully acknowledged.

2.5 Zeiss *IOLMaster*: Description and clinical evaluation
2.5.1 The Zeiss *IOLMaster*

The Zeiss *IOLMaster* is a new device primarily intended to aid ophthalmic surgeons in the calculation of intraocular lens implant power in cataract surgery. The device has utility in optometric research by virtue of its non-contact approach in the measurement of axial length, anterior chamber depth and central corneal curvature. The gold standard method of axial length measurement in research has been A-scan ultrasonography. This method requires contact between the cornea and the measurement probe, thus requiring the use of a topical corneal anaesthetic.

IOLMaster axial length measurements are based on the principle of partial coherence interferometry (PCI) (Haigis, *et al.*, 2000; Hitzenberger, C. 1991). The *IOLMaster*

measures axial length from the anterior corneal surface to the retinal pigment epithelium. A correction factor is used to take account of the distance between the retinal pigment epithelium and the internal limiting membrane. This ensures compatibility between optical and ultrasonic measurements of axial length.
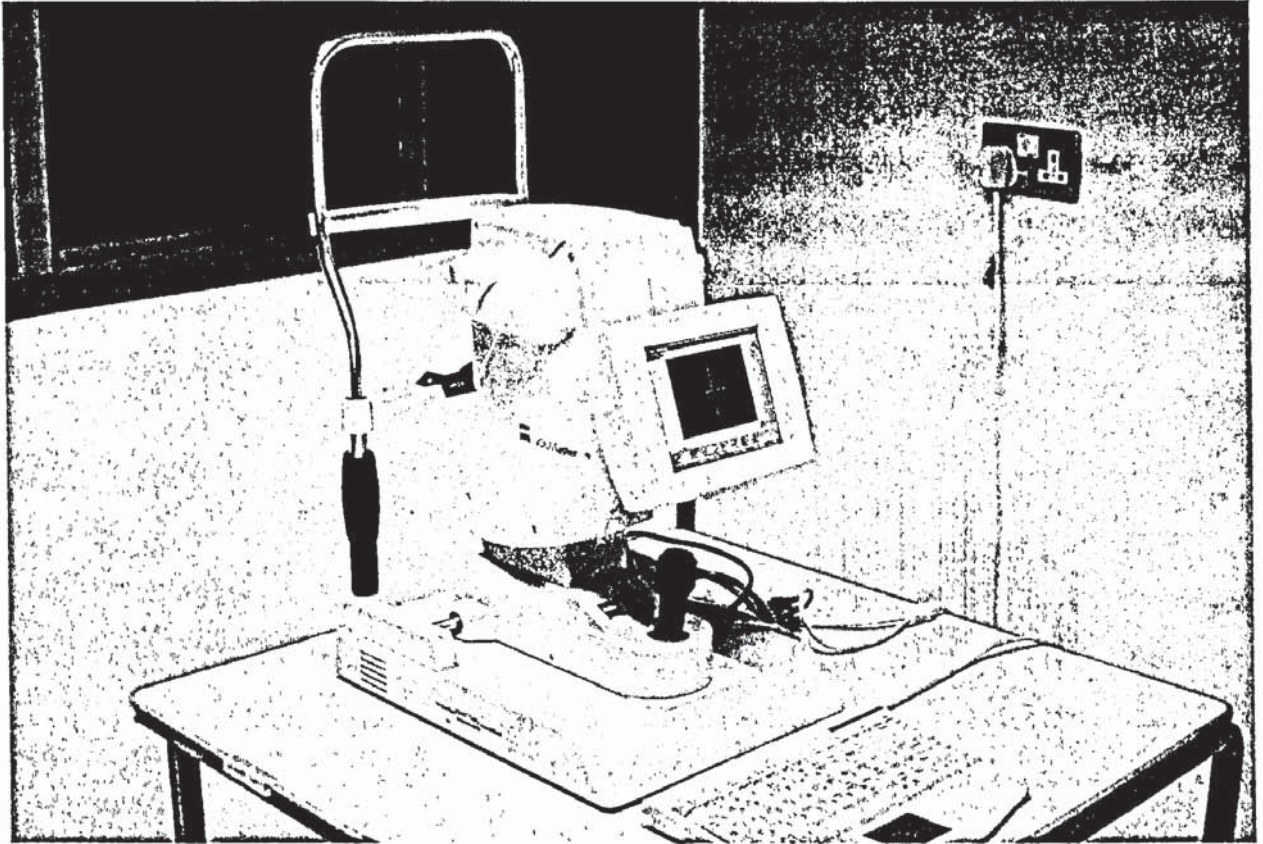
Figure 2.10. Zeiss *IOLMaster*.

Anterior chamber depth measurement is achieved by image analysis of a narrow slit beam of light directed obliquely into the anterior chamber. An optical section is formed through the anterior segment. The *IOLMaster* is aligned such that the posterior surface of the cornea and anterior surface of the crystalline lens are within the image analysis area. This area is identified by a green rectangle on the instrument screen. Measurement is initiated by pressing the joystick button. The *IOLMaster* takes an average of 5 individual measurements as the estimate of anterior chamber depth. Practical use of the instrument has shown that these measurements are best taken in dim room illumination to minimize stray light reflections within the anterior chamber and to increase image contrast.

Corneal curvature is measured by computer analysis of the Purkinje 1 images formed from 6 hexagonally arranged infra-red LEDs. The instrument produces a measure of corneal radius to 0.01 mm for the two principal meridians, with axis measurement to 1°. An

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estimate of magnitude and axis of corneal astigmatism is produced in minus cylinder form. Biometric data can be stored in hard copy format via a standard printer port, stored on 3.5" floppy disc, or stored in internal memory. It should be noted that data in the internal memory is deleted after 100 days, and there is sufficient storage space for only 20 subjects.

Additionally, the *IOLMaster* has facility to calculate the power of intra-ocular lens implant required to produce a given post-operative refraction in cataract patients.

2.5.2 Clinical evaluation of the Zeiss *IOLMaster*

This work was carried out in collaboration with Mr. J. Santodomingo-Rubido. A full account of this work in given in Santodomingo-Rubido *et al.*, (2002).

Methods

Corneal curvature, anterior chamber depth and axial length were measured in 52 subjects (104 eyes). These measurements were repeated during a second session to assess repeatability. Corneal curvature, anterior chamber depth and axial length were measured using *Eyesys* video keratoscope (EyeSys Technologies), Javal-Schiotz keratometer (Topcon, Japan), and A-scan ultrasonography (Stortz *Omega Compu-Scan Biometric Ruler*, Stortz International, St. Louis, USA) to assess validity. A-scan ultrasonography was carried out following the topical instillation of 0.5% proxymetacaine HCl (*Minims*®, Chauvin Pharmaceuticals) to induce corneal anaesthesia. Subjects were instructed to observe a Maltese cross target at a distance of 6 metres with the fellow eye to control fixation.

Results

Corneal curvature. Results were analysed by vector analysis to enable the assessment of both radius of curvature and axis orientation of principal corneal meridians. Validity of the *IOLMaster* results was assessed by comparison with Javal-Schiotz keratometer and *Eyesys* video keratoscope with regard to the mean keratometry reading, and J_0 and J_{45} vectors. *IOLMaster* measurements were closer in agreement with the Javal-Schiotz keratometer (mean difference −0.03 mm) than the *EyeSys* videokeratoscope (mean difference 0.06). Figure 2.11 shows a Bland-Altman (1986) plot for *IOLMaster* corneal curvature validity against keratometry and videokeratoscopy. Mean difference and 95% confidence for validity and repeatability are shown in tables 2.2 and 2.3 respectively.
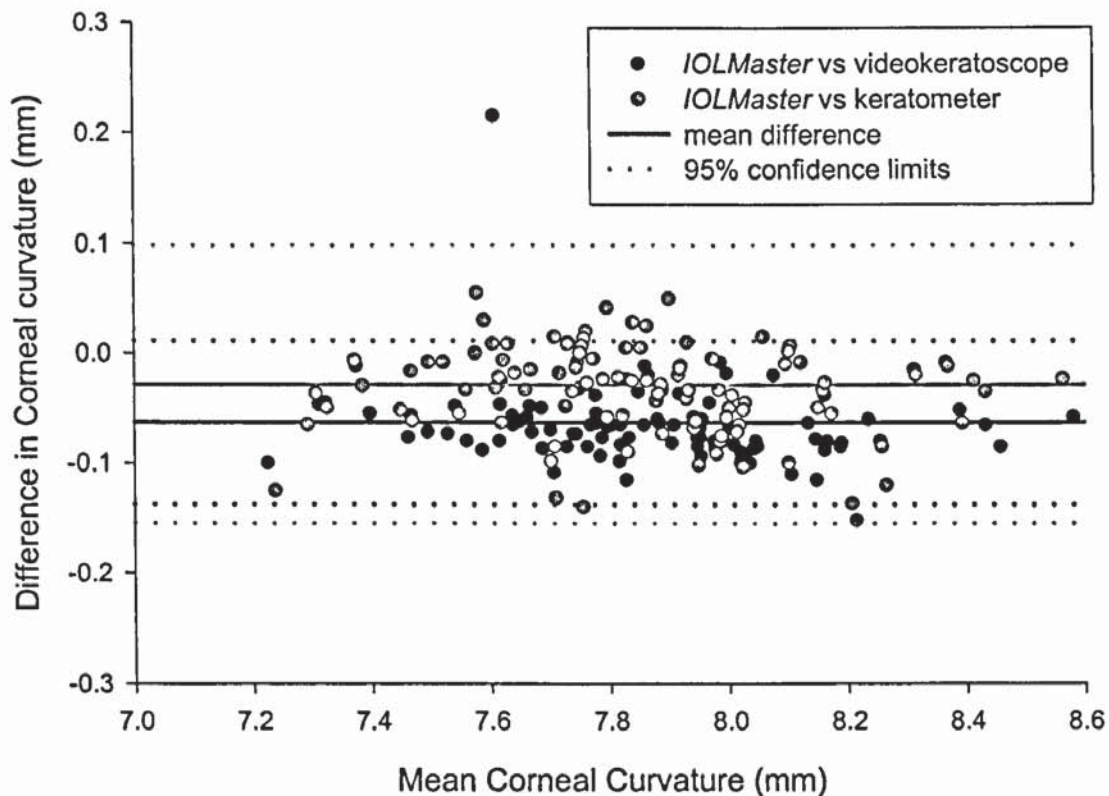
Figure 2.11. Validity of *IOLMaster* corneal curvature measurements.

Instrument	Function	Mean difference (mm)	95% confidence limits
Javal-Schiotz	Mean k	-0.03	0.13
	J_0	0.01	0.11
	J_{45}	0.00	0.06
EyeSys	Mean k	-0.06	0.07
	J_0	-0.01	0.08
	J_{45}	-0.03	0.06

Table 2.2. Validity of *IOLMaster* corneal curvature measurements

Function	Mean difference (mm)	95% confidence limits
Mean k	0.00	0.04
J_0	0.00	0.05
J_{45}	0.00	0.03

Table 2.3. Repeatability of *IOLMaster* corneal curvature measurements.

Anterior chamber depth. Results were analysed by a Bland-Altman (1986) plot. The difference between anterior chamber depth (ACD) measurements by *IOLMaster* and A-scan ultrasonography was plotted against the mean of the two measures (Figure 2.12). A-scan measurements of ACD were found to be significantly shorter than measurements made by *IOLMaster*. Mean difference in ACD was –0.06 mm (SD 0.25 mm) across the sample range of 2.85 to 4.40 mm. This finding was statistically significant at the 2% level.
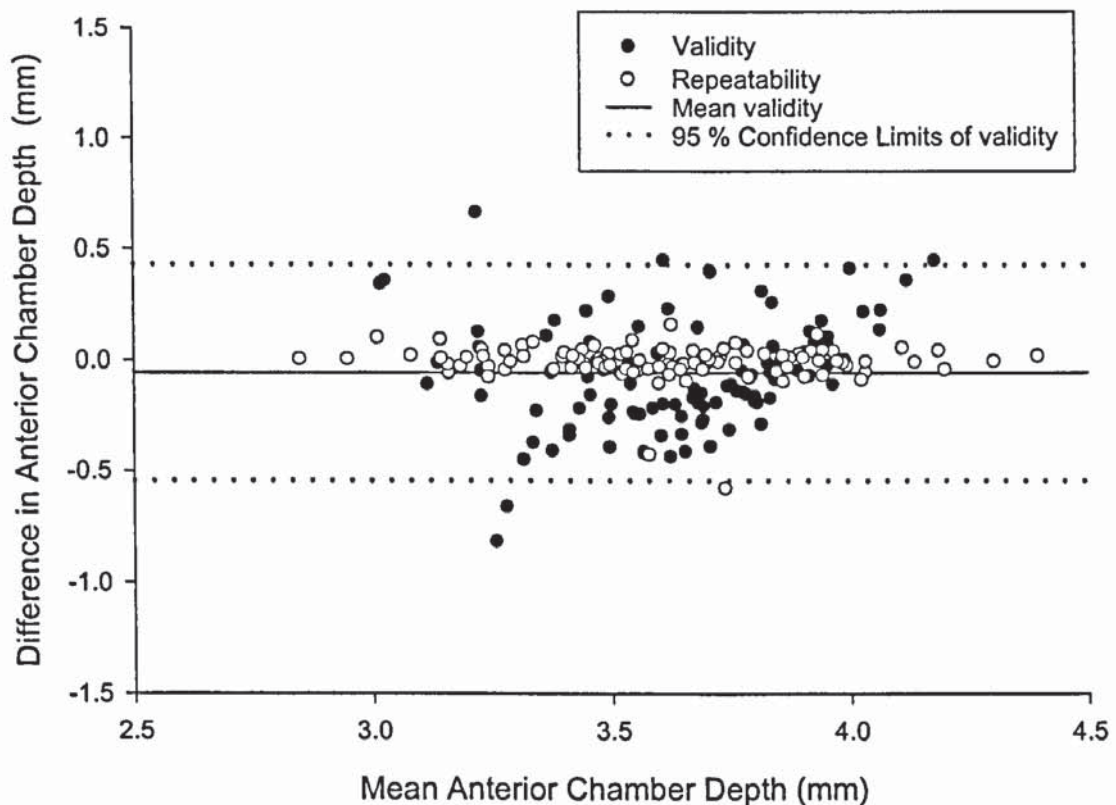
Figure 2.12. Validity and repeatability of anterior chamber depth as measured by *IOLMaster*.

Axial length. Results were analysed by Bland-Altman plot. Figure 2.13 shows the results for validity and repeatability. In terms of validity, a mean difference in axial length measurements of 0.02 mm (SD 0.32 mm) was found between *IOLMaster* and A-scan ultrasonography. This difference was not statistically significant ($p = 0.47$) and no bias across the measurement range (22.40-27.99 mm) was apparent. In terms of repeatability, mean difference between initial and subsequent measurements of axial length was 0.00 mm (SD 0.04 mm). Previous studies have shown the repeatability of A-scan

ultrasonography to be in the order of 0.1 to 0.15 mm (Butcher and O'Brien, 1991; Raj *et al.*, 1998), which demonstrates the significant advance that the *IOLMaster* brings to ocular biometric studies
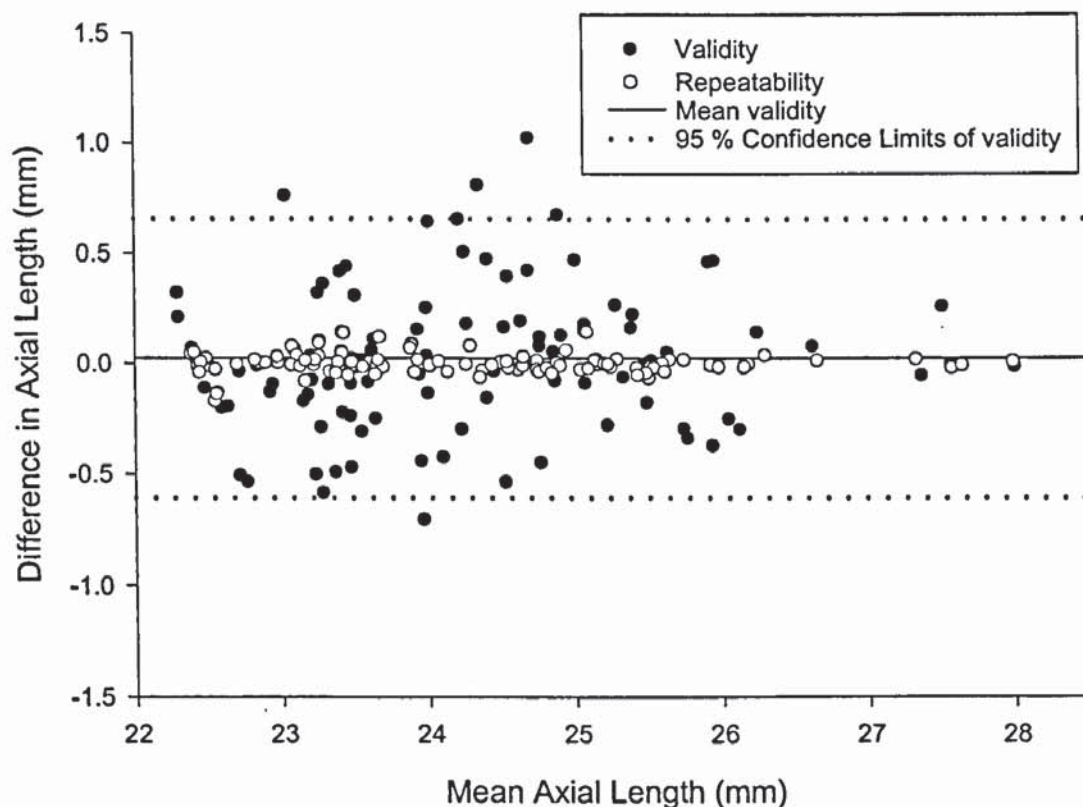
Figure 2.13. Validity and repeatability of axial length as measured by *IOLMaster*

The Zeiss *IOLMaster* is an ideal device for the rapid acquisition of highly accurate and repeatable ocular biometric data. The instrument is well suited to longitudinal and cross-sectional data collection in the study of myopia onset and progression (Bullimore *et al.*, 2002).

2.6 Modifications to enable measurement of peripheral retinal contour using the Zeiss *IOLMaster*

Previously, retinal contour has been calculated from A-scan ultrasonography and peripheral refraction measurements (Dunne, 1995; Logan *et al.*, 1995). The introduction of the *IOLMaster* has allowed the direct measurement of peripheral dimensions of the posterior segment in all meridians, thus allowing a complete evaluation of peripheral posterior retinal curvature. Appendix 3 details modifications to the *IOLMaster* to allow

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structured measurement of retinal contour. Initial data on the repeatability of the technique is included.

2.7 *EyeSys* Corneal Analysis System

The *EyeSys* device is primarily used in the assessment of corneal topography prior to refractive surgery procedures, or in cases of corneal pathology such as keratoconus. In the case of this study, the utility of the *EyeSys* device was for the measurement of horizontal visible iris diameter (HVID) and rate of peripheral corneal flattening (*p* value, Douthwaite *et al.*, 1999), and validation of the Zeiss *IOLMaster*. The system is based around an 8 ring Placido disc which is imaged by the anterior corneal surface (Henson, 1996). Analysis of the image of the Placido disc produces a topographic map of the cornea. Regular and irregular astigmatism can be shown, as well as simulated central keratometry readings. The system has been shown to produce valid results, and is therefore suitable for research purposes (Wilson *et al.*, 1992).

2.8 Lloyd Instruments P3 X-Y pen plotter

This device is designed to be used as a 2-axis analogue plotting device. A pen holder can be moved over an A3 paper bed through 2 axes (X and Y). The position of the pen holder along each of the axes is proportional to the voltage applied to the 2 control input channels. Each input channel has 3 selectable input voltage ranges (0-1 v, 0-10 v and 0-100 v), and a trimming amplifier to allow calibration (zero volts position) of the plotter to the controlling device.

2.9 Thandar TG501 function generator

The Thandar TG501 single channel function generator enables the production of sine, square and triangular waveforms over a wide range of frequencies. Electronic outputs at 50 ohm and TTL (transistor-transistor logic) standards are available simultaneously. Waveform frequency is controlled by a calibrated rotary dial linked to a series of frequency range switches. Frequency range is 0.005 Hz to 5 MHz. Analogue control of waveform amplitude, dc offset and waveform asymmetry are available on the front panel. The device can be set to run continuously, produce a single waveform cycle, or be triggered from an external gating signal.

2.10 X-Y Plotter controller/function generator interface

Purpose

This device had the following functions:

- To control x-y movements of the Lloyd PL3 X-Y plotter.
- To provide 3 sets of preset x-y positions for the x-y plotter.
- To connect an external signal (i.e. from a function generator) to the x-axis of the X-Y plotter, thus enabling the presentation of sinusoidal dynamic accommodative stimuli to a subject.

Figure 2.14 shows the circuit diagram designed for the X-Y plotter control system. Circuit design by E. Mallen.

Circuit diagram
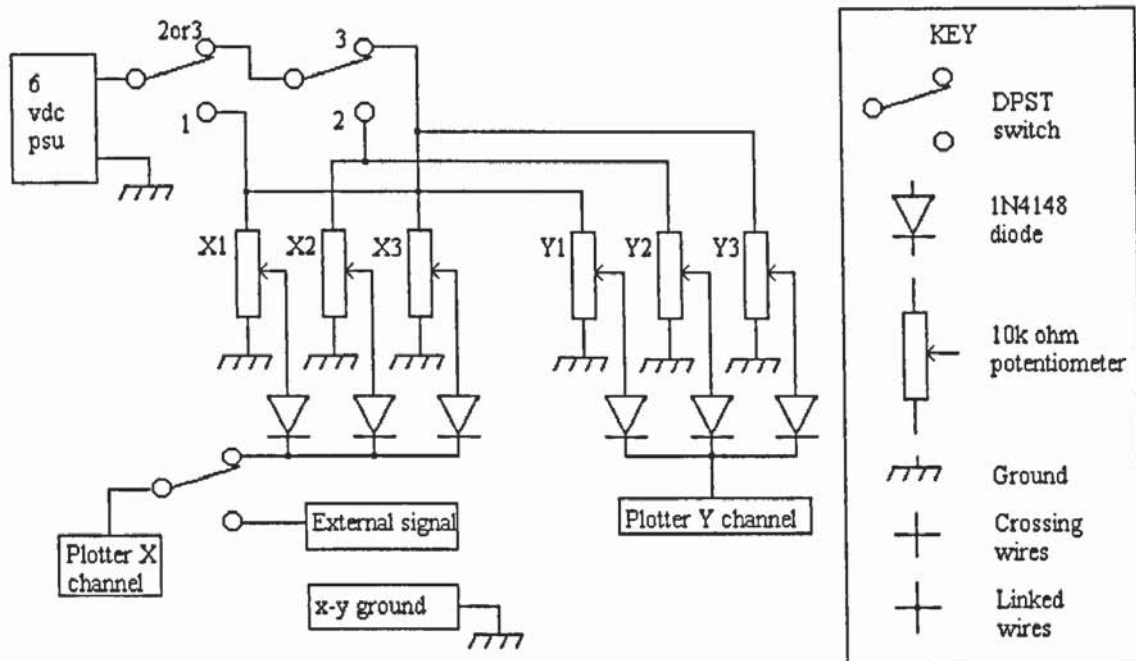
Figure 2.14. Circuit diagram of X-Y plotter controller/function generator interface.

Operation

The device contains 6 potentiometers, 3 assigned to the X channel and 3 assigned to the Y channel, arranged in three groups. Two double pole single throw (DPST) switches control the power supply to each group of potentiometers. The output terminal of each potentiometer is connected to the anode terminal of a 1N4148 silicon signal diode. The cathode diode terminal for the three potentiometers in a particular group are then

commoned. This feature means that only the output from the potentiometer set to the highest voltage will be sent to the x-y plotter channel (highest takes precedence). A third switch allows the user to switch between potentiometer output and external signal input with respect to the x channel on the X-Y plotter. Thus, a function generator signal can be used to drive the x plotter channel. Connection to this facility was achieved via a BNC connector.

The power supply unit used for this device was a Uniross 1200R regulated supply, connected to the unit via a 2.5 mm d.c. power connector. The output of the power supply was set to 6 v.d.c.

The device was designed and constructed by the author. Electronic components and hardware were supplied by CPC Ltd, Preston, Lancashire, UK.

2.11 Clinical evaluation of the Shin-Nippon NVision-K 5001 autorefractor

The Shin-Nippon NVision-K 5001 is a new instrument combining infra-red autorefraction and autokeratometry in a single device. A clinical evaluation of this instrument was carried out in collaboration with Mr. L. Davies to assess validity and repeatability of refraction and keratometric measurements. Autorefraction and autokeratometry was carried out on 99 healthy volunteers; these results were compared with subjective refraction and Javal-Schiotz keratometry results to assess validity. Repeatability was assessed by comparison of initial autorefraction and autokeratometry readings with subsequent measurements 7-14 days later.

Mean spherical equivalent (MSE) autorefractor results showed slight hypermetropic bias compared to subjective refraction ($+0.14 \pm 0.35$ D); mixed factor ANOVA revealed no significant difference between the two refraction techniques ($p = 0.67$). Mean intersession repeatability of autorefraction was 0.11 D (MSE). Autokeratometry readings compared well with manual keratometer results. Mean difference in corneal curvature readings was 0.02 ± 0.09 mm for the horizontal meridian ($p = 0.56$), and 0.01 ± 0.14 mm for the vertical meridian ($p = 0.88$). No significant difference was found in autokeratometric measurements between sessions.

The Shin-Nippon NVision-K 5001 produced valid and repeatable refraction and keratometric measurements. Conversion of the instrument to enable continuous recording of accommodation is under investigation (see supporting publications).

CHAPTER 3

AUTONOMIC PROFILE AND MYOPIA IN YOUNG ADULTS

3.1 Introduction

A clinical feature of the onset and progression of myopia has been accommodative inaccuracy during near vision (Gwiazda *et al.*, 1993). Progressing myopes have been shown to exhibit small but significant lags of accommodation when carrying out near tasks (McBrien and Millodot, 1986b; Rosenfield and Gilmartin, 1988; Abbott *et al.*, 1998). It remains unclear whether this accommodative inaccuracy is a precursor to myopic progression, or a result of myopic progression. Portello and co-workers (Portello *et al.*, 1997) have shown higher lag of accommodation in subjects who later become myopic, while Goss (1991) has shown an increase in accommodative lag prior to the onset of myopia. It has been proposed that deficiency in the sympathetic inhibitory branch of accommodative control leads to post-task accommodative hysteresis (Gilmartin, 1998). Accommodative hysteresis induces myopic retinal blur, which, over time could act as a stimulus for axial elongation in young adult subjects exposed to intense near work (Flitcroft, 1998).

Considerable work is currently being undertaken to investigate the efficacy of myopia control procedures in children (Walline *et al.*, 2001; Hyman *et al.*, 2001; Ong *et al.*, 1999). It may be possible to control the rate of myopic progression in young adult subjects, or even eliminate the onset of myopia completely. In order for this to be achieved it is vital to identify reliable predictive factors to highlight susceptible individuals. Biometric studies of late onset myopes have found axial elongation to be the principal structural correlate (Wildsoet, 1998). This structural change takes place outside the normal age range for ocular growth (Goss and Winkler, 1983). It may be the case in humans that structural reformation is preceded by changes within the sclera to increase plasticity and thus aid tissue redistribution, as found in the tree shrew (Guggenheim and McBrien, 1996). Ideally, individuals at risk of late onset myopia could embark upon myopia prevention procedures prior to the onset of pre-clinical structural change. Such a strategy may improve the efficacy of treatment strategies, and consequently minimize myopic progression. The considerable evidence for environmental factors, such as intense near-work, in the development of late onset myopia highlights the need for a reliable screening programme to identify those at risk.

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The possible role of sympathetic inhibitory control of ciliary smooth muscle as a myopigenic factor has been reviewed by Gilmartin (1998). It has been postulated that a deficiency in this system may lead to increased post-task accommodative hysteresis, and consequently retinal blur. Over time, this retinal blur may exceed the critical level required to initiate structural changes in the globe, manifesting as elongation of the vitreous chamber and permanent myopia. Experimental work to date investigating sympathetic innervation of ciliary muscle *in vivo* has chiefly been carried out on small numbers of subjects, thus limiting the power of statistical analyses.

Post-task open-loop accommodative regression patterns were measured in dark-room conditions by Strang (1995). The technique used was shown to be repeatable across a range of refractive errors. Further work by Strang (1995) measured regression patterns in young (age 17-19 years) emmetropic subjects, coupled with longitudinal refractive and biometric follow-up measurements over a 2-year period. To measure post-task accommodative regression patterns, subjects were instructed to observe a high contrast Maltese cross target located at such a distance to provide an accommodative stimulus 3 D above the baseline tonic level. Task duration was 3 minutes. Dark-room conditions were then imposed. Post-task regression of accommodation was measured by Canon R-1 optometer in static mode for up to 90 seconds. Complete data was obtained on 19 subjects; 13 subjects were defined as having rapid post-task regression, and 6 subjects possessed slow regression patterns. Time course of post-task regression to the baseline tonic level for the 'rapid regression' group was within 20 seconds of open-loop conditions being imposed. A significant myopic shift (> -0.50 D) was observed in one subject out of the total cohort. This subject exhibited a slow post-task regression pattern. No significant myopic shift was observed in the remaining subjects.

Gilmartin and Winfield (1995) examined post-task regression properties under beta-blockade to establish the presence or absence of a sympathetic inhibitory branch of accommodation control. It was found that there was no significant difference in the profile of accommodation response under beta-adrenoceptor antagonism between emmetropes, early onset myopes and late onset myopes. The study concluded that a deficiency in sympathetic inhibition of accommodation was not a factor in late onset myopia. The small sample sizes used in this study (emmetropes N = 6, early onset myopes N = 5, late onset

myopes N=5) and the inter-subject variability of accommodation regression profiles under beta-adrenoceptor antagonism (Gilmartin *et al*, 2002b) means that this finding needs further investigation. A larger study of autonomic profile of accommodation control, combined with a regulated study of refractive change is required to address this question.

In relation to previous studies, the specific areas of interest in this chapter are:

- To monitor change in refractive error in a large sample of subjects over a 2.5 year period. Identification of subjects commencing myopic progression (i.e. late onset myopes) during the course of the study is of particular interest. The subjects in the study were selected on the grounds of their exposure to considerable amounts of near work.

- To profile each subject with regard to autonomic innervation of ciliary muscle, using more robust experimental protocols than have been used previously.

- To analyse refractive and autonomic data in order to investigate possible links between autonomic control of accommodation and late onset myopia, in particular the proposed association between sympathetic deficiency and late onset myopia.

- Conduct a cross-sectional study of the distribution of ciliary muscle control in a large sample of young adult subjects. This will be achieved by recruitment of additional subjects and combining the autonomic profile data from these subjects with the longitudinal study cohort. It will then be possible to correlate between sympathetic inhibitory facility in ciliary smooth muscle and refractive error in the largest group of subjects to date.

- To establish the prevalence of parental history of myopia for each subject, and cross-correlate between myopia onset and sympathetic facility.

3.2 Subjects

All subjects were undergraduate optometry students of Aston University. Initial refractive error screening was carried out on 96 students during the first week of the undergraduate autumn term (1999). At this stage subjects were given outline information on the nature and purpose of the study, together with exclusion criteria. Based on the findings of this initial work, 60 subjects were selected for participation in the autonomic profiling section study. Subjects not taking part in the autonomic profiling study were allowed to remain in the refractive error monitoring phase of the study. Table 3.1 summarizes the age, gender

and refractive distribution of the subject group that completed the 2.5-year longitudinal study of refractive error. Subject demographics represent data taken at the outset of the longitudinal study (October 1999).

Refractive group	Average mean sphere (D)	Mean age (years)	Age range	N	Gender (male:female)
Emmetropes (EMM)	+0.19 ± 0.34	18.8 ± 0.9	18 – 21	31	16:15
Early-onset myopes (EOM)	-3.13 ± 1.58	20.9 ± 2.1	19 – 24	8	5:3
Late-onset myopes (LOM)	-0.63	18	-	1	1:0

Table 3.1. Subject demographics. Longitudinal refractive error monitoring study.

All subjects were normally, healthy volunteers recruited under procedures approved by the Declaration of Helsinki and the Aston University Human Sciences Ethical Committee. Subjects were free of abnormal ocular conditions, and had visual acuity correctable to at least 6/6. Copies of information sheets and consent forms supplied to subjects, plus a full list of exclusion criteria can be found in Appendices 6 and 7. Informed consent was obtained from all subjects prior to the commencement of experimental work.

A further 20 young adult subjects were recruited from the undergraduate student population at Aston University, giving a total cohort of 60 subjects for the cross-sectional study of autonomic profile. Informed consent was obtained from these additional subjects. Refractive error, age and gender distributions for the subject cohort for the entire cross-sectional cohort are shown in table 3.2. Criteria for refractive groupings were as follows: emmetropes (EMM) mean refractive error between −0.49 and +1.00 D, and less than −0.50 DC; early-onset myopes (EOM) spherical refractive error of at least −0.50 D, with onset of myopia prior to 15 years of age (Goss and Winkler, 1983); late onset myopes (LOM) spherical refractive error of at least −0.50 D, with onset of myopia after 15 years of age.

Refractive group	Average mean sphere (D)	Mean age (years)	Age range	N	Gender (M:F)
Emmetropes (EMM)	+0.22 ± 0.31	22.1 ± 3.6	19-35	30	18 : 13
Early-onset myopes (EOM)	-3.53 ± 1.42	23.7 ± 3.7	18-31	14	6 : 7
Late-onset myopes (LOM)	-1.12 ± 1.02	21.4 ± 1.5	19-24	14	6 : 8
Hypermetropes (HYP)	+2.69 ± 2.21	19.5 ± 0.7	19-20	2	0 : 2

Table 3.2. Subject demographics – cross-sectional study of ANS profile.

3.3 Methods

3.3.1 Refractive error monitoring

Refraction data were collected on both eyes of all subjects at approximately 7-month intervals, thus providing 5 refraction data points over the 2.5-year study period. At each data point the refractive error was measured using a Shin-Nippon SRW-5000 infrared open view autorefractor. The subject was instructed to view an accommodative target (high contrast Snellen letters) at a distance of 6 metres while 6 autorefractor readings were taken on each eye. Luminance of the Snellen letter target was 50 cd/m^2. If unaided vision was less than 6/60, the subject observed a large (A4 size) high contrast Maltese cross target placed over the Snellen chart. Mean spherical error (MSE) was calculated for individual readings (MSE = sphere + cylinder/2). The numeric mean of the six individual MSE readings was calculated.

3.3.2 Autonomic profiling

Baseline measurements of refractive error and tonic accommodation were made on the right eye of each subject. Refractive error was measured with the subject fixating a high contrast Maltese cross at a distance of 6 metres, via a folded optical arrangement. Six readings of static distance refractive error were taken. Baseline tonic accommodation was measured using the Shin-Nippon SRW-5000 in static mode. The subject sat in total darkness for 5 minutes prior to measurement to dissipate the effects of previous near-vision activities (Krumholz et al., 1986). Six readings of dark focus were taken over a period of approximately one minute. Tonic accommodation was calculated by subtracting the

distance static refractive error (expressed as mean sphere) from the mean dark focus measurement.

In keeping with previous studies (Gilmartin and Winfield, 1995) the beta-adrenoceptor agents timolol maleate 0.5% and betaxolol hydrochloride 0.5% were used in the profiling of the autonomic control of ciliary muscle. Timolol maleate is primarily used as an ocular hypotensive agent in the treatment of primary open angle glaucoma by reducing the secretion of aqueous humour. Timolol has a competitive affinity for both β_1 and β_2 subclasses of adrenoceptors (Liu, 1980). Of interest in accommodation studies is the antagonistic effect of timolol to the β_2 subclass of adrenoceptors in ciliary smooth muscle (Zetterstrom and Hahnenberger, 1988), to block the sympathetic inhibitory branch of accommodation control in susceptible subjects (Gilmartin, 1986). Betaxolol hydrochloride is a selective β-adrenoceptor antagonist, having affinity for only the β_1 subclass of receptor. Betaxolol hydrochloride is a useful control agent for timolol maleate due to the similar hypotensive effects of these substances (Gilmartin and Winfield, 1995).

The Shin-Nippon SRW-5000 autorefractor was used in continuous recording mode (see Chapter 2 for a full description of this system) to measure post-task regression of accommodation under open loop conditions following closed loop tasks. These tasks varied in terms of dioptric stimulus to accommodation and duration. Table 3.3 represents the task parameters for each trial.

Trial	Accommodative stimulus (D)	Task duration (s)	Duration of post-task monitoring (s)
Distance short (ds)	0	10	60
Distance long (dl)	0	180	60
Near short (ns)	3	10	60
Near long (nl)	3	180	60

Table 3.3. Experimental trials – ANS profiling.

The task involved viewing a high contrast Maltese cross target through a +5DS Badal optometer system. Luminance of the Maltese cross target was 15 cd/m^2. The Maltese cross was mounted on the carriage of an X-Y plotter to facilitate movement of the target along the visual axis (thus varying dioptric stimulus to accommodation).

The post-task open loop phase of the trial was achieved by removing the Maltese cross and instructing the subject to view a photographically reproduced Difference of Gaussian (DoG) target. The subject was instructed to observe the DoG target, rather than attempting to make the target clear to avoid artificially elevated accommodative responses under open-loop conditions (Stark and Atchison, 1994). Spatial frequency of the DoG was 0.2 cycles per degree (Kotulak and Schor, 1987). The DoG was placed at the −1D position within the Badal system. This position was selected to induce an amount of myopic blur on the DoG target to fog the appearance of the fine grain on the photographic paper. Additionally, this positioning placed the DoG further away from the local light source, which reduced luminance of the target to 6 cd/m^2. Figure 3.1 shows the layout of apparatus for this experiment.
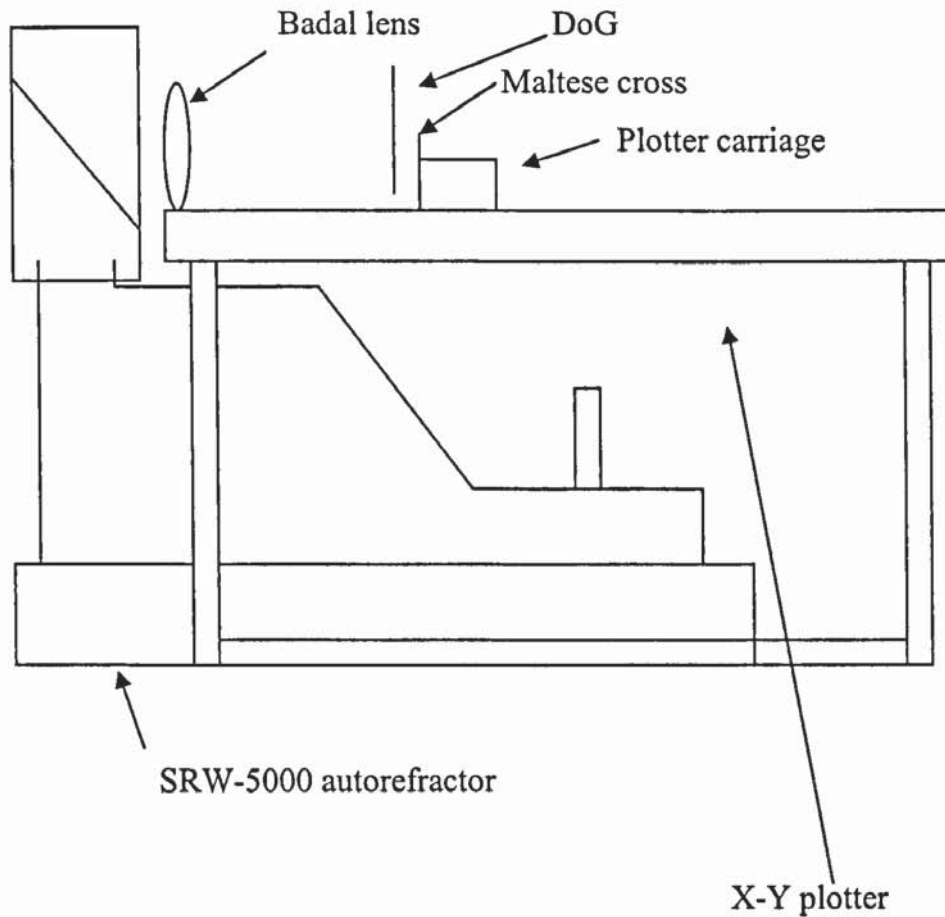
Figure 3.1. Layout of apparatus for measurement of autonomic profile of accommodation.
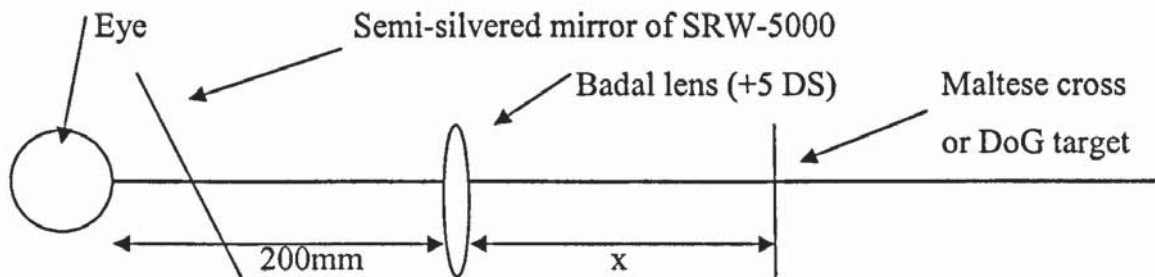
Figure 3.2. Arrangement of optical components for measurement of autonomic profile of accommodation.

Figure 3.2 shows the optical components for this experiment. The distance x in the Badal system was varied to produce the required accommodative stimulus. The DoG target was mounted on the pen carriage of the X-Y plotter; thus, the Y channel of the X-Y plotter was used to move the DoG target onto the visual axis at the appropriate time (i.e. when opening the loop).

The Shin-Nippon autorefractor measured accommodation at a frequency of 42 Hz throughout the closed and open loop phases of each trial. The response of only one eye was

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measured. The other eye was occluded using a patch. The refractive error of the eye under test was corrected using a standard, 58% water content daily disposable spherical soft contact lens (*1 day Acuvue, Johnson and Johnson*).

The measurements of post-task open-loop accommodative regression were carried out under three separate conditions of pharmacological intervention: one drop of 0.9% saline (*Minims*®, Chauvin Pharmaceuticals, Romford, Essex), one drop of 0.5% timolol maleate (non-selective β antagonist), or two drops of 0.5% betaxolol hydrochloride (β_1 antagonist; Alcon Pharmaceuticals, UK). Two drops betaxolol were used due to the lower ocular hyoptensive effectivity of this agent compared to timolol (Stewart *et al.*, 1986), thus equivalent hyoptensive effects were achieved. The order of these conditions were randomised between subjects. Intraocular pressure (IOP) was measured using a Keeler *Pulsair 3000* non-contact tonometer prior to the instillation of any drug. The topical anaesthetic proxymetacaine hydrochloride 0.5% was instilled prior to drug administration to aid the passage of the drug through the cornea and to inhibit reflex blinking. A period of 30 minutes following instillation was taken to enable intraocular absorption of the drug. Intraocular pressure measurement was repeated; the apparent hypotensive effect indicating intraocular absorption of the drug. A reduction in IOP of 3 to 5 mmHg was expected, indicating that the intraocular absorption was successful and had taken effect at the level of ciliary smooth muscle (see Appendix 5). Between trials the subject was allowed to rest for 5 minutes to avoid fatigue and to allow the dissipation of adaptive accommodative effects. A washout period of at least 3 days was allowed to elapse between pharmacological treatments to prevent contamination of a trial due to the sustained action of a previously administered agent.

Continuous accommodation measurements were saved to a *Microsoft Excel* spreadsheet. The filename for the spreadsheet was a unique numeric code to enable identification of the subject and trial parameters at a later date. The subject identity, accommodative task, task duration and pharmacological treatment conditions were held in a key file against the appropriate file number. This procedure was followed to prevent examiner bias in the interpretation of regression plots, thus making the experimental protocol double blind.

3.4 Results

3.4.1 Refractive error monitoring

Refractive change was measured by calculating the change in mean refractive error (MRE; defined as sphere + cylinder/2) between data point 1 (October 1999) and data point 5 (April 2002). A myopic shift of −0.50 D in MRE or greater was deemed a significant change. Complete refractive error data for the 2.5-year period were obtained on 84 subjects. Thirty-seven subjects were emmetropic at the start of the study (emmetropia defined as MRE between +1.00 and −0.50 D, and no astigmatic error greater than −0.50 DC). At the end of the study 12 of the 37 emmetropes exhibited myopic change of −0.50 D or more, indicating the late onset of myopia during the 2.5-year period. Mean myopic shift in this subset of subjects was −0.72 ± 0.20 D. With respect to the whole subject cohort, a clinically significant myopic change (-0.50 DS or greater) was observed in 27 out of 84 subjects. A summary table of longitudinal refractive error monitoring data is shown in Appendix 8.

One subject was omitted from data analysis due to the onset of keratoconus during the course of the longitudinal study.

3.4.2 Autonomic profiling

Complete autonomic profiles of ciliary muscle innervation were obtained on 40 subjects taking part in the concurrent longitudinal study of refractive error development, and on the additional 20 subjects, forming a bank of autonomic profile data on 60 young adult subjects. Group mean tonic accommodation (±SD) measured in darkness was 0.51 ± 0.50D.

Post-task accommodative regression recordings were saved into a separate spreadsheet for each trial. The recording of the accommodation response was filtered to remove blinks. A combined spreadsheet was formed to contain accommodation regression plots from all 12 trials for each subject. Figure 3.3 shows a combined accommodative response plot for a subject (CB − early onset myope) exhibiting delayed open-loop post-task regression of accommodation following the 3-minute, 3-dioptre task under timolol conditions (10 second 0 D and 3 D plots are omitted for clarity). The plot shows pure accommodative traces, filtered for blinks.
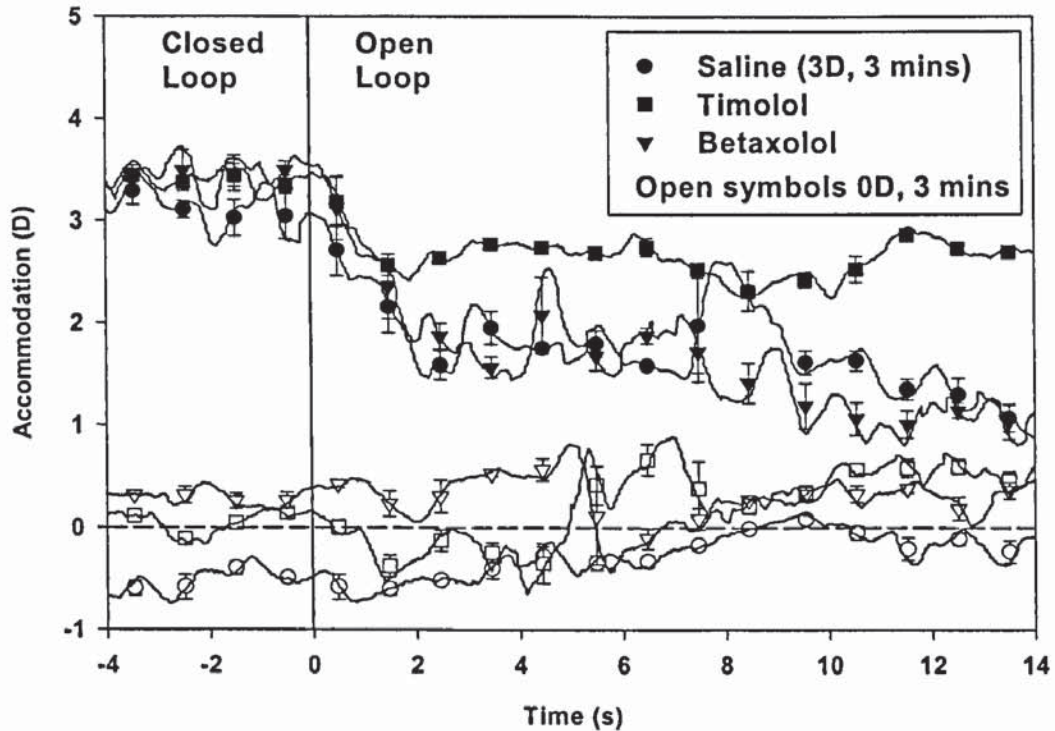
Figure 3.3. Accommodation regression profiles for 0 D and 3 D 3-minute tasks under timolol, betaxolol and saline conditions (CB).

An important consideration for statistical analysis was the effect of differential accommodative adaptation between 0 D (far) and 3 D (near) trials. To counter this effect, and to incorporate the 0 D control trials into the statistical tests, the post-task data points for the far trials were subtracted from post-task near trial values. The post-task regression of accommodation was expressed as a percentage regression with respect to the mean closed-loop accommodative response from the final 6 seconds of the task (i.e. before going open-loop). Figure 3.4 shows the percentage regression quotient plots for subject CB for 10 second and 3-minute trials under timolol. Symbols depict 1 second averaged data points, consisting of 42 continuous recording values. Error bars represent 1 standard deviation for each averaged data point. The graph clearly shows delay in post-task decay of the accommodative response under open-loop conditions following the 3-minute timolol trials. This effect is not apparent following 10-second timolol trials, indicating the slow onset of sympathetic inhibitory effects. Figure 3.5 compares 3-minute timolol and betaxolol regression profiles. Under betaxolol conditions, post-task regression of accommodation is more rapid compared to timolol conditions.

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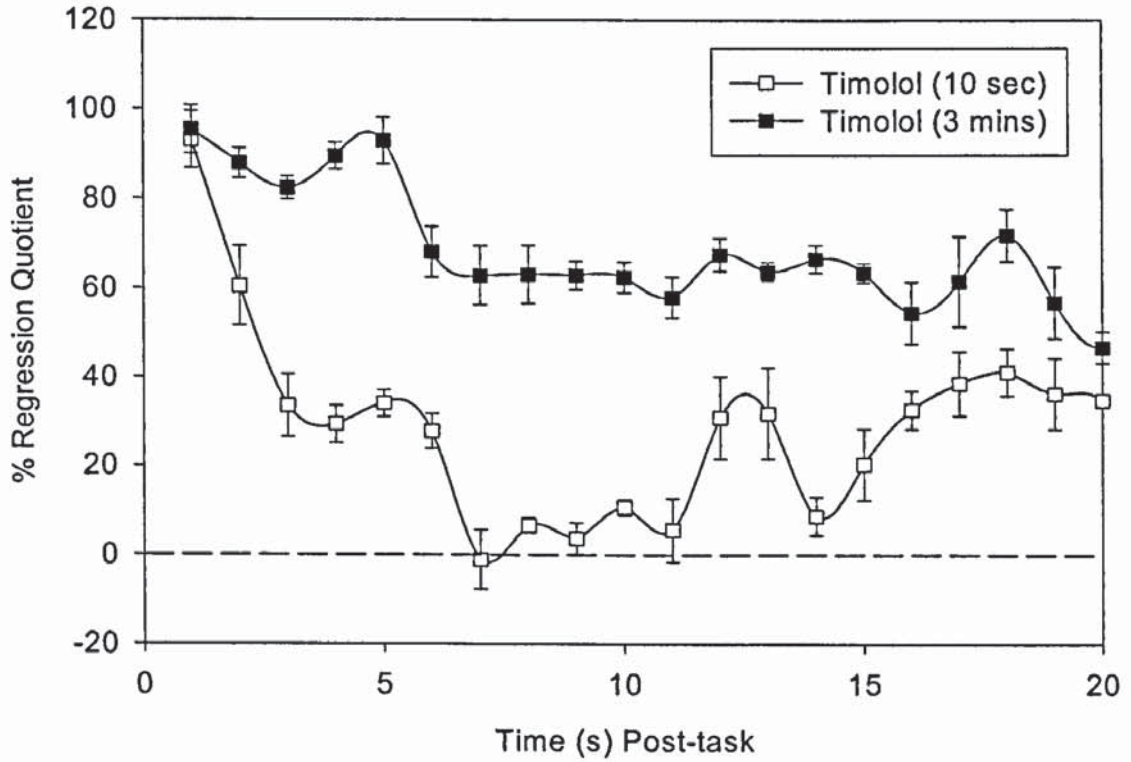
Figure 3.4. Regression quotient (%) plots for 10 second and 3-minute timolol trials (CB).
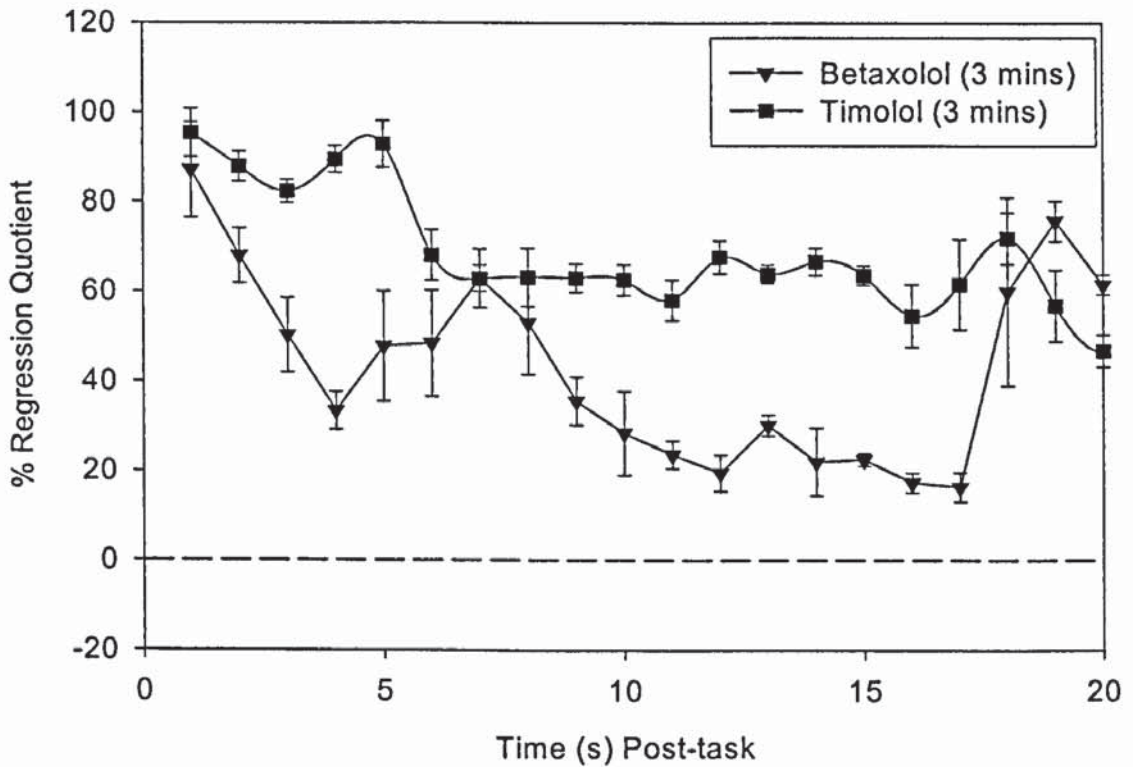
Figure 3.5. Regression quotient (%) plots for 3-minute trials, timolol vs betaxolol (CB).

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Figures 3.3 to 3.5 show an accommodative regression response to the non-selective β antagonist timolol maleate; from this it is deduced that this subject (CB) possesses a sympathetic inhibitory branch of accommodation control (Gilmartin and Winfield, 1995). Figure 3.6 compares the post-task regression profiles for 10 second and 3-minute trials under betaxolol conditions. The regression profiles for the 10 second and 3-minute trial match closely under betaxolol conditions, indicating that task duration has no significant effect on the post-task open-loop response with selective (β_1) blockade.
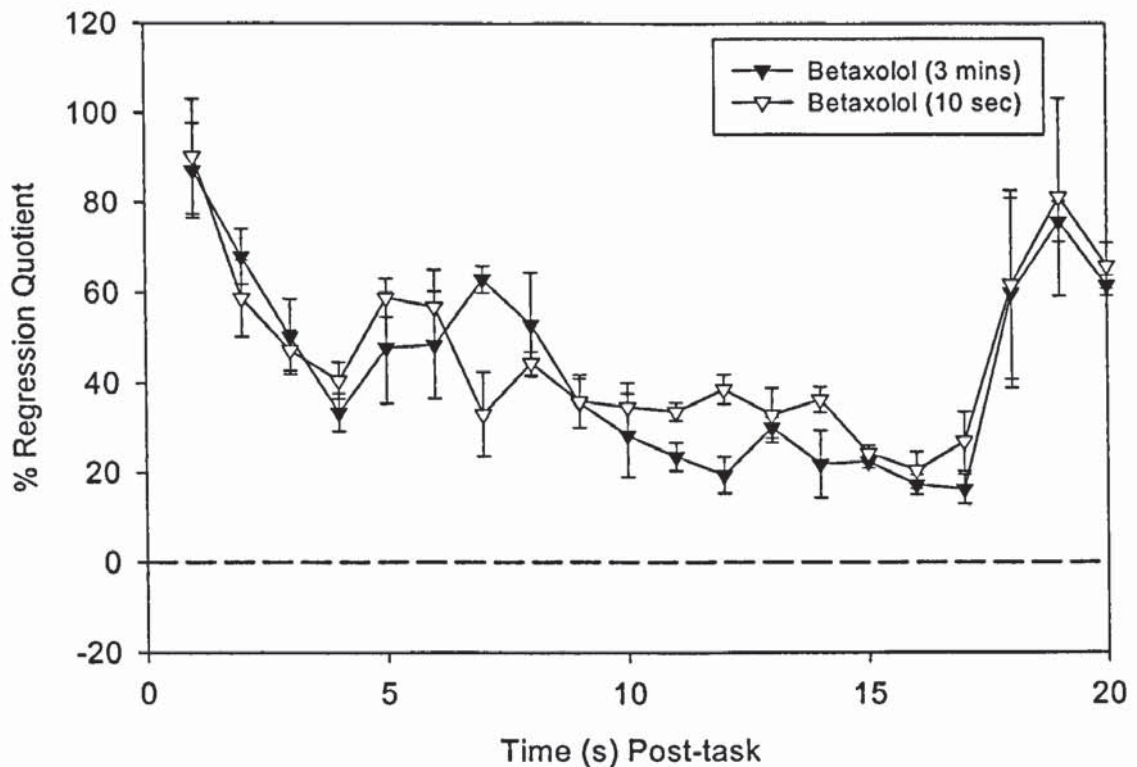
Figure 3.6. Regression quotient (%) plots for 10 second and 3-minute betaxolol trials (CB).

Sample data are shown from subject RU (an emmetrope) in figures 3.7 to 3.9. Figure 3.7 shows percentage regression profiles for 10 second and 3 minute timolol trials. In contrast to subject CB, both the 10 second and 3 minute timolol trials show similar regression rates under open-loop conditions, indicating that β blockade had little effect on post-task accommodative regression (compare with figure 3.4 for subject CB).
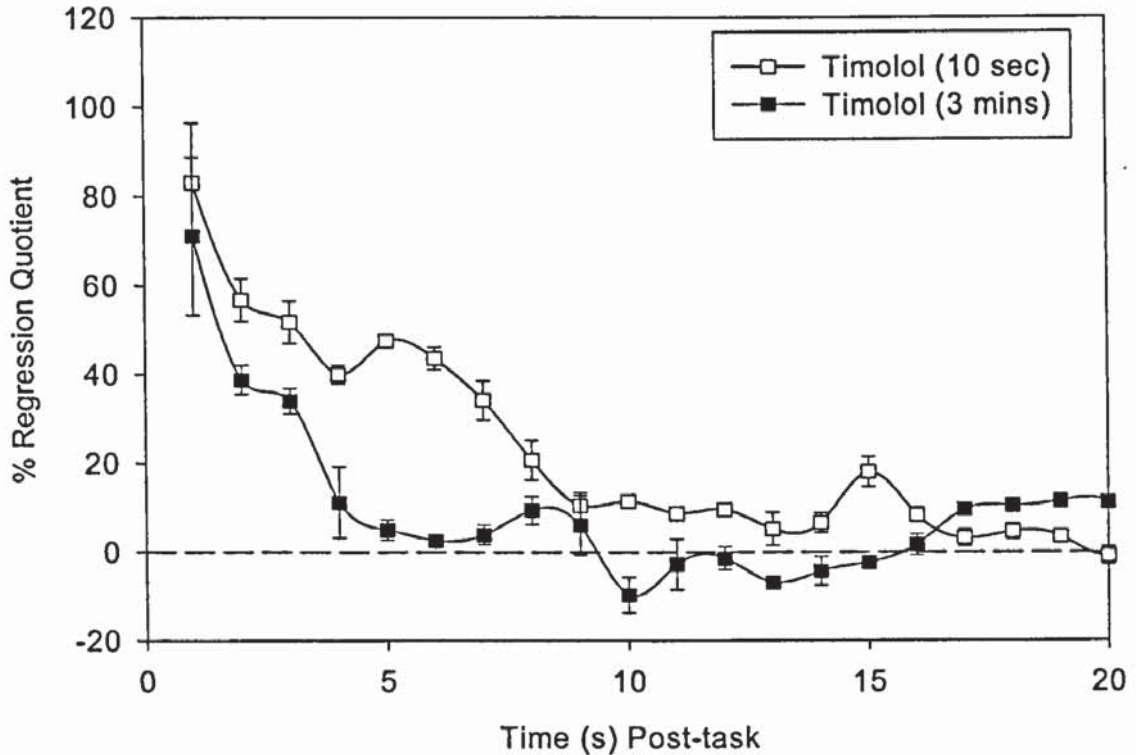
Figure 3.7. Regression quotient (%) plots for 10 second and 3-minute timolol trials (RU).

Timolol and betaxolol 3-minute trials are compared in figure 3.8. Once again, contrary to the findings in subject CB, no timolol effect is observed. From these effects it can be deduced that subject RU has deficiency in, or limited sympathetic inhibitory facility in ciliary smooth muscle control. Figure 3.9 shows 10 second and 3-minute betaxolol trials. In this figure, similar characteristics to those found for subject CB (Figure 3.6) are seen, i.e. similar regression rates both with and without sustained parasympathetic activity under selective β_1 antagonism.

The 6 groups of regression data (i.e. saline short task and long task, timolol short task and long task, and betaxolol short task and long task) were subjected to a 2 factor repeated measures ANOVA (*Statview* 5.0, SAS Corporation) to determine the significance of task effects, drug effects, and task:drug interaction effects. Regression data for 15 seconds following the closed-loop task were included in the analysis. A Scheffe's *post-hoc* test was used to identify the significant drug/task duration factor for each subject. A significant main and interaction effect of timolol following the 3 minute task was required in order to indentify sympathetic facility, Scheffe's *post-hoc* test provides a robust test of significance

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between a number of treatment conditions (Diekhoff, 1992) and provides protection against Type 1 errors (Armstrong *et al.*, 2000).
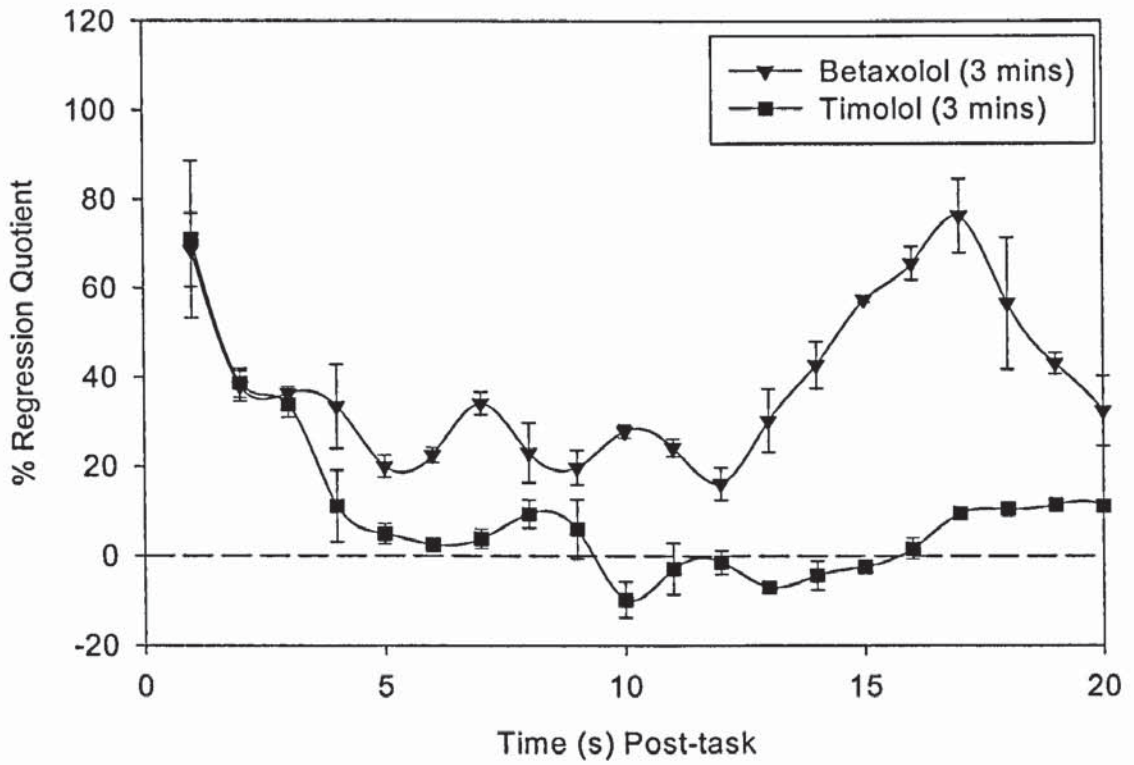
Figure 3.8. Regression quotient (%) plots for 3-minute trials, timolol vs betaxolol (RU).
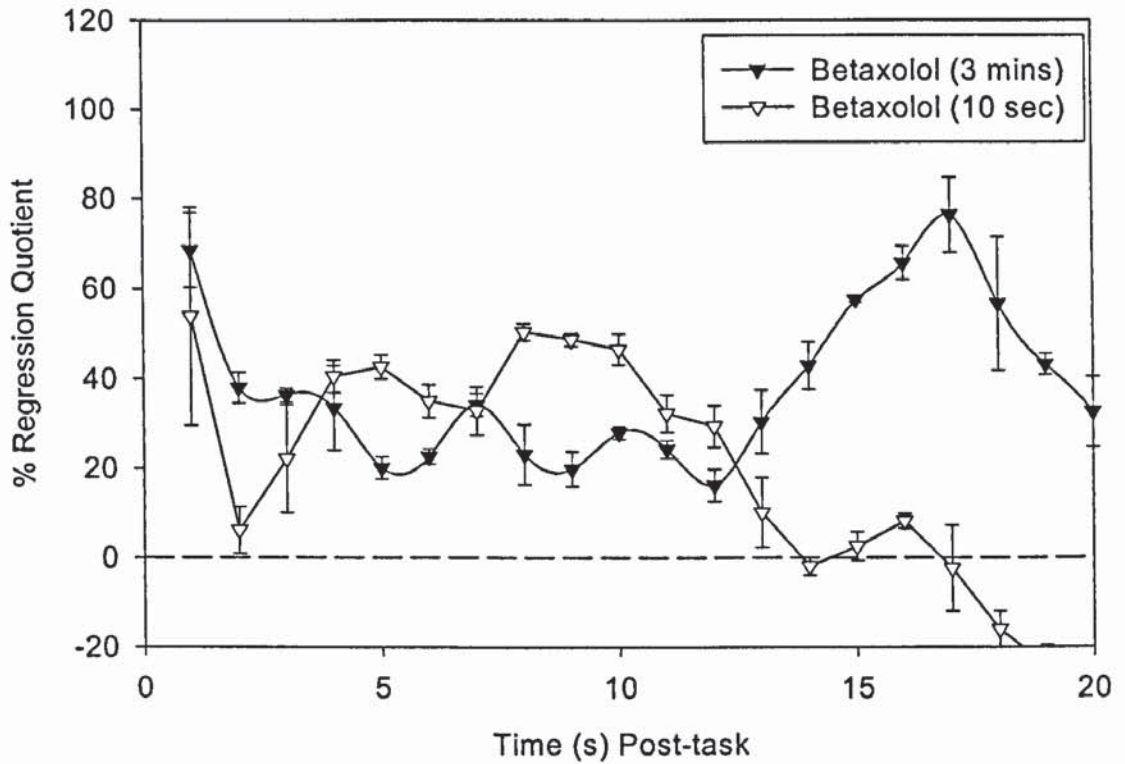
Figure 3.9. Regression quotient (%) plots for 10 second and 3-minute betaxolol trials (RU).

From the 40 subjects profiled, 10 subjects (5 male, 5 female) showed a significant retardation of open-loop accommodative regression under timolol conditions following a sustained near task. From this it can be deduced that 25% of subjects in the cohort demonstrate sympathetic inhibitory control of ciliary smooth muscle.

3.4.3 Correlation between autonomic profile and myopia onset

From the 40 subjects undergoing autonomic profiling, 10 initially emmetropic subjects developed LOM during the 2.5 year period. Thirteen cases of myopic progression were also observed. Table 3.4 shows the number of subjects demonstrating a timolol response, correlated with the onset of LOM, myopia progression and stability of refraction. A timolol response (defined earlier) suggests the existence of sympathetic inhibition of accommodation in an individual.

	N	Timolol responder	Timolol non-responder	% timolol responders
LOM development	10	2	8	20
Progressing myope	13	3	10	23
Stable myope	6	2	4	33
Stable emmetrope	21	5	16	24

Table 3.4. Relationship between refractive stability, myopia progression and timolol response.

Of the subjects demonstrating stable emmetropia during the course of the 2.5 year period, 24% demonstrated sympathetic facility. Similar values are noted for subjects showing LOM development, and progressing myopia. A higher proportion of timolol responders are noted in the 'stable myope' group; this may be due to the small sample size of this group.

3.4.4 Cross-sectional study of autonomic profile

Response to timolol under open-loop conditions following a sustained near task, thus indicating the presence of sympathetic facility, was tested statistically in the 20 additional young adult subjects. The relative proportion of subjects demonstrating retarded open-loop accommodative regression under timolol conditions following a sustained closed-loop near task are shown in table 3.5 against refractive error group. The percentage representation of timolol responders in each refractive group is also shown. Combined accommodative regression quotient plots are presented in Appendix 10.

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Refractive group	N	Response to timolol	No response to timolol	% responders
Emmetropes (EMM)	30	8	22	27
Early-onset myopes (EOM)	14	3	11	21
Late-onset myopes (LOM)	14	4	10	29
Hypermetropes (HYP)	2	1	1	50
ALL SUBJECTS	60	16	44	27

Table 3.5. Cross-sectional study: Subjects demonstrating an accommodative response to timolol.

Data from family history of myopia questionnaires were collated. For emmetropes, early onset and late onset myopes, the prevalence of parental myopia within each refractive group is shown in Table 3.6. Cross correlation between autonomic profile and prevalence of parental myopia is shown in Table 3.7

Refractive group	Neither parent myopic (%)	One myopic parent (%)	Two myopic parents (%)
EMM	65	35	0
EOM	15	54	31
LOM	43	57	0

Table 3.6. Prevalence of parental myopia according to refractive group.

ANS profile	Neither parent myopic (%)	One myopic parent (%)	Two myopic parents (%)
Sympathetic facility	56	38	6
Sympathetic deficit	44	49	7

Table 3.7. Cross correlation: autonomic profile and parental myopia.

3.5 Discussion

In this study the refractive error of a large subject group has been systematically monitored over a 2.5-year period. The cohort contained a significant proportion (78%) of initially

emmetropic subjects. During the course of the study, all subjects were exposed to substantial amounts of near work. The initiation of late onset myopic change has been observed in a number of initially emmetropic subjects. Further myopic progression has been recorded in subjects with pre-existing myopia. It has thus been possible to explore the suggested correlation between deficiency of sympathetic inhibitory facility in ciliary smooth muscle and predisposition to late onset myopia following periods of intense near work.

The experimental design employed in this work is particularly robust with regard to the detection of sympathetic facility due to the multiple controls that were built into the protocol. In order to identify a subject possessing sympathetic inhibitory facility, a retardation of open-loop accommodation to the tonic level must be seen following a sustained task at near, where a substantial amount of parasympathetic activity has been in play (Gilmartin 1986, 1998), with concurrent sympathetic blockade. The use of 10 second and 3-minute task durations provides a control for the temporal aspect of the relationship between parasympathetic and sympathetic activity, since sympathetic facility only becomes apparent after 20-40 seconds of concurrent parasympathetic activity (Törnqvist 1967; Rosenfield and Gilmartin, 1989).

The control for overall accommodative demand was facilitated by the use of 0 D and 3 D (above tonic level) trials. From the findings of Gilmartin and Bullimore (1991), the 0 D should not invoke input from the sympathetic system, thus providing an effective control for the 3 D trial which should stimulate sufficient parasympathetic activity to elicit a sympathetic inhibitory response in subjects with this facility. As used in previous studies, betaxolol hydrochloride and saline provide pharmacological controls for the non-selective β antagonist timolol maleate (Gilmartin and Winfield, 1995). This regime provides a two-way control for timolol maleate; saline as a pharmacologically inert control, and betaxolol as a control for ocular hypotensive effects. Overall, the experimental design, supported by robust statistical analysis, has formed a fine filter in the determination of the presence or absence of inhibitory sympathetic control of accommodation. It has been possible to detect and exclude subjects exhibiting general post-task hysteresis from the sympathetic group, except where delayed post-task open-loop regression is only observed following a sustained near task under β_2 blockade.

Results from this work have failed to demonstrate a link between absence of sympathetic inhibition of accommodation and the onset of late onset myopia in a young adult subject cohort. In subject groups showing development of LOM, or progression of existing myopia, 25-30% of individuals demonstrate the presence of sympathetic inhibitory control of ciliary smooth muscle. This finding is in direct support of the results from recent study by Gilmartin and Winfield (1995). Gilmartin (1998) has discussed the principal features of sympathetic accommodative control facility: inhibitory in nature, slow time course (20-40 sec), low magnitude (no more than approximately 2 D of negative accommodation), augmented by concurrent parasympathetic activity. The present study would support the notion that, under normal closed-loop viewing conditions, sympathetic facility may be too subtle to have a direct effect on the overall accommodative response. As a consequence, it may be that the absence of such a system does not place an individual at greater risk of LOM development than those possessing sympathetic facility.

Age of subjects used in this study must also be taken into account. Mean age of subjects at the end of the refractive error monitoring period was 22.2 years. It is feasible that late onset myopia could become manifest after this time, perhaps altering the relative proportion of subjects with sympathetic deficit developing LOM. A broader longitudinal study, conducted over a wider timescale (e.g. 18 to 25 years of age) may reveal a different picture.

The cross-sectional aspect of this work forms the largest study to date examining the autonomic profile of ciliary muscle innervation in human subjects. From the 60 subjects examined, it is seen that 27% of young adult subjects have access to a sympathetic inhibitory branch of ciliary smooth muscle control. Further, it is apparent that the proportion of subjects exhibiting sympathetic facility is similar between emmetropes, early onset myopes and late onset myopes. This work confirms the findings of Gilmartin and Winfield (1995), i.e. that access to a sympathetic inhibitory facility is a general feature of the human accommodative system. In addition, efficacy of sympathetic inhibitory facility exhibits considerable inter-subject variability (Gilmartin *et al.*, 2002b). It is concluded that a deficit in sympathetic facility is not a primary risk factor in late onset myopia, or indeed myopia in general.

The mean age of subjects in the cross-sectional cohort is also relatively young (21.7 years). In currently emmetropic subjects, it is possible that LOM will develop at some time in the future. The ergonomics of the near visual tasks undertaken to date may not have provided a sufficient myopigenic factor to induce LOM. As a result, conclusions from the present study may not reveal the full extent of the relationship between LOM and sympathetic facility. It may be useful to conduct a cross sectional study of individuals undertaking intense near work on a daily basis, for example, visual display terminal users or data entry clerks. An optometric examination, questionnaire to determine refractive history and past visual habits, coupled with an ANS profile strategy may highlight a stronger link between a deficiency in sympathetic inhibition and propensity to develop LOM.

The experimental design and statistical tests employed in the longitudinal and cross-section aspects of this work have assumed, based on previous work, that sympathetic inhibition of accommodation is either present or totally absent in an individual. It may be that a graded sympathetic inhibitory response exists in a proportion of subjects in this study. Indeed, it was found that the open-loop accommodative responses a small number of subjects exhibited the basic features seen in the classic model of active sympathetic facility, but definite presence of sympathetic facility just failed to be shown statistically. Investigation of a graded sympathetic response should now be carried out. The efficacy of a wider range of autonomic agents should be evaluated with a view to more targeted receptor interaction. With reference to the model of open-loop accommodation responses proposed by Gilmartin and co-workers (Gilmartin *et al.,* 1992), it may be the case that a continuum of post-task accommodative responses exists. Examination of the dose effects of targeted antagonistic autonomic agents may allow an evaluation of the potential for graded sympathetic facility.

Parental history of myopia was examined in terms of refractive group and access to sympathetic facility. Not surprisingly, the early onset myopic group had a higher proportion of subjects with myopic parents when compared to the emmetropic group, thus demonstrating the familial influences in early onset myopia. It is interesting to note that the late onset myopes showed single parent myopia history in 57% of cases. Due to the bias of environmental factors in the genesis of late onset myopia, it was predicted that family history of myopia would be similar between emmetropes and late onset myopes. This finding may be as a result of low sample size (N = 14) in the late onset group. When

examined in terms of access to sympathetic facility, no trends in family history of myopia were evident.

CHAPTER 4
BIOMETRIC INVESTIGATION OF REFRACTIVE ERROR

4.1 Introduction

Axial length elongation as the principal biometric correlate of myopia has been well established in both early onset (Goss *et al*, 1990) and late onset myopia (McBrien and Millodot, 1987b). McBrien and Adams (1997) demonstrated elongation of the vitreous chamber as the significant factor in myopic onset and progression in an adult subject cohort; change in other biometric correlates (corneal curvature, anterior chamber depth and crystalline lens thickness) were minimal and statistically insignificant. Invariably, these studies have used A-scan ultrasonic techniques to measure axial length. In recent years the use of partial coherence interferometry (PCI) and laser Doppler interferometry (LDI) techniques have demonstrated accurate and repeatable measurement of axial length (Hitzenberger, 1991; Haigis *et al.*, 2000). A commercial device for ocular biometric measurement based on PCI (Zeiss *IOLMaster*) has recently become available, and has been evaluated in human subjects (Santodomingo-Rubido *et al.*, 2002; Lam *et al.*, 2001). This new device offers significant advantages over traditional biometric measurement techniques both in terms of resolution and clinical utility (see Chapter 2).

Variation in peripheral refraction between refractive groups has been of interest for a number of decades. Rempt *et al.* (1971) identified 5 classes of skiagram in a large sample of subjects. The pattern of peripheral astigmatism was largely symmetrical between temporal and nasal retina in the majority of cases. Myopic eyes tended to exhibit reducing myopia at increasing eccentricities, coupled with low peripheral astigmatism. Recently, Mutti *et al.* (2000b) have used an autorefraction technique to demonstrate, using peripheral refraction, prolate retinal shape in myopic children. This study only examined the nasal peripheral retina. Facility now exists to re-evaluate peripheral astigmatism and ocular shape with novel instrumentation.

The purpose of the work reported in this chapter was to measure ocular biometric parameters for different refractive groups using new measurement techniques. Two approaches were taken: firstly, the distribution of ocular biometric factors was examined between refractive groups to establish a profile of ocular dimensions; secondly, in a

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subgroup of subjects, biometric change was correlated with refractive change over a 12 month period.

4.2 Subjects

Subjects were undergraduate or postgraduate optometry students at Aston University. A total of 70 subjects were recruited, consisting of 2 hypermetropes (HYP), 28 emmetropes (EMM) 27 early onset myopes (EOM), and 13 late onset myopes (LOM). Age range of the subjects was 18 to 25 years (mean age 19.52 ± 1.72 years). Ethnicity distribution of the subjects group was: 25 European, 44 Asian and 1 Far-Eastern. Forty subjects were also participants in the longitudinal study of refractive error (see Chapter 3), allowing correlation between refractive and biometric change. Participants in the experiment were free of abnormal ocular conditions (confirmed by slit lamp and direct ophthalmoscopy) and had visual acuity correctable to 6/6 or better in both eyes. Informed consent was obtained from all subjects prior to commencement of experimental work. Subjects did not receive any form of payment.

4.3 Methods

4.3.1 Corneal curvature

Central corneal curvature was measured three times in quick succession in both eyes using the Zeiss *IOLMaster*. Subjects were instructed to view the internal fixation spot of the *IOLMaster*. Measurements were made in dim room illumination conditions (approximately 20 cd/m^2). Radius measurements for both principal meridians from each set of 3 readings were averaged to provide a mean corneal curvature value.

4.3.2 Anterior chamber depth

The anterior chamber depth (ACD) of both eyes was measured using the Zeiss *IOLMaster* device. The *IOLMaster* automatically made five readings of ACD, and expressed the average of these readings in millimetres to 2 decimal places. The subject viewed the internal fixation target during measurement. To maximize measurement accuracy, the room illumination was reduced during ACD measurements to enhance the contrast of the image available for analysis. Average background room luminance was 5 cd/m^2.

4.3.3 Axial length

Three measurements of axial length were taken on both eyes of all subjects using the *IOLMaster*. Subjects were instructed to observe the *IOLMaster* internal fixation light. Measurements were averaged for each eye and expressed to 2 decimal places.

4.3.4 Axial length:Corneal curvature ratio

Data from 5.3.1 and 5.3.3 were used to calculate the axial length to corneal curvature ratio in all subjects.

4.3.5 Peripheral refraction

Comparison between axial and peripheral measurements of ocular refraction and eye length gives valuable information regarding the shape of the posterior portion of the globe (Mutti *et al.*, 1997; Love *et al.*, 2000).

The mean spherical refraction of six static autorefractor readings was measured in both eyes viewing a high contrast Maltese target in the primary position. The Maltese cross was fixed to a flat wall at a distance of 6 metres, and was equivalent to a 6/120 Snellen letter in size. A large target size was chosen to ensure good fixation in subjects with higher degrees of ametropia. Subjects with good unaided vision were instructed to fixate the central intersection of the cross limbs.

For assessment of peripheral refraction, the eyes were rotated through 30° to the temporal side to view a second high contrast Maltese cross target. Eye rotation was calculated by tangent scale method from the relationship *tan30 x 6 (m) = 3.46 (m)*. Peripheral 30° targets were thus placed 3.46 metres either side of the primary position target. From the basic geometric relationship it can be seen that the peripheral 30° targets were further away from the subject than the primary position target. Dioptric distance of the primary position target was $6m^{-1} = 0.17$ D. Dioptic distance of the 30° target was found from *6/cos30 = 6.93*, and $6.93\ m^{-1} = 0.14$ D. This small difference (0.03D) in accommodative demand between primary position and peripheral targets was considered insignificant, since it was less than the repeatability of mean spherical error readings taken with the Shin-Nippon SRW-5000 (0.04D, Mallen *et al.*, 2001). The mean spherical average of six autorefractor readings was calculated. The eyes were rotated through 30° to the nasal side to observe a third Maltese cross target. Six further readings of mean spherical error were taken and averaged.

Comparison of central and peripheral refraction with axial and peripheral eye length was carried out by analysis of subsequent *IOLMaster* measurements. The above procedure was repeated, with autorefractor readings being replaced by the average of three *IOLMaster* axial and peripheral length measurements. Primary position readings were carried out with the subject fixating the instrument's internal target. Fixation targets for the peripheral measurements were the $30°$ Maltese cross targets. Relative peripheral length was calculated by subtracting axial length from peripheral length measurements; a negative relative peripheral length reading indicating relative hypermetropia at that retinal location.

4.3.6 Intraocular pressure

Intraocular pressure (IOP) was measured using the Keeler *Pulsair 3000* non-contact tonometer. An average of 4 readings were taken for each eye. Readings were carried out at the same time of day for all subjects to prevent the normal diurnal variation of intraocular pressure adding bias to the distribution of results. Subjects were asked to avoid the consumption of alcohol or coffee in the 90 minutes immediately preceding IOP measurement. Buckingham and Young (1986) demonstrated an increase in IOP following the consumption of coffee, and a fall in IOP following the consumption of alcohol.

4.3.7 Eye volume

Eye volume was calculated for both eyes of all subjects. The formulae, as used by Harper (2001), can be found in Appendix 11. The calculation is based on axial length, retinal contour, apical corneal radius, corneal asphericity and corneal diameter. The globe was divided into 5 sections: corneal section, anterior nasal part, anterior temporal part, posterior nasal and posterior temporal part. Volume for each section was calculated; volumes of the 5 sections were then summed to give total ocular volume in mm^3. Retinal contour was calculated by fitting a second order polynomial function (of the form $y = ax^2 + bx + c$) to peripheral refraction measurements up to $30°$ temporal and nasal to fixation. Corneal asphericity and corneal diameter measurements were taken from *EyeSys* corneal topography data. Corneal shape was defined by the conic section equation: $y^2 = 2 r_0 x - px^2$, where r_0 = corneal apical radius, $p = 1 - e^2$.

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4.4 Results

Initial biometric data were obtained from 70 subjects. Follow-up biometric data was taken in 60 subjects. Ten initially emmetropic subjects from the follow-up group developed late onset myopia during the course of the longitudinal study of refractive error. Data from these 10 subjects is analysed separately in terms of the correlation between change in axial length, anterior chamber depth and corneal curvature, and refractive change. Group averaged mean refractive error (sphere + cylinder/2) were: emmetropes +0.33 ± 0.80 D; early onset myopes −4.08 ± 2.75 D; and late onset myopes −0.81 ± 0.57 D.

4.4.1 Corneal curvature

Initial values of central corneal curvature were obtained from 70 subjects (140 eyes) and correlated against mean spherical refractive error. Figure 4.1 Shows a plot of mean corneal curvature against mean spherical refractive error (MRE). Linear regression analysis reveals a weak relationship between central corneal radius and mean refractive error. Separate linear regressions were calculated for right (solid line) and left eyes (broken line) due to the inherent interaction between eyes (Ray and O'Day, 1985); right eyes: $r^2 = 0.07$, y = 0.03x + 7.79, p <0.05, left eyes: $r^2 = 0.09$, y = 0.03x + 7.79, p = 0.01. Mean corneal radius (all subjects) was 7.75 ± 0.30 (SD) mm. Average (± SD) mean corneal radius for right eyes according to refractive group were: emmetropes 7.86 ± 0.24 mm; early onset myopes 7.68 ± 0.30 mm; late onset myopes 7.70 ± 0.34 mm. No statistically significant difference in central corneal radius was found between refractive groups (ANOVA with Scheffe's *post-hoc* test: EMM vs EOM, $p = 0.10$; EMM vs LOM, $p = 0.25$; EOM vs LOM, $p = 0.98$). Similar values were found for left eyes.

Figure 4.2 shows mean change in central corneal curvature against change in MRE in subjects becoming myopic during the longitudinal study of refractive error. A weak negative correlation was found between these two variables, indicating a reduction in corneal curvature concurrent with LOM progression. Note that data shown in figure 4.2 represent all subjects in the 'became myopic' group, with >0.50 D of myopia progression being shown during the 2.5 year study period. As a consequence, a number of subjects showed myopic progression of less than 0.50 D between biometric data points.
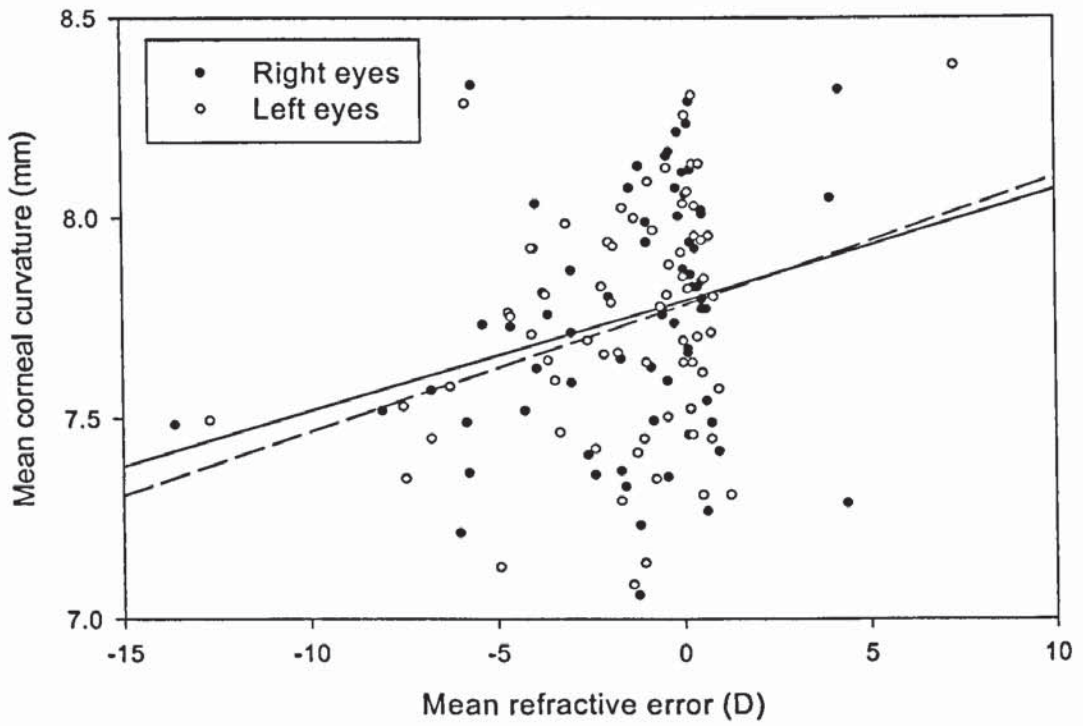
Figure 4.1 Mean corneal curvature vs MRE. All subjects.
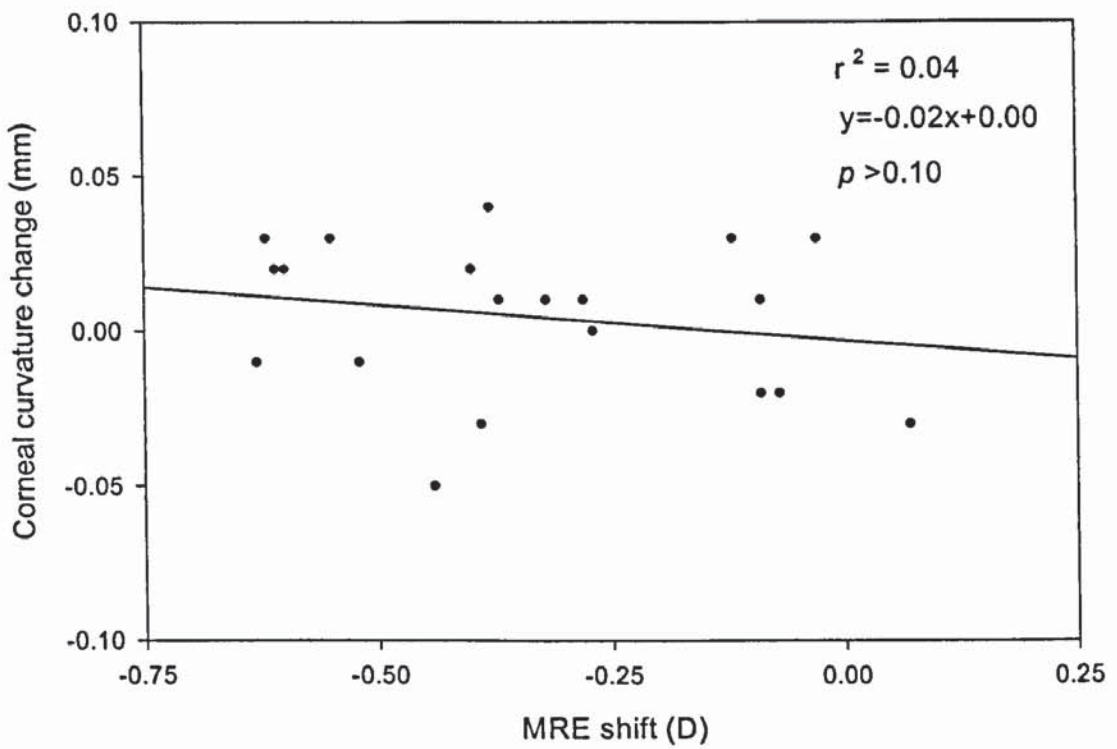
Figure 4.2. Corneal curvature change over 12 months against MRE change in LOM group.

4.4.2 Anterior chamber depth

Mean group ACD was 3.12 ± 0.18 mm. A negative correlation was found between ACD and MRE (figure 4.3). Separate linear regressions were calculated for right (solid line) and left eyes (broken line); right eyes: $r^2 = 0.23$, $y = -0.05x + 3.58$, $p <0.01$, left eyes: $r^2 = 0.21$, $y = -0.05x + 3.57$, $p <0.01$. Group mean ACD (± SD) for right eyes for each refractive group were as follows: emmetropes 3.52 ± 0.25 mm; early onset myopes 3.78 ± 0.21 mm; late onset myopes 3.66 ± 0.25 mm. Statistical testing revealed a significant difference in ACD between emmetropes and early onset myopes ($p = <0.01$). Differences in ACD between other refractive group combinations were not statistically significant (ANOVA with Scheffe's *post-hoc* test: EMM vs LOM, $p = 0.22$; EOM vs LOM, $p = 0.25$).

Change in anterior chamber depth against change in MRE in the LOM group is shown in figure 4.4. Again, a weak correlation is shown indicating a deepening of the anterior chamber as myopia progresses.
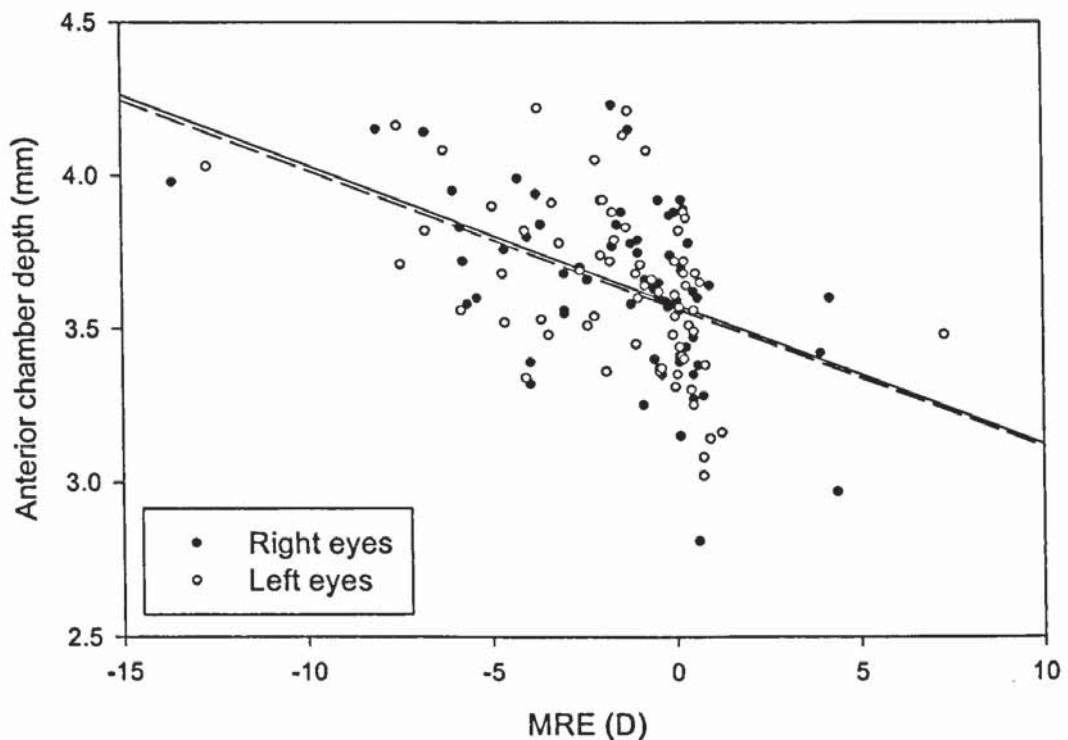
Figure 4.3 Anterior chamber depth vs MRE. All subjects.
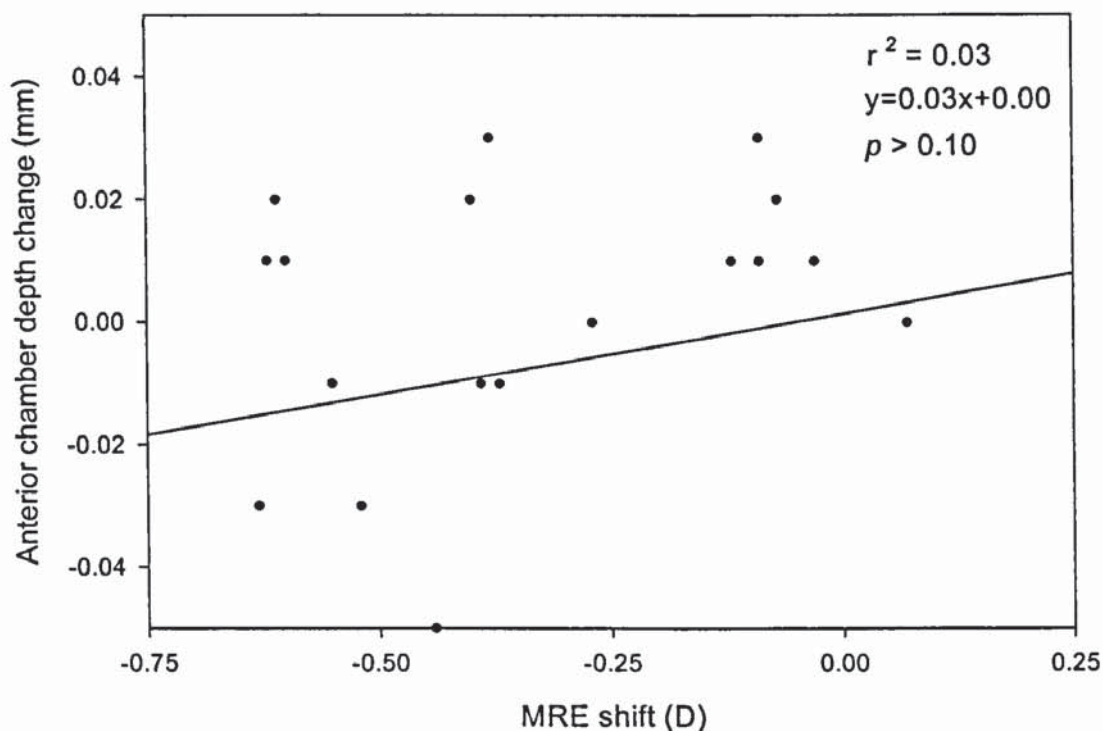
Figure 4.4. Anterior chamber depth change over 12 months against MRE change in LOM group.

4.4.3 Axial length.

The correlation between axial length and MRE for the whole subject cohort is shown in figure 4.5. A strong negative relationship between axial length and mean spherical refractive error is evident. Separate linear regressions were calculated for right (solid line) and left eyes (broken line); right eye: $r^2 = 0.66$, $y = -0.37x + 23.64$, $p <0.01$, left eye: $r^2 = 0.63$, $y = -0.36x + 23.61$, $p <0.01$. Group mean axial length measurements ($\pm$ SD) for right eyes for each refractive group were as follows: emmetropes 23.46 $\pm$ 0.69 mm; early onset myopes 25.26 $\pm$ 1.09 mm; late onset myopes 23.79 $\pm$ 1.02 mm. Statistical significance was observed between early onset myopes and emmetropes ($p = <0.01$), and early- and late-onset myopes ($p = <0.01$). No statistically significant difference in axial length was found between emmetropes and late onset myopes ($p = 0.56$).

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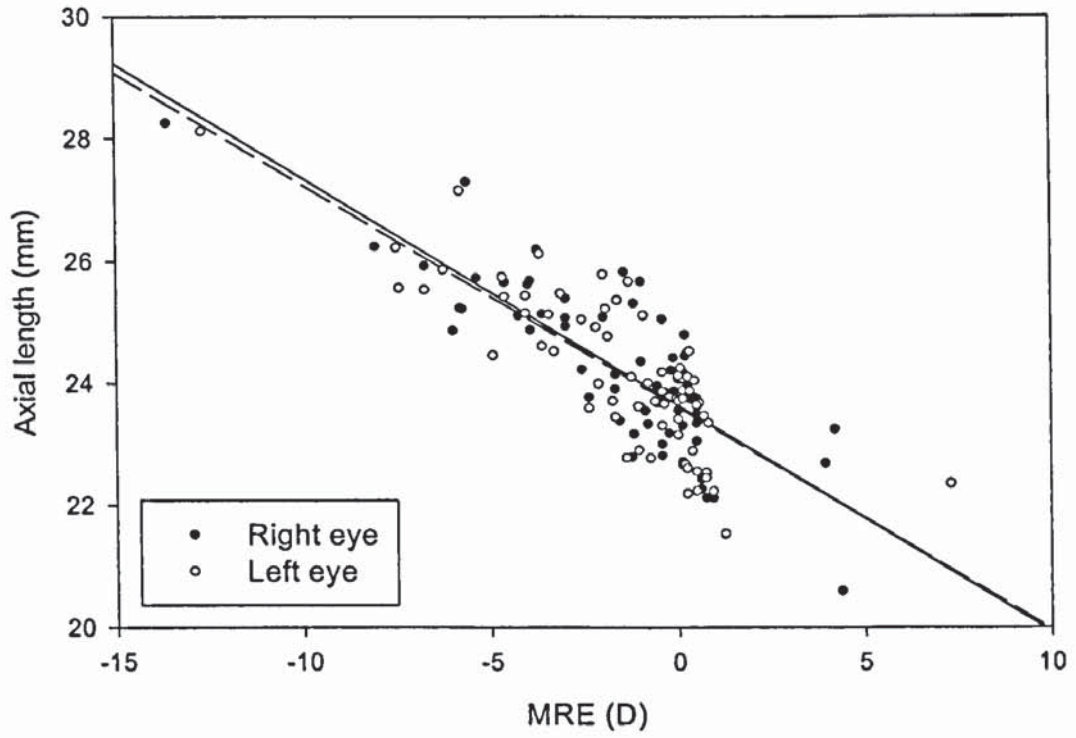
Figure 4.5. Axial length vs MRE for all subjects.

The correlation between changes in axial length and MRE for the LOM group is illustrated in figure 4.6.
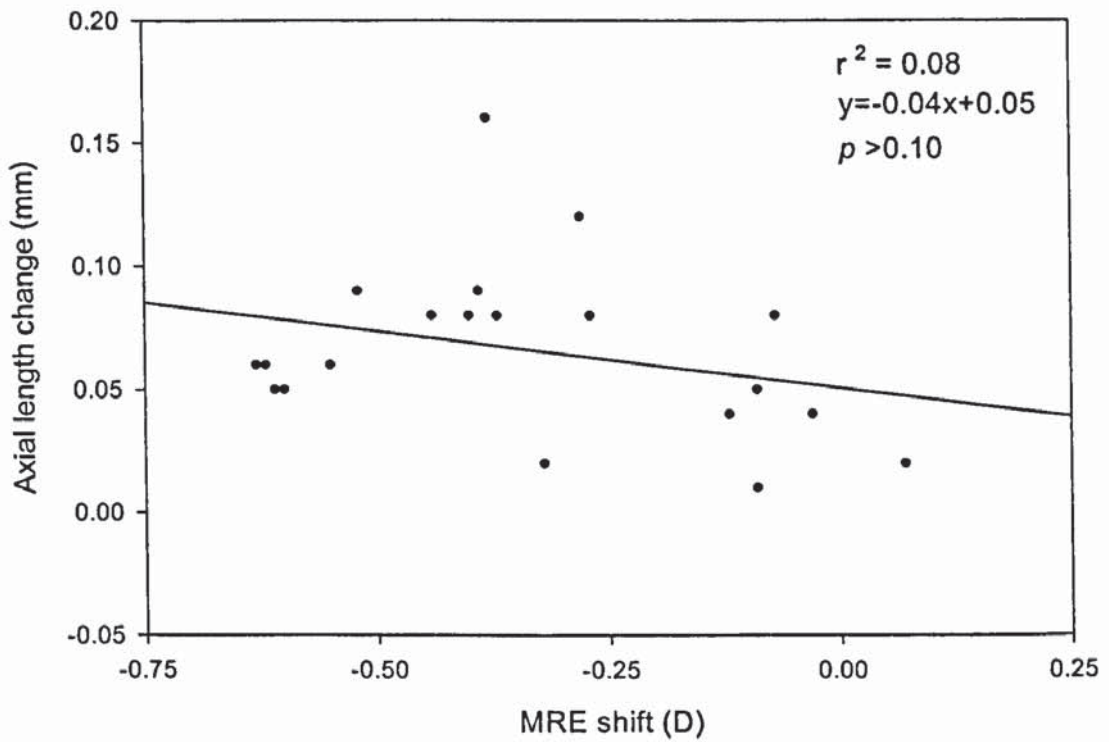
Figure 4.6. Axial length change over 12 months against MRE change in LOM group.

4.4.4 Axial length:Corneal curvature ratio

Group values for AL:CC ratio are plotted against mean refractive error in figure 4.7. Linear regression analysis shows a strong correlation between these two factors (r^2 0.90, p <0.01, y = -0.06x + 3.03 for right eye data; identical values were obtained from linear regression of left eye data). When categorised according to refractive error, difference in AL:CC ratio was found to be statistically significant between all refractive error groups (p < 0.02). Averaged group values for AL:CC ($\pm$ SD) were: emmetropes 2.99 $\pm$ 0.06; early onset myopes 3.29 $\pm$ 0.15; late onset myopes 3.09 $\pm$ 0.10.
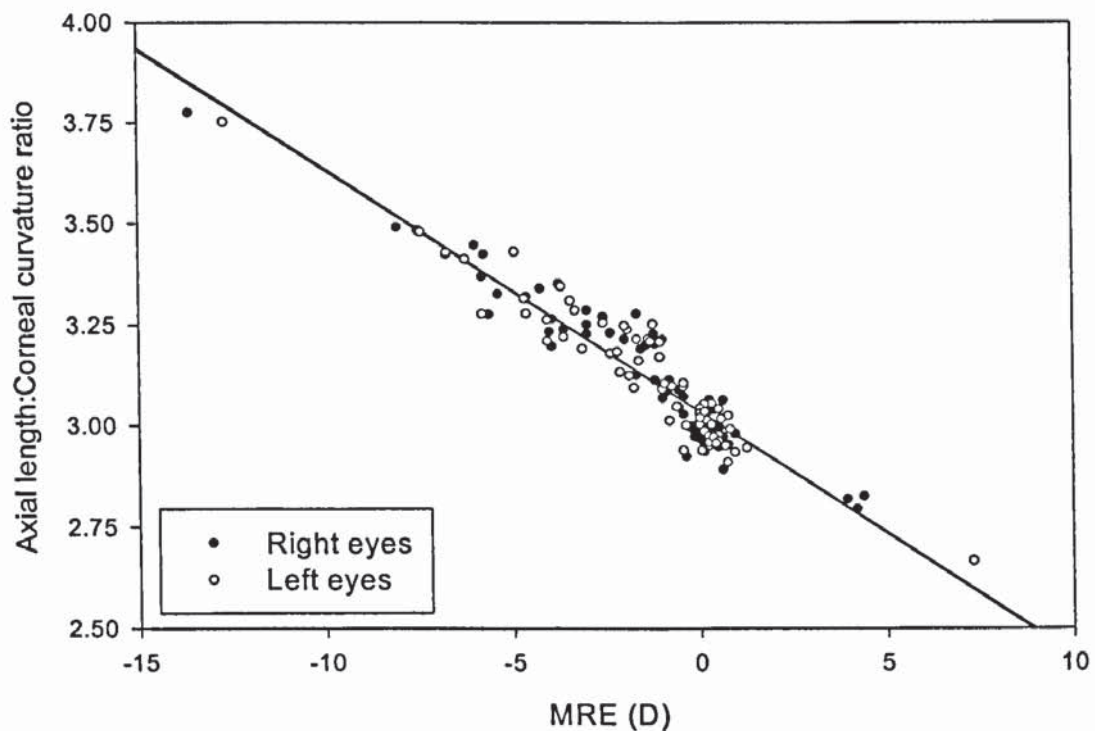
Figure 4.7. AL:CC ratio vs MRE.

4.4.5 Peripheral refraction

Central and peripheral (30° temporally and nasally) refraction measurements were obtained in 68 subjects. Relative peripheral MRE values were calculated by subtracting peripheral MRE values from central MRE values. From this, relative peripheral hyperopia or myopia can be identified. Regression plots of relative peripheral refraction against central MRE are shown in figures 4.8 to 4.11. Data is represented as four regression plots; relative mean spherical refractive error at 30° peripheral retinal locations temporally and nasally for right and left eyes. General negative correlations are apparent between central and peripheral refraction in all four analyses. A stronger correlation is observed between peripheral

refraction in the temporal retina and central refraction compared to nasal peripheral refraction. This suggests that the temporal retinal curvature undergoes a larger shift towards a prolate elliptical shape with increasing myopia than the nasal retina.
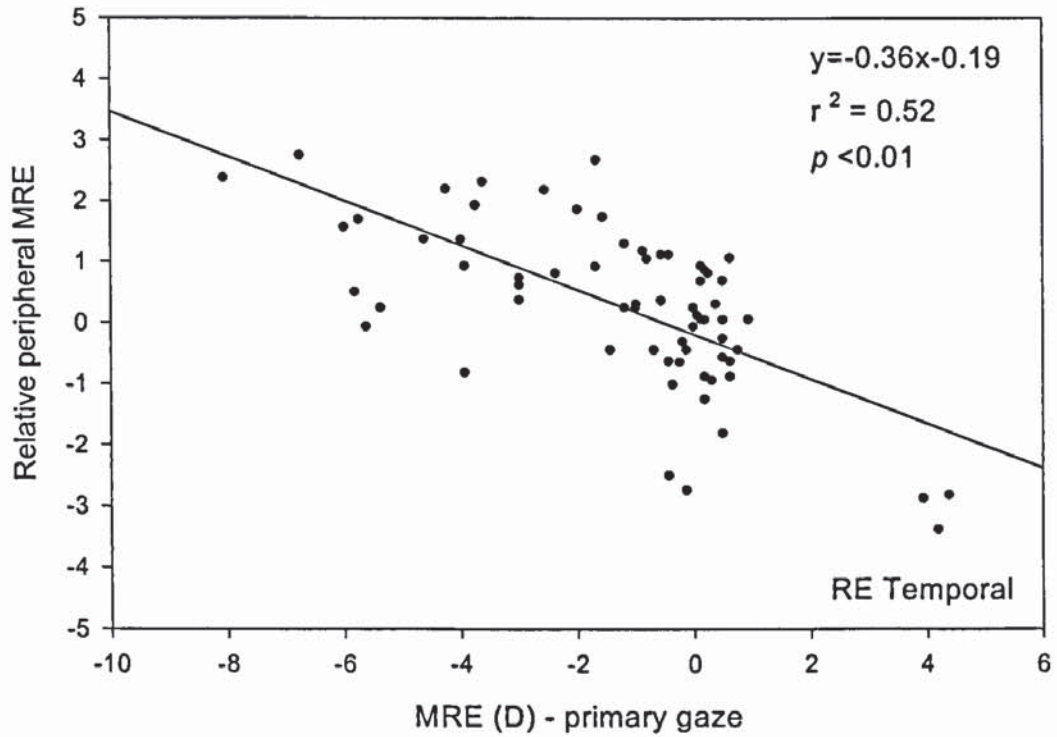
Figure 4.8. Relative peripheral refraction – RE 30° temporal.
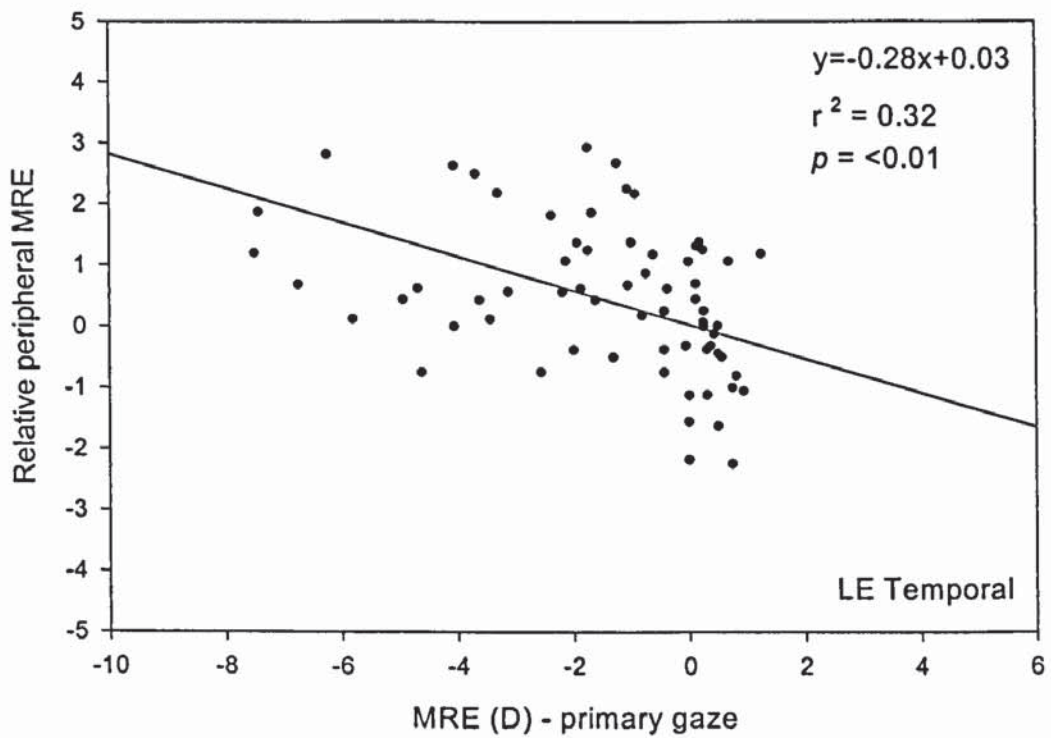
Figure 4.9. Relative peripheral refraction – LE 30° temporal.
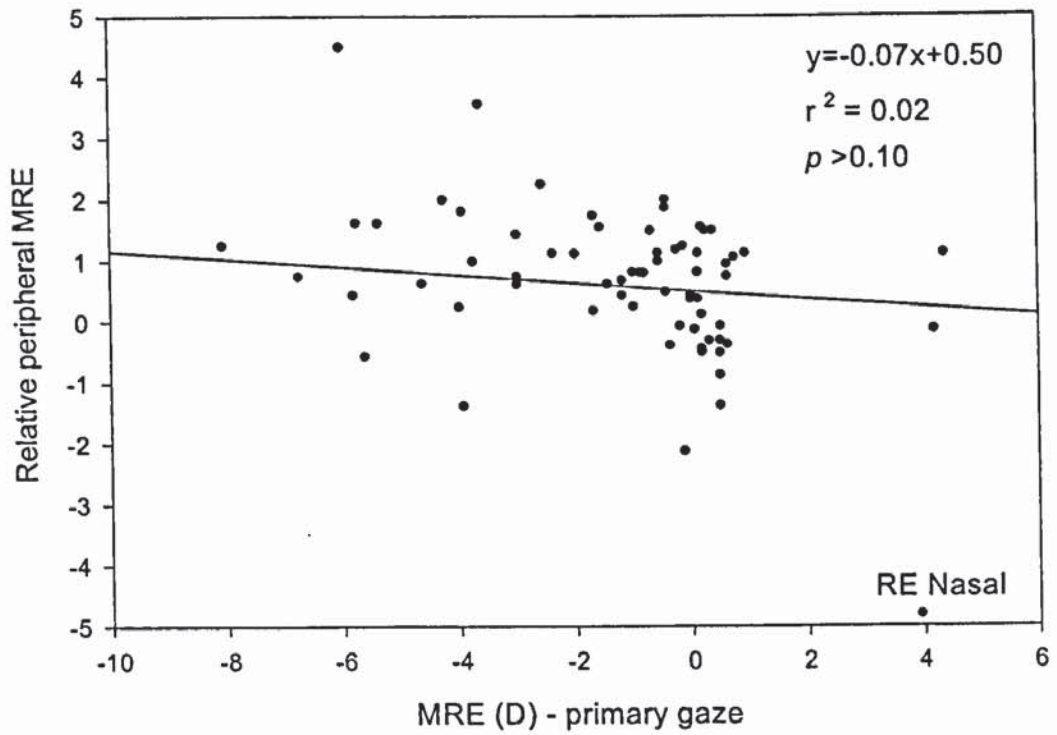
Figure 4.10. Relative peripheral refraction – RE 30° nasal.
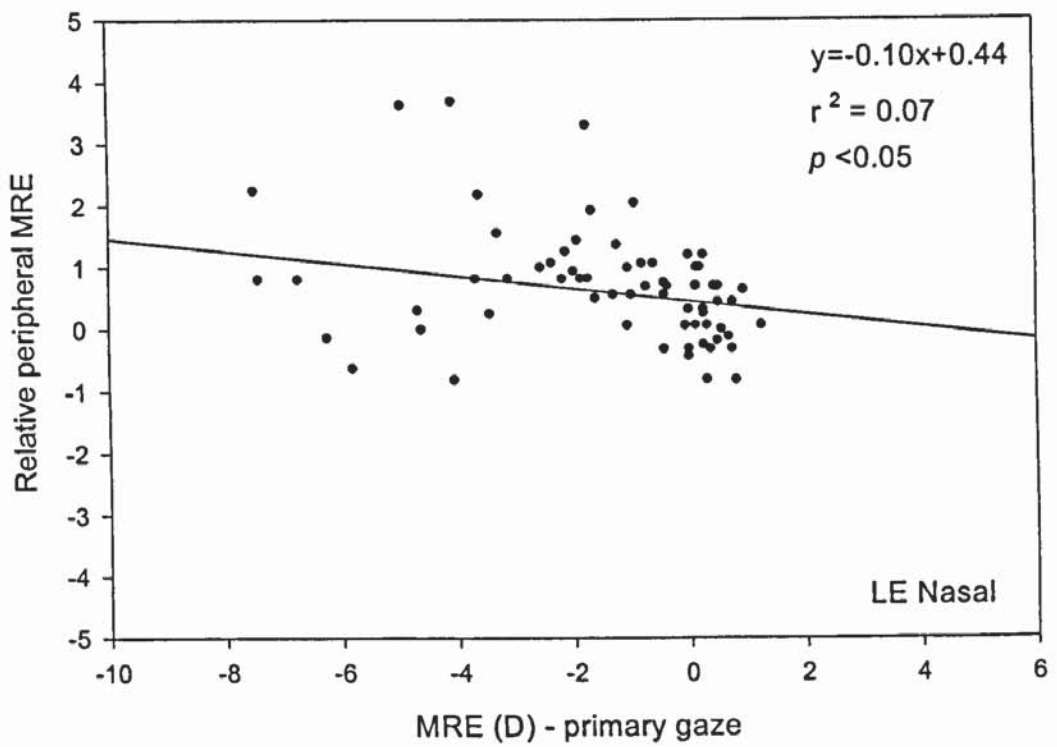
Figure 4.11. Relative peripheral refraction – LE 30° nasal.

Refractive group	R 30° temp	L 30° temp	R 30° nasal	L 30° nasal
Hypermetropes	-3.02±0.31 D	-1.10±2.91 D	-1.27±3.17 D	-0.79±2.04 D
Emmetropes	-0.26±0.89 D	-0.11±1.22 D	+0.39±0.89 D	+0.33±0.84 D
Early onset myopes	+1.23±1.41 D	+1.16±1.14 D	+0.90±1.53 D	+0.95±1.17 D
Late onset myopes	+0.37±0.73 D	+0.37±0.95 D	+0.81±0.54 D	+0.69±0.59 D

Table 4.1. Relative peripheral refraction summary.

Relative peripheral refraction values were found to be significantly different between refractive error groups ($p = 0.02$). Variation between right and left eyes was not significant ($p = 0.70$). Table 4.1 shows mean (±SD) relative peripheral spherical equivalents for 30° peripheral point in temporal (temp) and nasal retinae for each refractive error group. The small number of hypermetropic eyes examined revealed, on average, relative myopia in the peripheral retina. Emmetropic eyes were seen to possess a generally spherical retinal contour; the temporal retina being relatively slightly myopic and the nasal retina showing slight hypermetropia. Early onset myopic eyes show relative peripheral hypermetropia; this effect being more marked in the temporal peripheral retina. Late onset myopes also showed relative peripheral hypermetropia, but to a lesser degree than early onset myopes. It is interesting to note that in the late onset myopes, the asymmetry of peripheral refraction is reversed compared to early onset myopes; i.e. the nasal retina exhibiting greater relative hypermetropia than the temporal retina.

Relative peripheral length measurements agreed well with peripheral refraction values as an indicator of retinal contour. Correlation coefficient (r^2) between relative peripheral length and relative peripheral mean sphere was 0.38 ($y = -0.21x - 0.39$, $p < 0.01$). Table 4.2 shows mean relative peripheral length values (±SD) for emmetropes, early onset myopes and late onset myopes.

Refractive group	R 30° temp	L 30° temp	R 30° nasal	L 30° nasal
EMM	-0.41±0.25 mm	-0.40±0.25 mm	-0.25±0.17 mm	-0.29±0.16mm
EOM	-1.04±0.59 mm	-0.74±0.33 mm	-0.43±0.63 mm	-0.61±0.44mm
LOM	-0.58±0.28 mm	-0.50±0.24 mm	-0.31±0.20 mm	-0.36±0.34mm

Table 4.2. Relative peripheral length.
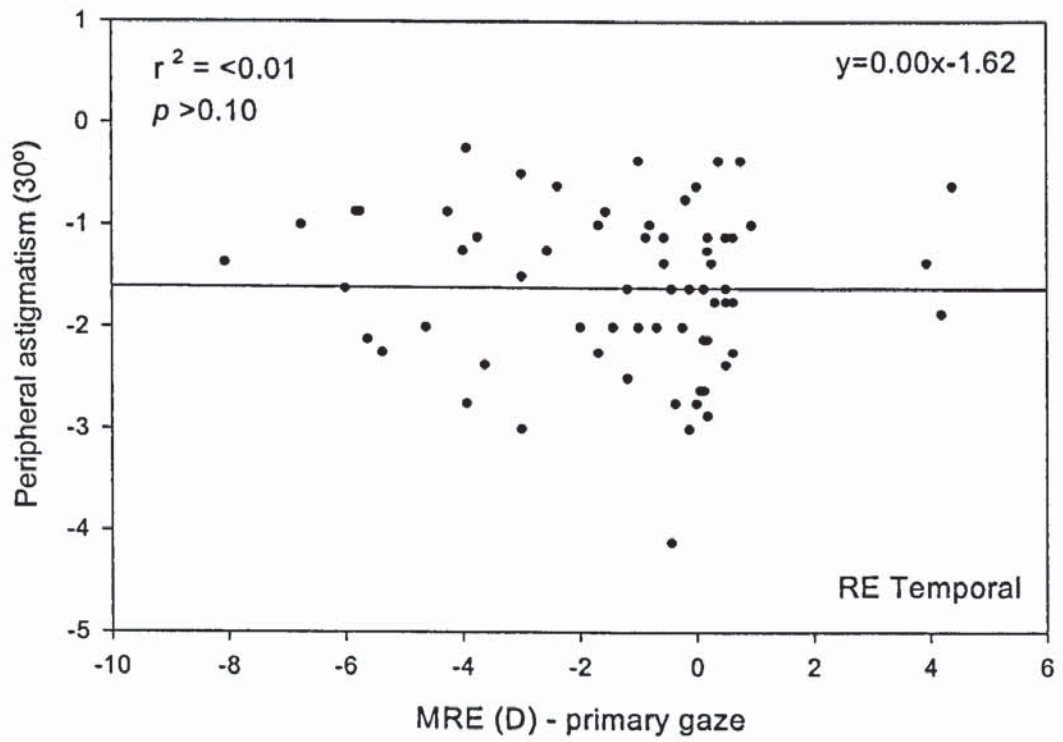
Figure 4.12. Peripheral astigmatism – RE 30° temporal.
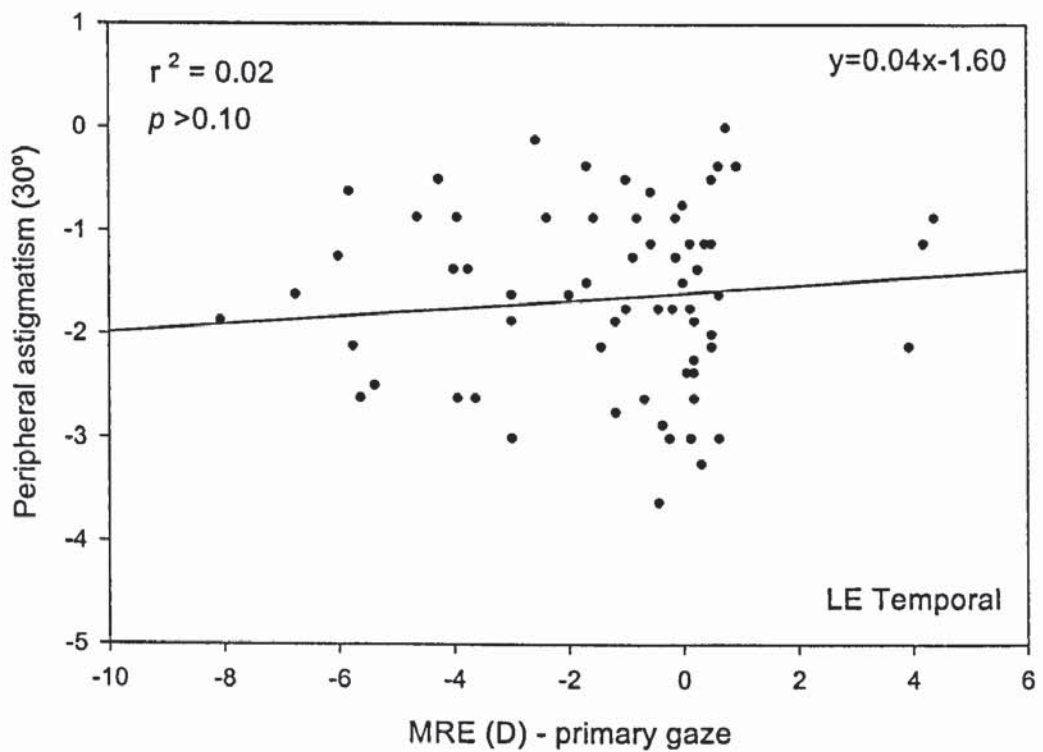
Figure 4.13. Peripheral astigmatism – LE 30° temporal.
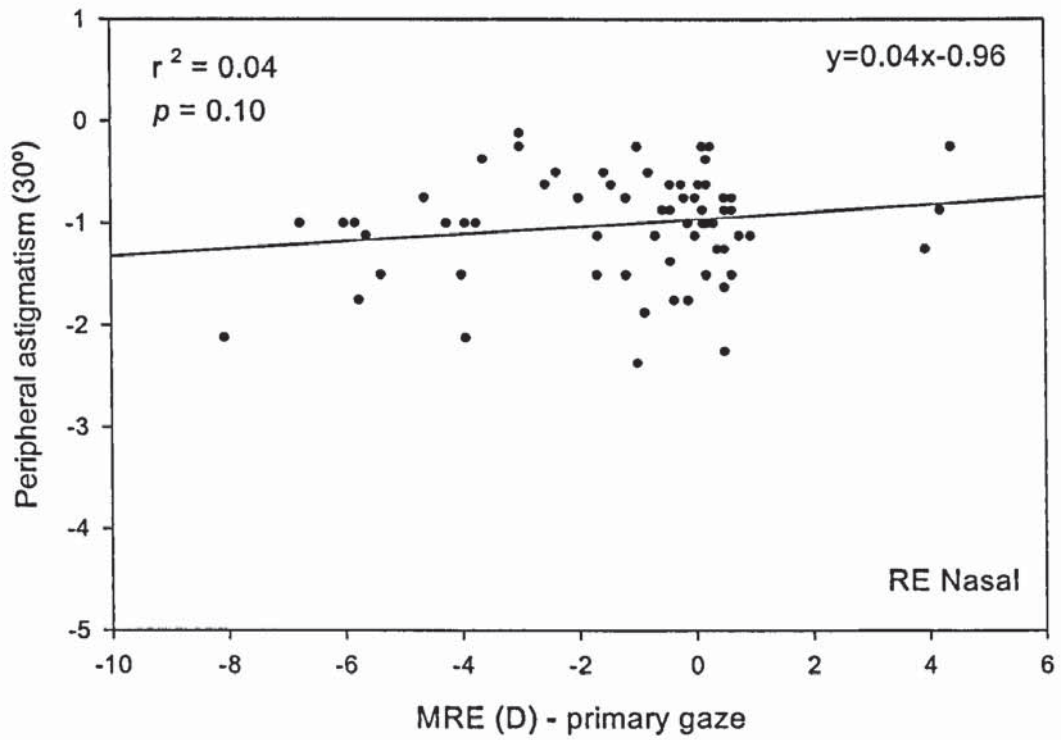
Figure 4.14. Peripheral astigmatism – RE 30° nasal.
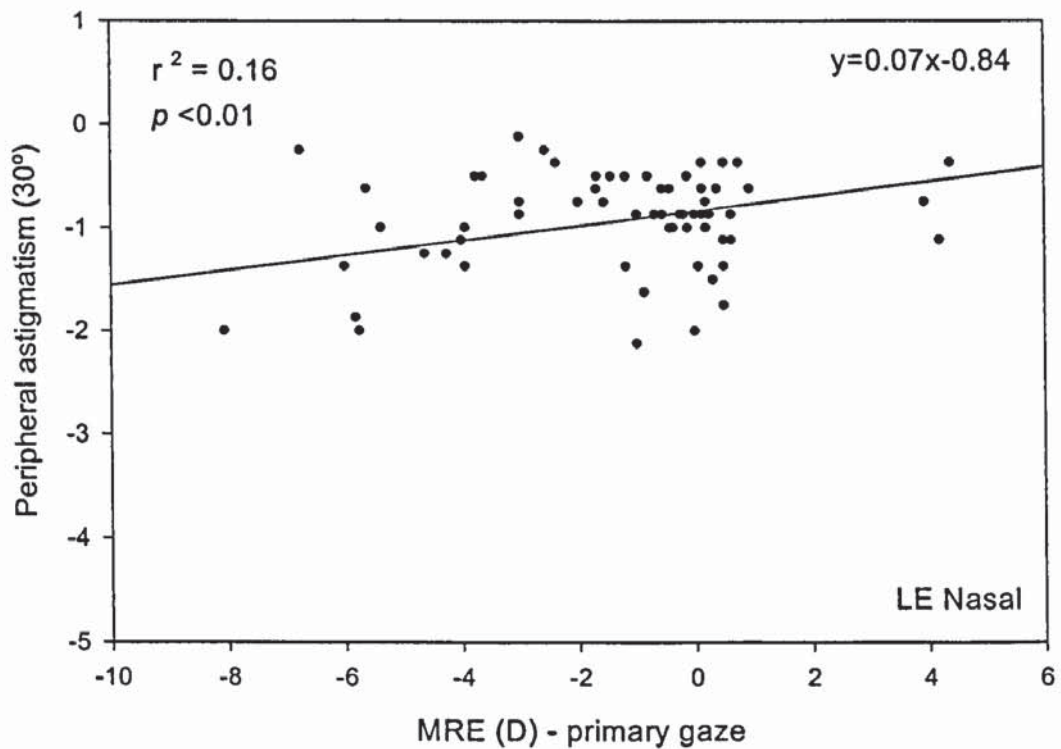
Figure 4.15. Peripheral astigmatism – LE 30° nasal.

Figure 4.12 to 4.15 plot peripheral astigmatism against mean spherical refraction in primary gaze. Relatively weak correlations are seen between peripheral astigmatism and

central refraction. Peripheral astigmatism was greatest temporally. All refractive groups showed significantly greater oblique cylinder values in the temporal periphery (p = <0.0001). ANOVA and Scheffe's *post-hoc* test showed that refractive error did not have a significant effect on degree of peripheral astigmatism, as suggested by regression analysis. Table 4.3 lists group mean peripheral astigmatic values (± SD) at 30° temporally and nasally for all refractive groups.

Refractive group	30° Temporal	30° Nasal
Hypermetropes	-1.33±0.58 DC	-0.77±0.40 DC
Emmetropes	-1.80±0.91 DC	-0.92±0.40 DC
Early onset myopes	-1.52±0.81 DC	-1.05±0.64 DC
Late onset myopes	-1.63±0.66 DC	-1.00±0.46 DC

Table 4.3. Peripheral astigmatism and refractive error group.

4.4.6 Intraocular pressure

Intraocular pressure measurements obtained from the right eyes of 70 subjects were correlated with mean spherical refractive error (figure 4.16). A weak positive correlation is shown between IOP and mean spherical refractive error. Mean IOP was calculated for EOM, LOM, EMM, stable refraction and progressing myope groups to enable between group comparisons. Table 4.4 shows a mean group IOP for each refractive category. ANOVA revealed the overall variation in IOP across refractive group to be insignificant (p = 0.71). Scheffe's *post-hoc* test revealed no significant variation in IOP between any two refractive error groups.
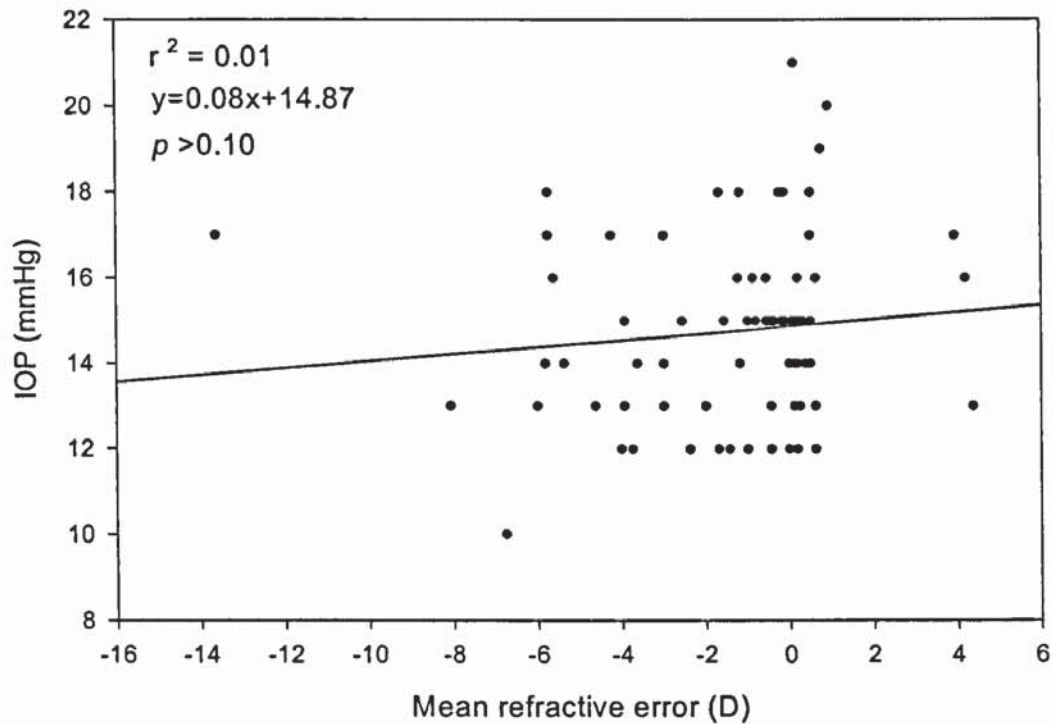
Figure 4.16. IOP against MRE for right eye of all subjects.

Refractive group	Mean IOP (mmHg) ± SD	N
Hypermetropes	14.50±2.12	2
Emmetropes	14.89±2.38	28
Early onset myopes	14.44±2.19	27
Late onset myopes	14.92±1.93	13

Table 4.4. Mean IOP as a function of refractive group.

Comparison of IOP between subjects with stable refractive error (N = 49) and subjects with progressing myopia (N = 21) revealed group mean values of 14.68 ± 2.20 mmHg and 14.90 ± 2.21 mmHg respectively. ANOVA showed this small difference between groups to be statistically insignificant ($p = 0.77$).

4.4.7 Eye volume

Figure 4.17 shows the relationship between mean refractive error and eye volume for the right eyes of all subjects. Similar values for linear regression co-efficient and statistical significance were found for left eyes ($r^2 = 0.66$, y = -0.13x + 5.273, $p < 0.001$). Eye volume

is expressed in mm^3. Mean eye volume for the whole subject cohort was 5.49 x 10^3 mm^3 for right eyes and 5.47 x 10^3 mm^3 for left eyes.
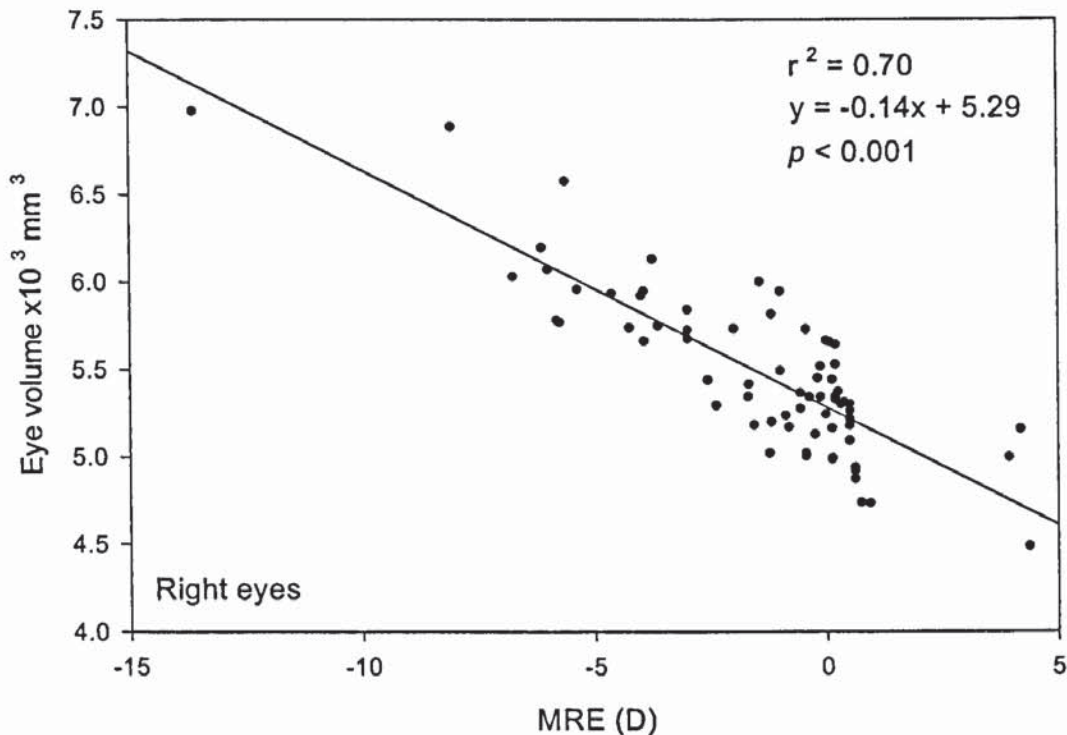
Figure 4.17. Eye volume against MRE – Right eyes.

4.5 Discussion

Measurement of a range of biometric factors using new instrumentation has been carried out. Of the biometric factors measured, the AL:CC ratio shows the strongest correlation with magnitude of refractive error. This relationship has been shown to hold over a wide range of refractive error.

No significant difference in central corneal radius was found between late- and early onset myopic eyes, thus confirming the results of McBrien and Millodot (1987b). Myopic eyes (both early- and late-onset) did exhibit steeper central corneal curvature, but this finding was also not significant. Anterior chamber depth was significantly greater in early onset myopic eyes compared to emmetropic eyes, but in contrast to the findings of McBrien and Millodot (1987), not significantly different between emmetropes and late onset myopes. This finding may be as a consequence of the relatively low levels of late onset myopia found (mean –0.81 DS compared to –1.29 DS from the McBrien and Millodot 1987 study). Axial length was seen to be significantly longer in early onset myopic eyes compared to

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emmetropic eyes, as shown by previous studies. The increased axial length in late onset myopes was not significantly different compared to emmetropes. Again, the relatively low magnitudes of late onset myopia may be the limiting factor with regard to statistical significance. It may be the case that the late onset myopes in this study will progress further into myopia, thus revealing a significant difference in axial length compared to the emmetropic group. At the time of data collection, the subject cohort was relatively young (mean age 19.52 years) compared to other studies demonstrating late onset myopia (e.g. McBrien and Adams, 1997, mean age of LOMs 29.3 years). As a result, large degrees of late onset myopia were not envisaged.

Biometric change was measured alongside concurrent monitoring of refractive error in 60 subjects. A subset of 10 subjects from this group developed LOM. Relatively weak correlations were found between change in biometric dimensions and myopia progression. This was due to the relatively small sample size and the short time interval (1 year) over which biometric monitoring was possible. In some subjects, minimal shifts in myopia were observed between biometric measurement sessions. The strongest biometric correlation with refractive error change was axial length. A weaker correlation between ACD and MRE was observed, indicating that the primary structural correlate in LOM is elongation of the vitreous chamber. This finding is in accordance with the reports of McBrien and Adams (1997).

Peripheral astigmatism was found to be greatest temporally, thus confirming the results of Millodot (1981). Similar values of peripheral astigmatism were observed in all refractive groups, as noted by Mutti et al. (2000b) in children. Correlation of relative peripheral mean sphere with central refraction revealed a greater change in the temporal retina of early onset myopic eyes towards a prolate shape than the nasal retina, as observed by Gilmartin et al. (2002a) in Caucasian subjects. A possible cause of this effect may be the agonist-antagonistic forces applied to the globe by the oblique muscles during convergence (Greene, 1991) and the site of muscle insertion in the sclera. It may be the case that in the thinner sclera in a myopic eye is more amenable to distortion as a result of extraocular muscle tension. The direction of muscle action on the globe during convergence could explain the asymmetrical prolate distortion of the globe in myopia, i.e. exaggerated in the temporal side. The shape of the bony orbit may also have an influence on ocular shape in the myopic eye. The orbital cavity is asymmetrical in shape, with the apex directed nasally

in the skull (Snell and Lemp, 1989). This shape may influence ocular growth by restricting globe expansion on the temporal side, thus favouring a more prolate retinal contour on the temporal aspect. It is interesting to note in the recent report by Gilmartin *et al.* (2002a) that temporal/nasal asymmetry was found to be less marked in Taiwanese Chinese eyes compared to Caucasian eyes. Greater relative hypermetropia was observed in the nasal retina of both emmetropic and early onset myopic eyes. This similarity between these refractive groups may be explained by the relatively low magnitude of late onset myopia found in this study.

It has been shown that relative peripheral length measurements made with the *IOLMaster* are a valid and reliable alternative to peripheral refraction measurements. Measurements of retinal shape made with this technique are independent of accommodative effects, and are thus more reliable that autorefraction techniques. Facility exists in the *IOLMaster* to make high resolution measurements of the globe during accommodation and convergence. It has been demonstrated that repeatable retinal contour measurements, and concurrent measurements of axial length whilst carrying out an accommodative task can be made (Appendix 3). Further work is recommended to measure dimensions of the globe at various retinal points during a range of visual tasks. It may be possible to detect differences in ocular dimensions during near visual tasks; these differences may vary between refractive groups (See Chapter 9). Further, it would be interesting to monitor retinal contour change in myopia development, either refractively or biometrically, to chart the change in retinal shape in progressing myopia.

In the young adult cohort examined in this study, no statistically significant variation in IOP was found between refractive error groups. Age of onset of myopic progression, and stability of myopia also failed to have a significant effect on IOP. These findings support the general consensus that IOP has little association with myopia onset (Rosenfield, 1998). Further work is required in this area to evaluate the effects of accommodation and vergence on IOP, and the possibility of differential effects in myopic eyes. It is accepted that IOP falls during the exertion of accommodative effort (Armaly and Rubin, 1961; Mauger *et al.*, 1984). It would be of interest to examine the extent of IOP reduction during accommodation between refractive groups, and between stable and progressing myopes.

Eye volume correlated well with mean refractive error; myopic eyes having greater volume than emmetropic and hypermetropic eyes. Eye volume calculations were based on measurements taken principally in the horizontal plane. Further work in this area may benefit from taking into account additional ocular dimensions in the vertical plane.

In future longitudinal studies of late onset myopia it will be possible to use the *IOLMaster* to measure biometric factors, in particular to calculate AL:CC ratios, in a large sample of initially emmetropic subjects. Large scale data collection will be possible due to the non-invasive nature of the *IOLMaster*, enabling a high subject throughput rate.

CHAPTER 5

OCULOMOTOR INVESTIGATION OF REFRACTIVE ERROR

5.1 Introduction

It has been shown by a number of workers that the oculomotor and accommodation responses are linked (Hung *et al.*, 1996). Accommodation to a near object produces concurrent convergence to maintain bifoveal fixation, and thus a single binocularly fused percept. Features of the oculomotor response have been studied as possible factors in the onset and progression of myopia, but in many cases the results have been equivocal (Goss and Zhai, 1994). Examination of trends in near point heterophoria as a function of absolute refractive error, risk of refractive error development, and refractive stability has not shown consistent relationships (Goss and Rosenfield, 1998). A study investigating oculomotor factors before the onset of myopia in adolescents (Drobe and de Saint-André, 1995) found that emmetropic subjects that later became myopic exhibited a generally more convergent (esophoric) ocular posture at near, less hypermetropia and greater lag of accommodation at near than emmetropic subjects that remained emmetropic. Goss (1991) identified near point ortho- or esophoria as a significant risk factor for myopia development. In contrast, Goss and Jackson (1996a) defined near heterophoria of 3Δ exo- to 1Δ eso- as risk factors.

McBrien and Millodot (1986b) found a significant positive correlation between accommodative response gradient and refractive error for the stimulus range 0 to 5 D. Accommodative response gradient was lowest in late onset myopes, followed by early onset myopes, emmetropes and hypermetropes. The authors concluded that significant differences were present in the oculomotor response between refractive groups. It was suggested that variation in autonomic control of accommodation between refractive groups may be responsible for these observations. In children, Mutti *et al.* (2002) have shown that lag of accommodation to near tasks increases following the onset of juvenile myopia. Evidence from this longitudinal study (Orinda Longitudinal Study of Myopia) has shown, however, that lag of accommodation does not differ significantly between stable emmetropes and pre-myopic emmetropes. This work suggests that increased lag of accommodation occurs as a result of myopia, rather than acting as a pre-cursor to myopia. Additional work by McBrien and Millodot (1986a) found amplitude of accommodation to be highest in late onset myopes and lowest in hyperopes from a cohort of age matched

subjects. Observed differences in amplitude of accommodation were statistically significant.

Recently, Mutti *et al.* (2000a) assessed the effect of response AC/A ratio as a risk factor in myopia development. The subject group consisted of 828 children, including 726 non-myopes, taken from the Orinda Longitudinal Study of Myopia. Measurements of response AC/A ratio, refractive error and ocular biometry were made. Significantly higher response AC/A ratios were found in myopic subjects (age adjusted group means: myopes 6.39 Δ/D, emmetropes 3.94 Δ/D, hypermetropes 3.40 Δ/D). No significant difference in stimulus AC/A ratio was observed between refractive groups. Additionally, a high response AC/A ratio (>5.84 Δ/D) in non-myopic individuals increased the risk of subsequent myopia development. It was proposed that the increased response AC/A ratio in myopes resulted from a state of pseudocycloplegia; this being induced by mechanical factors affecting the crystalline lens and choroid. Reduction in the accommodative response due to these restricting factors would result in a requirement for greater accommodative input to maintain clear vision at near. Accommodative convergence would increase as a result of this higher level of accommodative effort. Although increased AC/A ratio was clearly associated with myopia in this study, the value of this measurement as a predictor of myopia may be limitied, since myopia onset occurred rapidly following elevation of AC/A ratio. Gwiazda *et al.* (1999) also noted higher response AC/A ratio in myopic children. In both of the above studies it was suggested that children exhibiting high AC/A ratio or esophoria at near must accommodate less during near vision in order to reduce convergence and maintain single binocular vision. This reduction in accommodative response may induce hyperopic retinal blur, which, based on evidence from animal work, may encourage the development of myopia.

In adult subjects (college students), a study by Jiang (1995) has identified elevated AC/A ratio as a predictor of late onset myopia. Response AC/A ratio was found to be significantly higher in progressing myopes compared to stable emmetropes. During the course of this longitudinal study, 6 subjects from the 'initially emmetropic' group (N=33) developed LOM. Response AC/A ratio was found to be higher in the subjects subsequently developing LOM compared with subjects remaining emmetropic.

The purpose of the present study was to investigate features of the oculomotor system in a cohort of similar aged young adults. Trends in oculomotor profile with regard to refractive error, particularly differences between early onset and late onset myopic subjects, were examined. Further, cross-correlation with autonomic profile data from Chapter 3 is implemented to explore trends between sympathetic inhibitory facility and overall oculomotor function.

5.2 Subjects

All subjects were undergraduate optometry students at Aston University. The cohort of subjects consisted of participants in the longitudinal study of refractive error with concurrent autonomic profiling (40 subjects, see Chapter 3 for details) plus 20 additional subjects to form a cross-sectional study (N = 60). Informed consent was obtained from all subjects prior to commencement of experimental work.

5.3 Methods

All subjects were screened for abnormal ocular conditions by slit lamp examination and direct ophthalmoscopy. A full distance (6 metre) binocular subjective refraction was carried out to determine best spectacle refraction. The spherical end point was defined as the most positive or least negative sphere giving best visual acuity.

5.3.1 Accommodative convergence : Accommodation (AC/A ratio)

AC/A ratio was measured in all subjects by the gradient method using negative lenses (-3.00 DS) and Maddox wing test. Near heterophoria was measured with the subjects habitual distance correction (if used) in place. Accommodation was stimulated by the insertion of a pair of –3.00 DS lenses into the trial lens holders on the Maddox wing. The subject was instructed to keep the tangent scale of the Maddox wing clear and report the displacement of the arrow target. AC/A ratio was taken as the difference in heterophoria between the two accommodative states divided the difference in accommodative stimulus. It has been shown that measuring gradient AC/A ratio with positive or negative spherical lenses produces similar results (Rosenfield and Baker, 1998).

5.3.2 Amplitude of accommodation

Monocular (fellow eye occluded) measurements of amplitude of accommodation were carried out using an RAF rule. Distance refractive correction was fitted to the subject in a

trial frame. The subject was instructed to observe the N5 text on the RAF rule target and keep it clear. Viewing distance of the target was reduced until the subject reported blur. Target distance was reduced further until the text was illegible. Target distance was then increased until the text was clear. This dioptric distance was taken as the amplitude of accommodation. Target luminance levels during measurement were around 40 cd/m^2.

5.3.3 Lag of accommodation

The distance refractive error of the subject was corrected using a disposable soft contact lens (*1 Day Acuvue, Johnson and Johnson*). Non-lens wearers had a full anterior segment examination prior to contact lens fitting. Established contact lens wearers were allowed 20 minutes settling time following lens fitting to allow adequate adaptation and stable vision. Novice lens wearers were given additional adaptation time, up to 40 minutes in one case. The subject observed a detailed distance fixation target (Snellen letter chart at 6 metres via a folded optical arrangement). Six autorefractor readings were taken using the Shin-Nippon SRW-5000. Distance aurorefractor readings were taken to identify any over- or under-correction by the contact lenses, which was recorded as residual refractive error. The apparatus was rearranged to allow the subject to fixate to a Maltese cross target located within a Badal lens system, on the visual axis. Seidemann and Schaeffel (2002b) have demonstrated that monocular measurement along the visual axis provides higher estimates of accommodative lag than binocular measurements with the target presented along the midline between the eyes. The target distance within the Badal system provided a 3 D stimulus to accommodation. Six autorefractor readings were taken. The average mean sphere reading of the six measurements was taken as the mean accommodation response to the near stimulus. The residual refractive error was subtracted from the mean near accommodation response to give the corrected near response. The difference between the corrected near response and the accommodative demand (i.e. 3 D) was taken as the lag of accommodation.

5.3.4 Heterophoria at distance and near

Distance horizontal heterophoria was carried out by Maddox rod. Best distance refractive correction was set up in a trial frame and fitted to the subject. A red Maddox rod was placed before the right eye. The spotlight on a distance (6 metre) test chart was used as the target. Room lights were dimmed to give a background luminance of 5 cd/m^2. Trial case prisms were placed over the Maddox rod to align subjectively the spot and line images.

Minimum prism power required to align the images was taken as a measure of horizontal distance heterophoria.

Near horizontal heterophoria was measured using the Maddox wing test. Distance refractive correction was fitted to the subject in a trial frame. The subject was asked to report the position of the white arrow with respect to the tangent scale. A period of settling time was allowed to achieve a stable measure of heterophoria.

5.3.5 Tonic accommodation

Baseline distance refractive error was measured in normal room lighting conditions (50 cd/m^2). Subjects fixated a Snellen chart at 6 metres while 6 autorefractor readings were taken on the right eye (Shin-Nippon SRW-5000). Room lights were then extinguished. The subject sat in total darkness for 5 minutes to allow accommodation to regress to the baseline tonic level. A further 6 autorefractor readings were taken. Mean spherical refractive error (MRE) was calculated for distance and dark room conditions. Tonic accommodation (TA) was calculated by subtracting the distance MRE from the dark room MRE.

5.4 Results

Results for 58 subjects are presented in terms of the relative distribution of values for each parameter between refractive groups. Data from 2 hyperopic subjects was not included in the analyses. Results from 40 subjects in the longitudinal study of refractive error development were used to determine oculomotor variation in terms of refractive stability (i.e. trends between stable myopes and progressing myopes). Progressing myopes consisted of all myopes demonstrating a significant myopic progression (>-0.50 DS increase in mean spherical error) during the course of the longitudinal study. The 'progressing' group included early onset and late onset myopes.

5.4.1 Accommodative convergence : Accommodation (AC/A ratio)

Table 5.1 shows group mean AC/A ratio (± SD) as a function of refractive error group. Table 5.2 Shows AC/A ration as a function of refractive stability.

	EMM	EOM	LOM
AC/A ratio	2.89 ± 1.16	2.81 ± 1.24	3.23 ± 0.89
Number of subjects (N)	28	19	11

Table 5.1. AC/A ratio as a function of refractive group.

ANOVA and Scheffe's *post-hoc* test revealed no significant difference in AC/A ratio between refractive groups (EMM *vs* EOM, $p = 0.99$, EMM *vs* LOM, $p = 0.73$, EOM *vs* LOM, $p = 0.72$).

	Stable refraction	Progressing myopes
AC/A ratio	2.92 ± 1.15	2.92 ± 0.91
N	38	20

Table 5.2. AC/A ratio as a function of refractive stability.

(ANOVA: $p = 0.99$)

5.4.2 Amplitude of accommodation

Table 5.3 shows group averaged (± SD) amplitudes of accommodation for 3 refractive groups.

	EMM	EOM	LOM
Amplitude of accommodation (D)	9.50 ± 1.16	9.74 ± 1.11	9.32 ± 1.10
N	28	19	11

Table 5.3. Amplitude of accommodation as a function of refractive group

ANOVA and Scheffe's *post-hoc* test revealed no significant difference in amplitude of accommodation between the three refractive groups (EMM *vs* EOM, $p = 0.49$, EMM *vs* LOM, $p = 0.66$, EOM *vs* LOM, $p = 0.33$). Similarly, no significant difference in amplitude of accommodation was observed between subjects with stable refractive error or progressing myopia (mean amplitudes: 9.50 ± 1.17 D stable refraction; 9.63 ± 1.01 progressing myopia. $p = 0.69$)

5.4.3 Lag of accommodation

Group averaged lag of accommodation to a 3 D task ± SD are shown in table 5.4.

	EMM	EOM	LOM
Lag of accommodation (D)	0.61 ± 0.47	0.82 ± 0.25	0.82 ± 0.42
N	28	19	11

Table 5.4. Lag of accommodation as a function of refractive group.

ANOVA and Scheffe's *post-hoc* test revealed no significant difference in lag of accommodation between the three refractive groups (EMM *vs* EOM, $p = 0.47$, EMM *vs* LOM, $p = 0.45$, EOM *vs* LOM, $p = >0.99$).

	Stable refraction	Progressing myopes
Lag of accommodation (D)	0.56 ± 0.40	0.71 ± 0.38
N	38	20

Table 5.5. Lag of accommodation as a function of refractive stability.
(ANOVA: $p = 0.19$)

5.4.4 Heterophoria at distance and near

	EMM	EOM	LOM
Distance heterophoria (Δ)	1.70 ± 1.84 eso	2.26 ± 2.08 eso	1.36 ± 2.80 eso
Near heterophoria (Δ)	0.93 ± 2.32 exo	0.26 ± 3.54 eso	0.55 ± 3.56 exo
N	28	19	11

Table 5.6. Horizontal heterophoria at distance and near as a function of refractive group.

ANOVA and Scheffe's *post-hoc* test revealed no significant difference in heterophoria at distance or near between the three refractive groups (Distance heterophoria: EMM *vs* EOM, $p = 0.68$, EMM *vs* LOM, $p = 0.90$, EOM *vs* LOM, $p = 0.54$. Near heterophoria: EMM *vs* EOM, $p = 0.43$, EMM *vs* LOM, $p = 0.94$, EOM *vs* LOM, $p = 0.78$).

Table 5.7 shows group mean horizontal heterophoria at distance and near as a function of refractive stability.

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	Stable refraction	*Progressing myopes*
Distance heterophoria (Δ)	1.95 ± 1.93 eso	1.60 ± 2.46 eso
Near heterophoria (Δ)	0.65 ± 2.76 exo	0.10 ± 3.48 exo
N	38	20

Table 5.7. Horizontal heterophoria at distance and near as a function of refractive stability.

(ANOVA: distance heterophoria, $p = 0.56$, near heterophoria, $p = 0.52$)

5.4.5 Tonic accommodation

Figure 5.1 shows group mean dark focus according to refractive error category in the longitudinal group. Error bars indicate 1 standard deviation. The mean accommodation response in darkness was lower in myopes than emmetropes, but these differences were not statistically significant (ANOVA and Scheffe's *post-hoc* test: EMM *vs* EOM, $p = 0.41$; EMM *vs* LOM, $p = 0.21$; EOM *vs* LOM, $p = 0.94$). Table 5.8 shows mean (± 1 standard deviation) dark focus values for EMMs, EOMs and LOMs.

Table 5.9 shows group mean values of dark focus for subjects with stable refraction and progressing myopes.
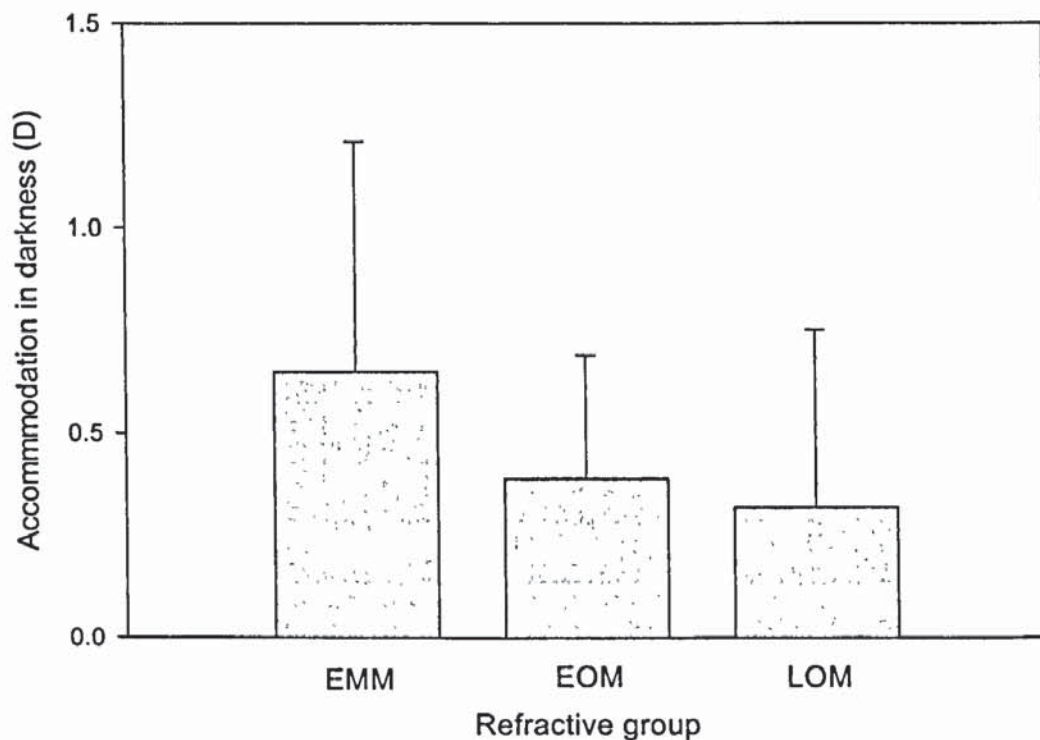
Figure 5.1. Mean dark focus as a function of refractive group.

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	EMM	EOM	LOM
Mean dark focus (D)	0.65 ± 0.56	0.39 ± 0.30	0.32 ± 0.43
N	28	19	11

Table 5.8. Dark focus as a function of refractive group.

	Stable refraction	Progressing myopes
Mean dark focus (D)	0.62 ± 0.47	0.46 ± 0.43
N	38	20

Table 5.9. Dark focus as a function of refractive stability.

(ANOVA: $p = 0.22$)

5.4.6 Cross-correlation between oculomotor factors and ANS profile

Autonomic profile results from Chapter 3 were used to identify subjects exhibiting the features of sympathetic inhibition of accommodation. Oculomotor data were categorized according to presence or absence of sympathetic facility. Table 5.10 shows mean oculomotor function results according to autonomic profile.

	Sympathetic facility	Sympathetic deficit	Significance (p) of difference
Distance heterophoria (Δ) ± SD	3.69 ± 2.57 eso	3.55 ± 2.41 eso	0.84
Near Heterophoria (Δ)	0.31 ± 3.59 exo	0.27 ± 3.48 exo	0.89
AC/A ratio	2.92 ± 1.31	2.95 ± 0.93	0.93
Amplitude of accommodation (D)	9.34 ± 1.12	9.67 ± 1.11	0.32
Near point of convergence (cm)	7.56 ± 1.55	7.36 ± 1.38	0.63
Lag of accommodation (D)	0.50 ± 0.29	0.65 ± 0.41	0.19
Dark focus (D)	0.56 ± 0.31	0.57 ± 0.49	0.98
N	15	43	-

Table 5.10. Cross-correlation between oculomotor function and autonomic profile.

5.5 Discussion

Although late onset myopes exhibited highest AC/A ratios (group mean values), the variation in stimulus AC/A ratio was not statistically significant between refractive groups. It must be noted that Mutti *et al.* (2000a) also failed to demonstrate a significant difference in stimulus AC/A between refractive groups, but found an elevated response AC/A ratio in myopic children. Further work is recommended in young adult subjects to examine response AC/A ratio between early- and late-onset myopes, and emmetropes.

Lag of accommodation for a near task was higher in myopes than emmetropes, but again failed to reach statistical significance. Average lag of accommodation was similar between early onset and late onset myopes. Larger variation in lag was observed between subjects with stable refractions and progressing myopes, with greater lag being evident in the progressing group. Again, statistical significance was not achieved. Evidence of a reduced accommodation response in progressing myopes supports the recent findings of Abbott *et al.* (1998). Failure to show statistical significance in this aspect of the study is most likely due to an inadequate sample size in each refractive group. Variation in measurements of lag of accommodation was greater than expected following a review of previous studies; consequently, an underestimation of sample size occurred. Appling the sample size calculations given by Armstrong *et al.* (2000) to this data shows that 52 subjects per group would be required to achieve statistical significance.

It appears from the trends identified in this work that in adults the closed-loop accommodation response is different in progressing myopes compared to emmetropes and stable myopes. Similar conclusions have been deduced from work in children (Gwiazda *et al.*, 1993a). It is interesting that accommodation responses are similar between emmetropes and stable myopes (Abbott *et al.*, 1998), perhaps indicating that the accuracy of the accommodation response is degraded during myopia, and subsequently improves once myopia has stabilized. Gwiazda *et al.* (1995) noted a reduction in slope of the accommodative stimulus/response curve and higher lag of accommodation at near in progressing myopic children; accommodative demand being varied by a series of negative spherical lenses. Once myopia had stabilized, slope of the accommodative stimulus/response function increased and near lags of accommodation reduced. A longitudinal study of accommodative stimulus/response function during progressing and

stable phases of young adult myopia development is required to confirm whether this relationship exists in older subjects.

Another feature of the accommodation response yet to be investigated is the effect of uncorrected refractive error on lag of accommodation. It may be the case that chronic retinal blur experienced while uncorrected affects the ability of the accommodative system to respond to blur as a retinotopic cue during near vision once corrective lenses have been prescribed, i.e. the newly corrected myope is more tolerant to blur, and thus demonstrates greater lags of accommodation at near. This increased lag of accommodation will be manifest as hyperopic defocus which may encourage an accelerated rate of myopia progression. It would be interesting to compare stimulus/response functions in subjects corrected soon after the onset of myopia with subjects corrected later in the progression period. It may be possible to deduce the amount of time spent uncorrected from the power of the first spectacle prescription issued.

No statistically significant difference in tonic accommodation (dark focus) was observed between emmetropes, early onset myopes and late onset myopes. Mean values of tonic accommodation were, however, highest in emmetropes and lowest in late onset myopes, thus supporting the findings of Rosenfield and Gilmartin (1987) and Jiang (1995). Cross-correlation between dark focus and presence of sympathetic facility showed that access to sympathetic inhibition of accommodation does not significantly influence tonic accommodation. This work supports the findings of Gilmartin and Hogan (1985b), i.e. variations in tonic accommodation between individuals are related to the parasympathetic branch of the ANS.

Accommodative responses to near vision tasks have been assessed under controlled laboratory conditions. In the real world situation, the near vision task may be somewhat different to the laboratory task in terms of task luminance, spectral output of task illumination system, contrast and size of textual material. Consequently, the everyday near vision tasks which are carried out places the visual system under different stresses to those simulated in the laboratory. Also, the pattern of near work activity, i.e. duration of near work exposure and frequency of breaks, may also vary between individuals. From this it can be seen that visual responses to near vision tasks in the real world environment should be examined. Remote photorefraction systems have been shown to give valid and

repeatable measurements of refractive state, accommodation response and pupil size (Wolffsohn *et al.*, 2002). Adaptation of such a system may facilitate the measurement of accommodation and vergence during the use of visual display units or when reading. Use of such apparatus may provide a more naturalistic profile of ocular responses to the near vision task.

Work in this chapter has been carried out on university students. It was assumed that these subjects were exposed to considerable amounts of nearwork, but no attempt to quantify patterns of nearwork was made. It is feasible, therefore, that some subjects were exposed to greater levels of nearwork load than others. For future studies of this type, a detailed record of nearwork activity carried out by the subject should be collated. A diary format may be used for the collection of this data. The addition of this feature to the experimental schedule will allow an approximation of the amount of time spent on near visual tasks. The Study of Progression of Adult Nearsightedness (SPAN) is currently using a paging and automatic telephone survey system to monitor subject activity at random intervals. From this it is possible to estimate daily nearwork activity of experimental participants (Bullimore *et al.*, 2002).

Cross-correlation between profile autonomic innervation of ciliary muscle and oculomotor function has shown little variation when subjects exhibiting sympathetic facility were compared with subjects with sympathetic deficit. Subjects with sympathetic facility had smaller lags of accommodation at near compared to subjects with sympathetic deficit, but this difference was not statistically significant.

It is concluded that no statistically significant effects can be identified in various aspects of the oculomotor response to differentiate between emmetropes, early onset myopes and late onset myopes. Trends have been identified from the data to suggest that progressing myopes exhibit less accurate accommodation responses, as shown in previous studies, but failed to hold following statistical testing as a result of small sample size. Larger cross sectional studies of this nature may reveal more definitive results due to increased statistical power.

CHAPTER 6

THE EFFECT OF SUSTAINED NEAR VISION AND β-ADRENOCEPTOR ANTAGONISM ON THE DYNAMIC ACCOMMODATION RESPONSE

6.1 Introduction

The accommodation response to a sinusoidally oscillating target can be divided into two components. The inward movement of the target produces an increasing retinotopic cue to accommodation, leading to an increase in parasympathetic activity and thus an increase in the accommodative response. This response is an active contraction of ciliary smooth muscle. The outward movement of the target causes a reduction in the accommodative demand, a reduction in parasympathetic activity, and consequently a reduction in the accommodation response. This response is a more passive relaxation of ciliary smooth muscle. It has been shown that accommodative response times to inward stepwise changes in accommodative demand (i.e. increases in demand) are faster than response times to outward stepwise changes in the stimulus (Culhane and Winn, 1997).

Previous investigation has shown that the gain and phase lag of dynamic accommodative responses to sinusoidally oscillating stimuli degrade as temporal frequency (oscillation rate) increases (Kruger and Pola, 1986). This study also examined the effects of blur, chromatic aberration and target size on the accuracy of dynamic accommodation responses. Combining a target size cue, or chromatic aberration cue to the blur cue improved the accuracy of the dynamic response to a moving stimulus.

Winn and Culhane (1998) have shown that topical administration of the non-selective β adrenoceptor antagonist timolol maleate reduces the gain of dynamic accommodative responses to sinusoidally oscillating stimuli under closed-loop conditions. This effect was observed at temporal frequencies of 0.3 Hz or less. Accommodative gain at higher frequencies was similar under timolol, and the control conditions of betaxolol hydrochloride, and normal saline. This work supported the findings of Strang (1995) using a similar experimental protocol.

The purpose of this work was to evaluate the effect of antagonism of β_2 receptors in ciliary smooth muscle on the closed loop dynamic accommodation response over a range of temporal frequencies, and to attempt to reproduce the results of Winn and Culhane (1998)

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in a larger sample size. Additionally, the effect of sustained static accommodative effort on subsequent dynamic accommodation responses over a range of temporal frequencies was to be evaluated. It is proposed that a period of sustained near-vision prior to a dynamic tracking task will enhance the gain and phase characteristics of the accommodative response at low and mid temporal frequencies; this response being mediated by the slow sympathetic branch of the autonomic nervous system (ANS). It is further proposed that prior treatment with the non-selective β adrenoceptor antagonist timolol maleate should abolish the effect of pre-adaptation at low and mid temporal frequencies. Potential also exists for further cross-correlation with baseline autonomic profile of ciliary muscle innervation. It will be interesting to examine the possibility of association between autonomic profile and adaptation effects of the dynamic accommodative response.

6.2 Subjects

All subjects (N = 10) were undergraduate optometry students at Aston University. The subjects selected for this experimental protocol were a subset of the cohort used in Chapter 3. As the experimental procedures utilized were quite lengthy and required long-term concentration, subject observation skill was used as one of the selection criteria. The added benefit of using a subset of the Chapter 3 subjects in this experiment is the addition of baseline autonomic profile information to the dynamic accommodation characteristics, thus allowing cross-correlation between two separate but related experiments. Mean age of subjects was 22.5 ± 2.8 years (range 21 to 30 years). The cohort consisted of 4 emmetropes, 2 early onset myopes and 4 late onset myopes. Subjects had normal visual acuity, correctable to at least 6/6 and were free of abnormal ocular conditions. All experimental procedures were explained, and subjects gave their informed consent prior to participation in the study. Appropriate exclusion criteria were employed owing to the use of β blocker eye drops in the experimental design, and the possible adverse reactions of certain individuals to these agents. Exclusion criteria are listed in Appendix 6.

6.3 Methods

6.3.1 Apparatus

The experimental rig for this study consisted of the following main components:

- Shin-Nippon SRW-5000 autorefractor.
- Pentium 500 PC, LabVIEW software suite and 'Dynamic 13' program. PC link to autorefractor to enable continuous recording of accommodation at 42 Hz.
- National Instruments BNC 2090 digital and analogue signal interface rack (accommodative stimulus monitoring) and PCI-1408 data acquisition card (image capture from Shin-Nippon SRW-5000).
- Lloyd instruments PL3 X-Y plotter. Maltese cross target fitted to plotter carriage to act as dynamic target. +5 DS Badal lens fitted to plotter housing.
- Thandar TG501 function generator. The 50 Ohm output of this device was used to drive the X-Y plotter.

Figure 6.1 shows the layout of the apparatus in side view. Figure 6.2 shows the arrangement of optical component within the experimental rig. A standard +5 DS Badal optical system was employed. The Badal lens was positioned 20 cm from the subject's eye. The distance x (in figure 6.2) was varied to produce the required stimulus to accommodation.
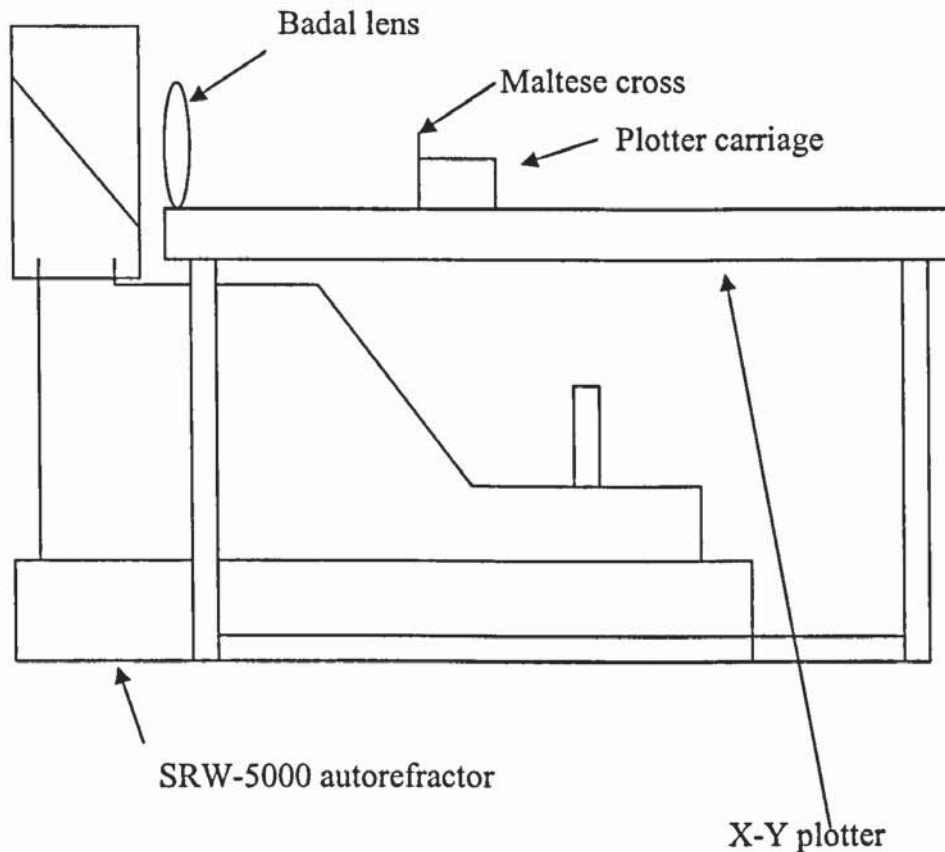
Figure 6.1. Layout of apparatus for measurement of dynamic accommodation.
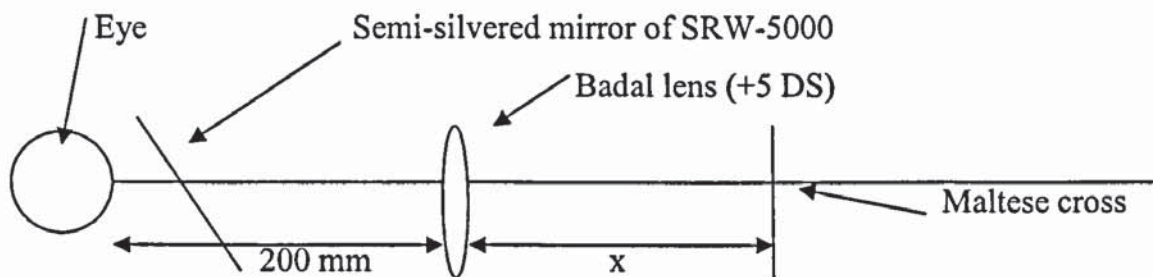
Figure 6.2. Arrangement of optical components for measurement of dynamic accommodation.

The function generator signal was used to drive the x-axis of the X-Z plotter, i.e. to control movement of the plotter carriage along the visual axis. The function generator was set to produce a symmetrical sinusoidal output waveform. The amplitude and DC offset of the function generator were adjusted such that a range of accommodative stimulus between 2 and 4 D was produced within the Badal system. The position of rest of the system (with function generator in standby mode) was set to the mid-point of the stimulus range, i.e. 3 D stimulus to accommodation.

The signal from the function generator was tapped and sent to an analogue input channel on the National Instruments BNC 2090 interface rack. This connection allows the Dynamic 13 LabVIEW program to monitor in real time the position of the X-Y plotter carriage during the experiment. This feature allowed simultaneous recording of the subject's accommodative response to the dynamic stimulus.

All subjects sat for a training session prior to the actual experimental trials. No drugs were instilled for the training sessions. Each subject was allowed to track the accommodative target at a range of temporal frequencies in order to familiarize the subject with the task. Subject performance, particularly fixation stability, was found to improve after training, thus improving the overall quality of data.

For each trial the subject was asked to track monocularly (fellow eye patched) the Maltese cross target. Subjects were instructed to "keep the target clear at all times" (Stark and Atchison, 1994). Any refractive error was fully corrected using an ultra-thin spherical soft contact lens (*1-Day Acuvue, Johnson and Johnson*), which was fitted following a slit lamp examination of the anterior eye. The frequency of the sinusoidal oscillation of the Maltese cross target was varied using the function generator. Frequencies of 0.05, 0.1, 0.2, 0.3, 0.4, 0.5 and 0.6 Hz were presented in separate randomised trials. Trials were conducted both with, and without pre-adaptation at the 3 D stimulus level. For trials with pre-adaptation the subject was instructed to observe the Maltese cross target at the stationary 3 D position for 3 minutes before commencement of the sinusoidal oscillations. This period of pre-adaptation enhances, if present, the slow sympathetic inhibitory branch of accommodative control in susceptible individuals (Gilmartin and Bullimore, 1987). For trials without pre-adaptation the target oscillations commenced at the start of the trial. A period of rest of 5 minutes was allowed between trials to allow the dissipation of transient accommodative adaptation effects.

The trials (both with and without pre-adaptation) were carried out under the following pharmacological treatments:

- One drop (volume approximately 26 μl; Hopkins and Pearson, 1998) of proxymetacaine hydrochloride (0.5%) and one drop of saline (0.9%). Baseline measurements.

- One drop of proxymetacaine hydrochloride (0.5%) and one drop of timolol maleate (0.5%). Non-selective β-adrenoceptor antagonist to block sympathetic inhibitory branch of accommodative control.

- One drop of proxymetacaine hydrochloride (0.5%) and two drops of betaxolol hydrochloride (0.5%). β_1 antagonist to act as intraocular pressure control against the timolol maleate trial.

The topical corneal anaesthetic proxymetacaine hydrochloride was instilled prior to the adrenergic agents to minimize reflex blinking and lacrimation, and to aid the passage of the drug across the cornea.

A 3-day (minimum) wash out period was allowed between the different pharmacological treatments to prevent data contamination due to the interaction of agents.

6.4 Results

For each trial, the accommodative stimulus and response data were plotted graphically in *Microsoft Excel* against time. The accommodative response was filtered for blinks by removing data points lying outside a 0 to 6 D range, and smoothed by averaging 7 consecutive data points (approximately 0.16 seconds) to remove measurement system noise and aid data analysis. The graphical package within *Excel* allows the x-y coordinates of any point on a curve to be identified by placing the cursor on the curve at the desired point. For each run of sinusoidal oscillations, six adjacent stimulus/response sine wave cycles were selected. The maxima and minima of stimulus and response functions were identified using the x-y coordinate facility. From this it was possible to calculate the mean accommodative response gain and phase lag for six adjacent cycles. Accommodative gain was calculated by dividing the mean amplitude of the accommodation response waveform by the mean amplitude of the stimulus waveform. Waveform amplitude was derived from the difference between y coordinate values for sinewave maxima and minima. Phase lag was derived from the difference in x coordinate values between adjacent stimulus maxima (or minima) and response maxima (or minima). Mean response phase lag for 6 complete sinusoidal cycles was expressed in degrees, where a whole sinusoidal cycle equals 360°. This technique for phase lag interpretation has been used in previous studies of dynamic accommodation (Kruger and Pola, 1986).

To avoid bias in the interpretation of the results, a coding system for continuous recording plots was employed. Following each recording session, dynamic plots were saved as a file within *Microsoft Excel* with a numeric code as the filename. The filename was a unique, but otherwise meaningless number. A key file was created to match the filename to the subject and experimental conditions utilized for each experimental trial. The key file was kept separate from the main data set. Once the accommodative gain and phase had been calculated for each trial, the code was broken to reveal the pharmacological and temporal states applicable to each trial.

Figures 6.3 to 6.5 show example stimulus/response profiles for sinusoidal oscillating target (2 to 4 D) for subject SM. Temporal frequencies of 0.05, 0.2 and 0.5 Hz are shown. Accommodative responses to lower temporal frequencies are characterised by a high gain profile with small phase lag. A small overall lag of accommodation can also be observed (figure 6.3). As temporal frequency is increased the accuracy of the dynamic accommodative response degrades. Figures 6.4 and 6.5 show 0.2 Hz and 0.5 Hz unadapted plots. Responses to increased temporal frequency are characterised by a reduction in accommodative response gain and an increase in phase lag.
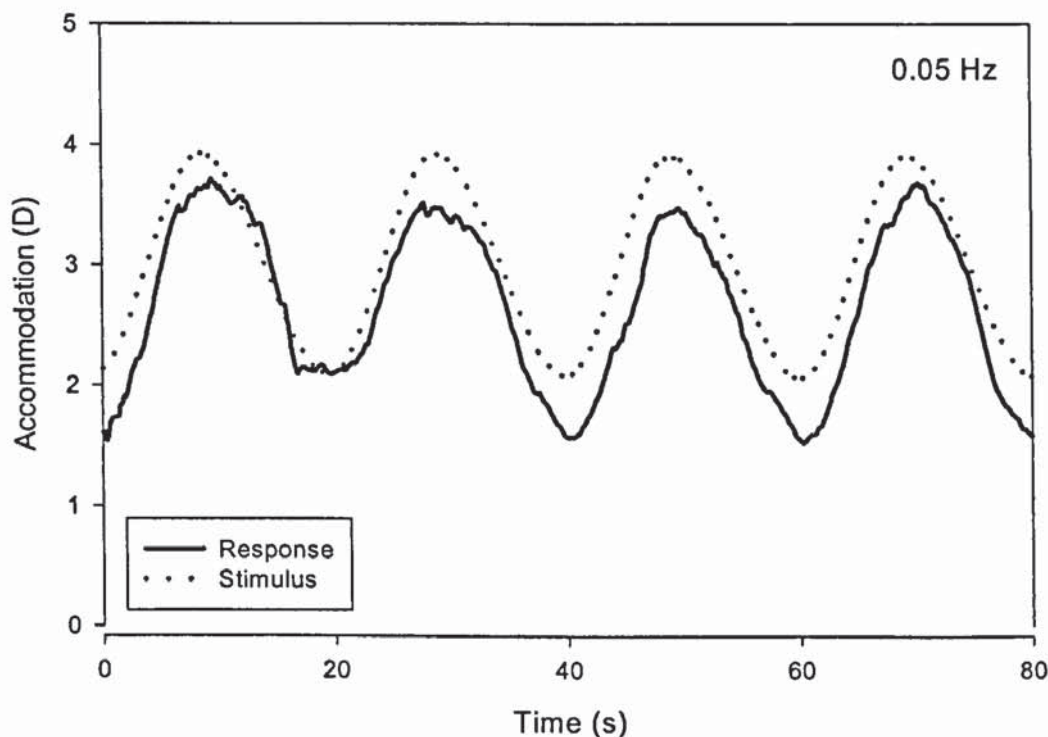
Figure 6.3. Dynamic stimulus/response plot (unadapted) at 0.05 Hz. Subject SM.
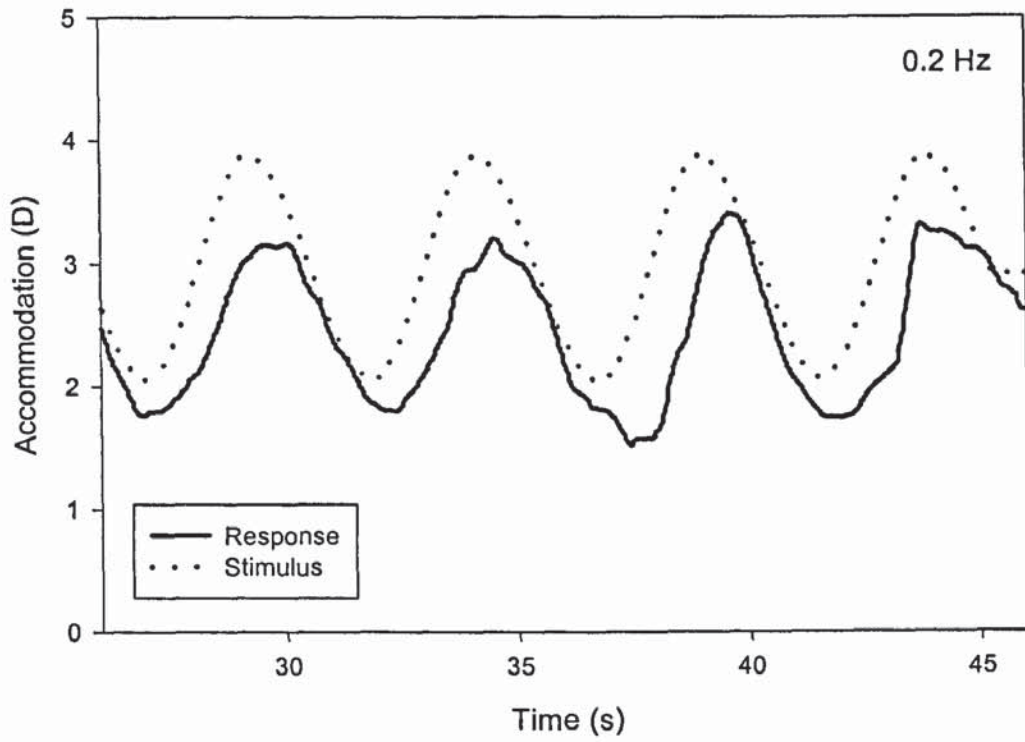
Figure 6.4. Dynamic stimulus/response plot (unadapted) at 0.2 Hz. Subject SM.
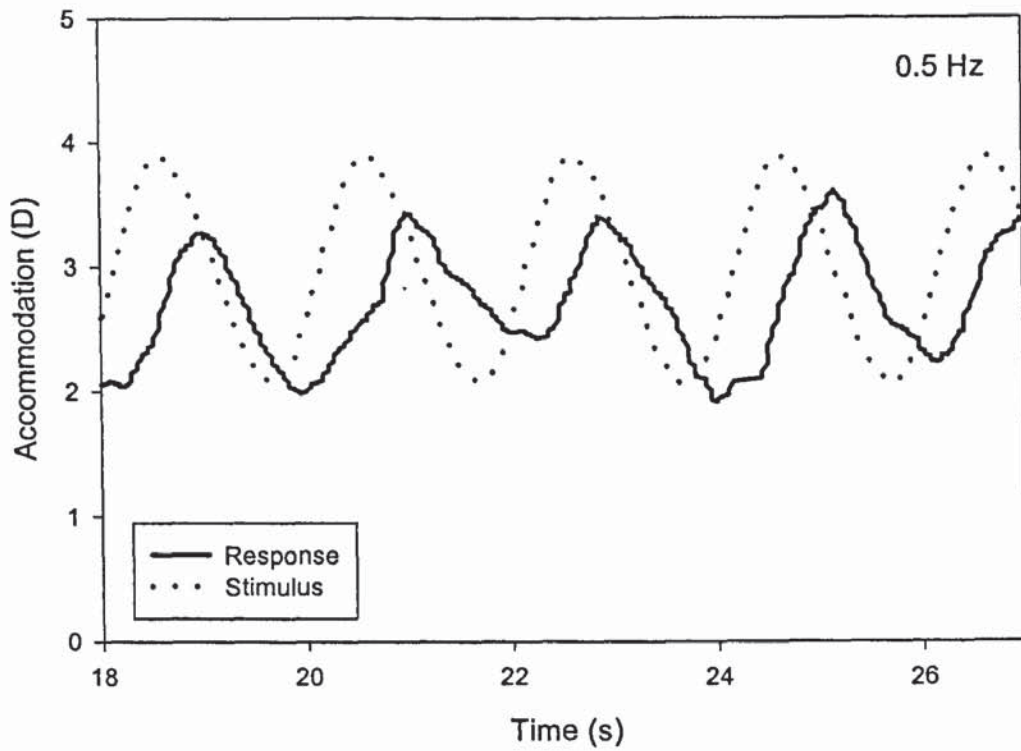
Figure 6.5. Dynamic stimulus/response plot (unadapted) at 0.5 Hz. Subject SM.

6.4.1 Accommodative gain

Results are presented graphically in bode plots. Group mean accommodative gain plots have linear axes for gain and logarithmic axes for temporal frequency. Accommodative gain plots for individual subjects can be found in appendix 9.

Figure 6.6 represents group mean accommodative gain values against temporal frequency for all 10 subjects in the experimental cohort. Two plots, Saline 1 and Saline 2, represent responses before and after the 3-minute adaptation task respectively. Error bars represent 1 standard deviation of the averaged data points. Accommodative gain decreases as the temporal frequency of target oscillation increases. A factorial ANOVA revealed statistically significant (p <0.01) reduction in accommodative gain due to the increase in temporal frequency. *Post-hoc* testing showed that mean accommodative gain values were significantly different at each temporal frequency (p <0.01) except for 0.4 Hz and 0.5 Hz trials where the difference in accommodative gain just failed to reach significance (p = 0.07). Figures 6.7 and 6.8 show group mean accommodative gain plots against temporal frequency under timolol and betaxolol conditions respectively.

Mean group accommodative gain for saline, timolol and betaxolol conditions without the 3-minute adaptive task are compared in figure 6.9.
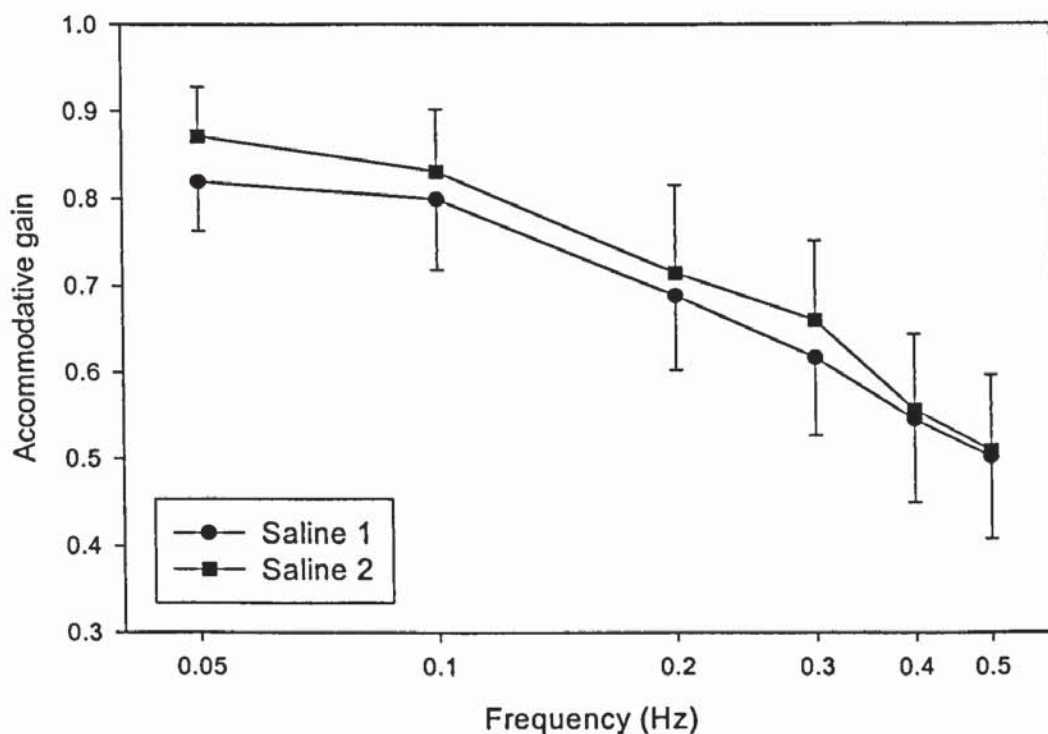
Figure 6.6. Mean accommodative gain results – saline 1 vs saline 2.
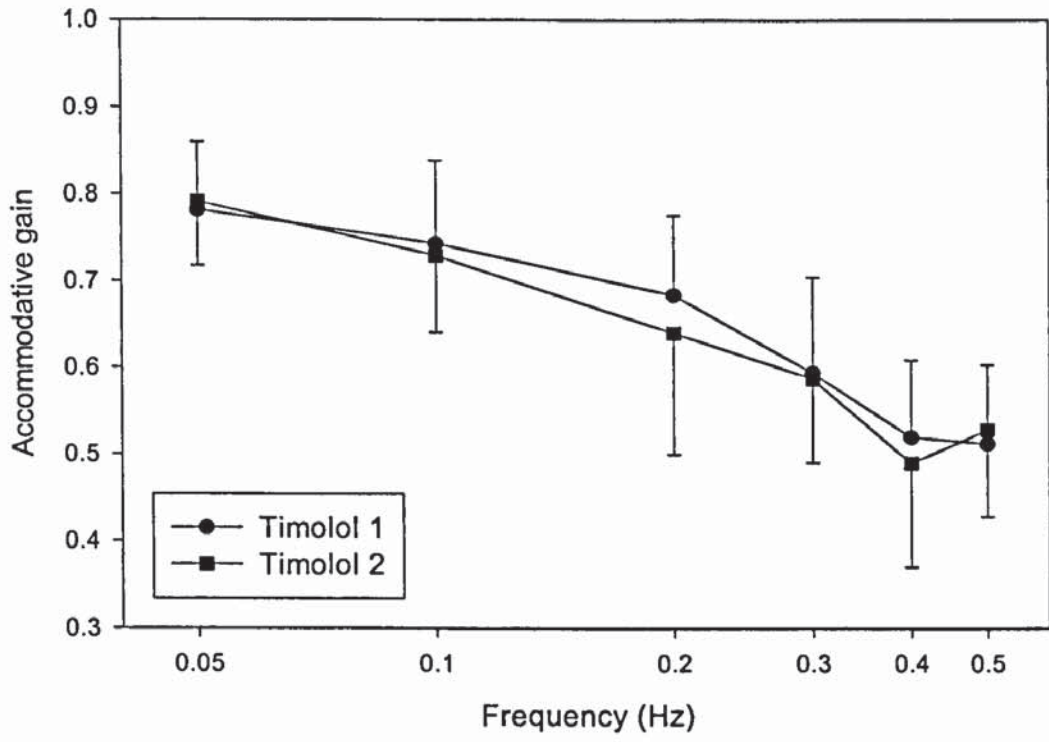
Figure 6.7. Mean accommodative gain results – timolol 1 vs timolol 2.
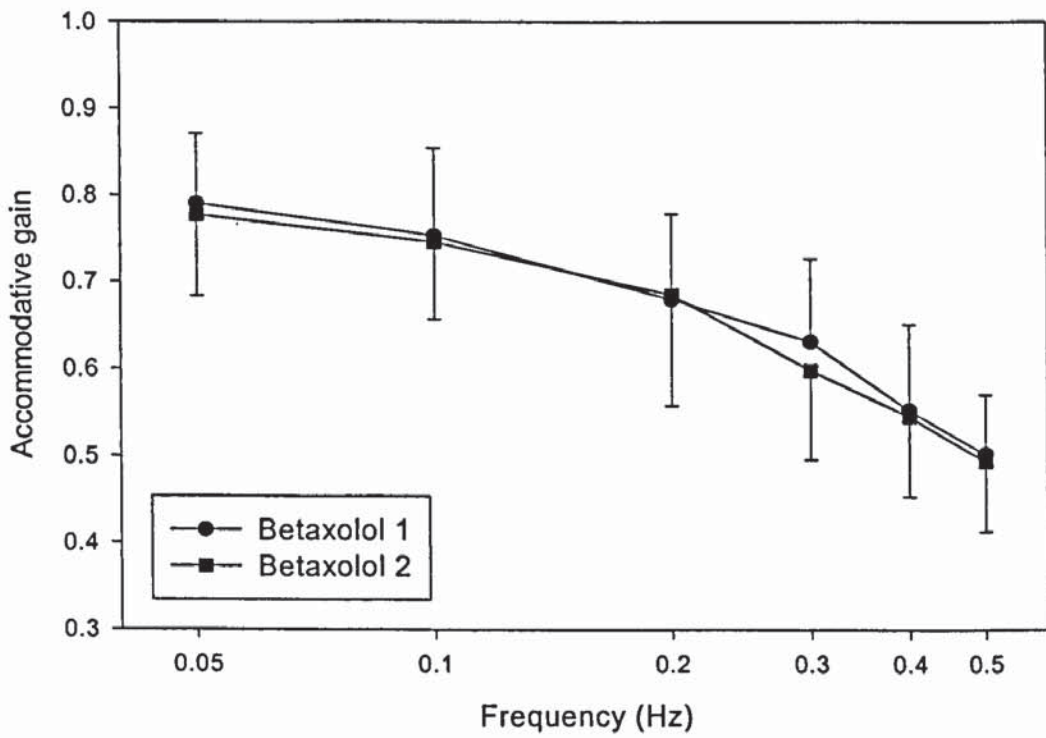
Figure 6.8. Mean accommodative gain results – betaxolol 1 vs betaxolol 2.
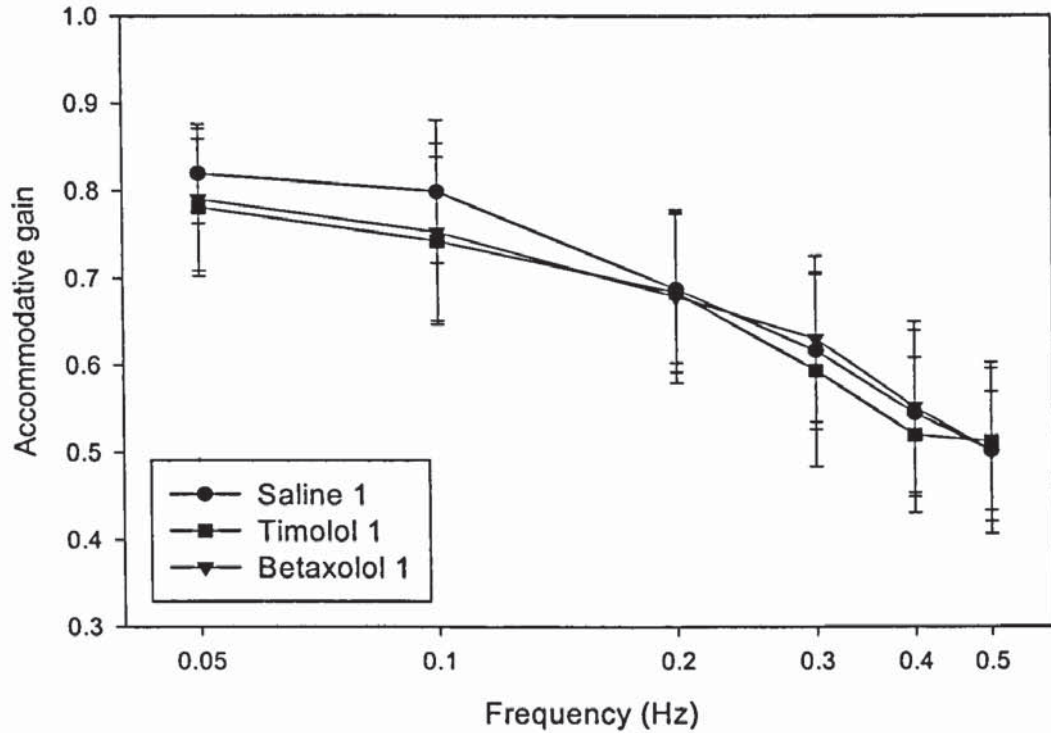
Figure 6.9. Mean accommodative gain results – saline 1, timolol 1, betaxolol 1.

Accommodative gain values (group averaged ± SD) for all drug and task conditions are listed in table 6.1.

Frequency (Hz)	Saline 1 (Gain)	Saline 2	Timolol 1	Timolol 2	Betaxolol 1	Betaxolol 2
0.05	0.82±0.06	0.87±0.07	0.78±0.07	0.79±0.07	0.79±0.08	0.78±0.09
0.1	0.80±0.08	0.83±0.07	0.74±0.10	0.73±0.09	0.75±0.10	0.75±0.09
0.2	0.69±0.09	0.71±0.10	0.68±0.09	0.64±0.14	0.68±0.10	0.68±0.13
0.3	0.62±0.09	0.66±0.08	0.59±0.11	0.59±0.10	0.63±0.10	0.60±0.10
0.4	0.55±0.10	0.56±0.09	0.52±0.09	0.49±0.12	0.55±0.10	0.55±0.09
0.5	0.50±0.09	0.51±0.09	0.51±0.09	0.53±0.10	0.50±0.07	0.49±0.08

Table 6.1. Mean accommodative gain against drug and task.

Overall, for all subjects at all temporal frequencies, the effect of the sustained near task failed to have a significant effect on closed-loop accommodative gain ($p = 0.27$). However, separate examination of the effect of a sustained task for each frequency reveals increased gain effects approaching statistical significance for temporal frequencies of 0.05 to 0.2 Hz.

6.4.2 Phase lag

Group mean phase lag plots have a linear axis for phase lag and a logarithmic axis for temporal frequency. Individual phase lag plots for each subject can be found in appendix 9. Figure 6.10 shows group mean results for 10 subjects illustrating the effect of a sustained 3-minute near task on the phase lag of the dynamic accommodation response. Filled circles indicate phase lag without the 3-minute adaptive task (saline 1), filled squares indicate phase lag following the sustained near task (saline 2). Error bars indicate 1 standard deviation for the mean data at each point. Phase lag of the accommodative response increases as stimulus temporal frequency increases. Averaged phase lag values for all subjects, drug conditions, adaptation states and temporal frequencies are listed in table 6.2.

The effect of timolol maleate on phase lag against saline and betaxolol control conditions is shown in figure 6.11. Plotted points represent average phase lag values for the whole subject group prior to exposure to the 3-minute sustained task for saline (Saline 1) timolol (Timolol 1) and betaxolol (Betaxolol 1).
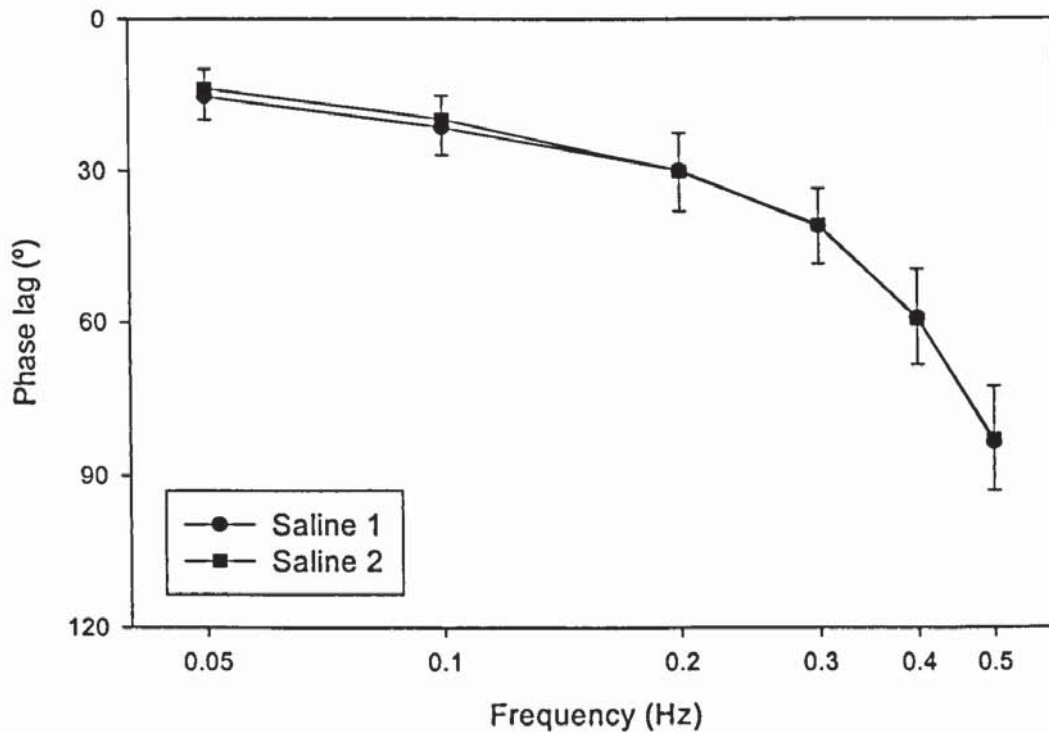
Figure 6.10. Mean phase lag results – saline 1 vs saline 2.
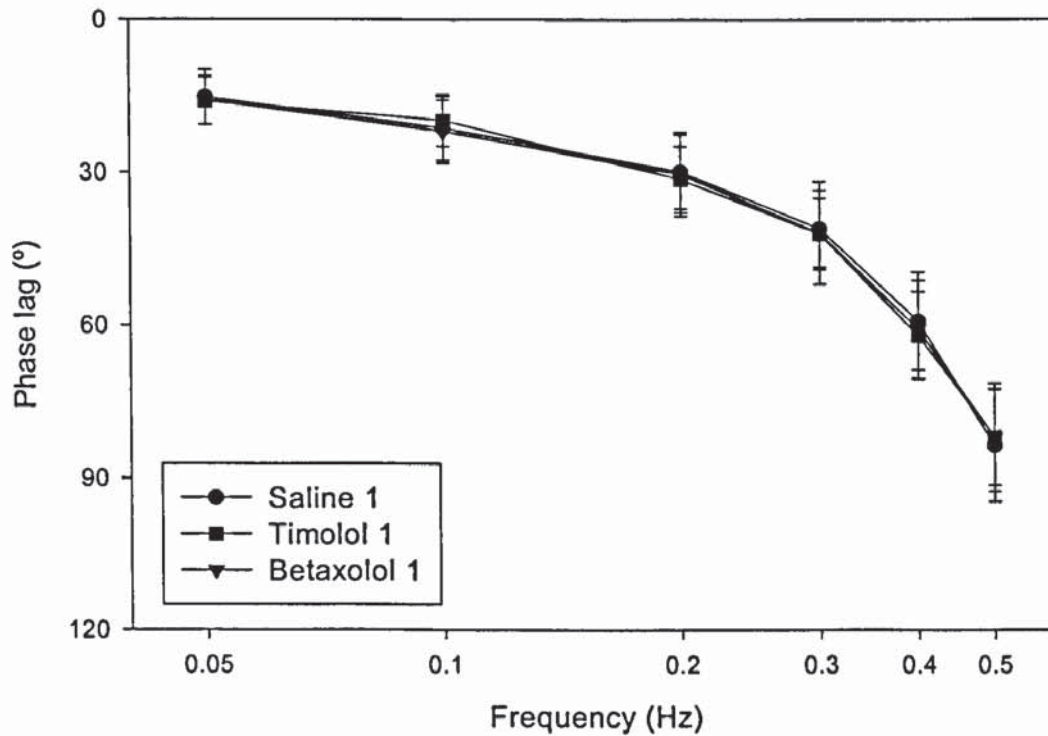
Figure 6.11. Mean phase lag results – saline 1, timolol 1, betaxolol 1.

Frequency (Hz)	Saline 1 (Lag °)	Saline 2	Timolol 1	Timolol 2	Betaxolol 1	Betaxolol 2
0.05	15.3±5.4	13.7±6.1	16.1±4.6	17.2±4.9	15.9±4.8	14.4±4.6
0.1	21.4±6.3	19.9±7.0	19.9±5.1	21.5±6.5	22.1±6.2	21.4±6.0
0.2	29.9±7.3	30.1±8.0	31.4±6.5	32.1±8.0	30.4±8.2	31.6±9.0
0.3	41.1±7.5	40.7±7.8	42.1±7.0	42.1±8.7	41.9±10.0	43.4±8.9
0.4	59.2±9.6	59.4±9.0	62.0±8.6	61.5±9.7	60.8±9.6	64.4±10.1
0.5	83.6±11.0	82.9±10.0	81.9±9.5	84.8±8.2	82.0±10.6	82.6±11.5

Table 6.2. Mean accommodative phase lag against drug and task.

Statistical testing (Factorial ANOVA) showed the increase in phase lag with increasing temporal frequency to be significant (p <0.01). Accommodative phase lag was significantly different at all frequencies. Near adaptation (3-minute, 3 D task) failed to have a significant effect on phase lag (p = 0.62). Pharmacological intervention (saline, timolol, betaxolol) also failed to significantly alter phase lag (p = 0.23).

6.4.3 Cross-correlation between dynamic accommodation and autonomic profile

All subjects in this study were also participants in the autonomic profiling experiment. Autonomic profiling results showed that all 10 subjects used in this study failed to demonstrate a differential accommodative regression response to timolol following a sustained near task. It is therefore deduced that all subjects in the study of dynamic accommodation do not have access to sympathetic inhibition of accommodation.

6.5 Discussion

In support of the findings of previous studies (Kruger and Pola, 1986; Winn and Culhane, 1998) a decrease in accommodative response gain coupled with an increase in response phase lag was observed as temporal frequency of a dynamic stimulus was increased. Execution of a sustained accommodative task increased the response gain during a subsequent dynamic tracking task at low to mid temporal frequencies, but this effect failed to achieve statistical significance. Instillation of timolol maleate and betaxolol hydrochloride produced reductions in accommodative response gain compared to a saline control condition. The reduction in gain observed under betaxolol conditions (i.e. selective β_1 antagonist) is contrary to previous findings (Strang, 1995).

From the results obtained, it can be seen that the closed-loop dynamic accommodation responses of subjects participating in this study were not significantly affected by the administration of the selective β_2-antagonist timolol maleate. A small reduction in accommodative response amplitude at low to mid temporal frequencies is observed following the instillation of selective and non-selective β-antagonistic agents. Failure to achieve statistical significance may be explained by sample size, although statistical significance has been demonstrated in similar experimental arrangements (Culhane, 1999; Winn et al., 2002). Phase lag was not affected by the use of autonomic drugs or sustained accommodative effort, thus suggesting that phase lag is primarily determined by the fast, parasympathetic branch of the ANS.

It is interesting to note from the results of Chapter 3, that all subjects taking part in this experimental work do not have access to sympathetic inhibition of accommodation. The lack of statistically significant variation in dynamic accommodative response following β-antagonism or sustained accommodative demand can be explained by the general lack of sympathetic facility in the subject cohort. It would be interesting to compare the effects of

sustained accommodation and β-antagonism on dynamic function in subjects with sympathetic facility. As the autonomic profiling study was conducted double blind, it was not possible to pre-select subjects with known ANS profile. This unforeseen error occurred as a consequence of the masked experimental protocol employed in ANS profiling. The general absence of sympathetic facility in the subjects used suggests that the small reductions in accommodative gain observed under selective and non-selective β blockade did not occur due to direct drug action on ciliary muscle innervation. It is suggested, perhaps, that these effects occurred as a result of the ocular hyoptensive effects of timolol and betaxolol altering the forces acting on the crystalline lens. In future studies it will be possible to compare dynamic responses of subjects demonstrating sympathetic inhibition with those with sympathetic deficit. Full autonomic profiling of ciliary muscle innervation should be carried out prior to studies of the effects of sympathetic innervation on the dynamic accommodation response.

In future work it may be possible to reveal a graded sympathetic response, i.e. show the relative efficacy of sympathetic facility in a subject group, rather than merely determine presence or absence of sympathetic facility. Subjects possessing relatively strong sympathetic innervation should show increased open-loop accommodative hysteresis under β_2 blockade following a sustained near task, and reduced dynamic accommodative response gain at low temporal frequencies under similar pharmacological conditions. Conversely, the dynamic accommodation and open-loop responses of subjects without access to sympathetic facility should not be affected by β_2 blockade. Within the bounds of these two extreme cases, it may be possible to demonstrate a graded sympathetic response. Density of receptors (i.e. the relative concentrations of β_2 receptors per unit area of ciliary smooth muscle) may contribute to the proposed graded sympathetic response. Dose effects of β_2 antagonistic agents should now be examined to evaluate the possibility of such a graded response. The effects of β_2 stimulation on the closed-loop dynamic accommodation response should also be investigated, perhaps utilizing the selective β_2 agonist salbutamol, or similar preparation.

The target for closed-loop sinusoidal dynamic recordings (i.e. a high contrast Maltese cross) was presented within a Badal lens system. It has been argued that the use of a Badal system in stimulus presentation can produce less accurate dynamic responses than target presentation in free space, due to the elimination of spatiotopic cues to accommodation

(Stark and Atchison, 1994). As the Badal system was used in all experimental trials, and therefore in all temporal frequency and pharmacological treatment states, the effect of reduced spatiotopic cues to accommodation were applied equally. Additionally, the use of a Badal system provides a given range of dynamic accommodative stimuli over a smaller spatial distance compared to free space presentation. Further, change in dynamic accommodative stimulus is linear, and target luminance remains constant at all stimulus levels.

CHAPTER 7
THE EFFECT OF SYMPATHETIC (α-ADRENOCEPTOR) AUGMENTATION ON THE DYNAMIC ACCOMMODATION RESPONSE

7.1 Introduction

Sympathetic inhibitory control of accommodation is mediated by the action of the neurotransmitter noradrenaline on adrenergic receptors (adrenoceptors) in ciliary smooth muscle (Alquist, 1948). Examination of human ciliary muscle strips from *post-mortem* eyes by van Alphen (1976) revealed the presence of β-adrenoceptors together with some evidence of the existence of α-adrenoceptors. Zetterstrom and Hahnenberger (1988) conducted further *in vitro* work on adrenoceptor distribution in human ciliary muscle, concluding that both β_2 and α_1 subtypes of adrenoceptor were present in fresh samples.

Culhane *et al.* (1999) demonstrated that augmentation of the sympathetic branch of the autonomic nervous system by the administration of the α_1 adrenoceptor agonist phenylephrine hydrochloride significantly increased the gain of dynamic accommodation responses at low and mid temporal frequencies. The phase lag of dynamic accommodation responses were not significantly affected by α_1 augmentation. It is known that as the temporal frequency of a dynamic accommodative stimulus increases, the gain of the closed-loop accommodation response reduces and the phase lag of the response waveform increases (Kruger and Pola, 1986; Culhane *et al.*, 1999). Further, augmentation of sympathetic inhibition of accommodation following sustained parasympathetic activity is well documented (Gilmartin and Bullimore, 1987).

This study aims to demonstrate the previously observed effects of α_1 pharmacological intervention and sustained accommodative effort on dynamic responses, but utilizing a new battery of instrumentation. Additionally, the combined effect of sustained accommodative demand and pharmacological augmentation of the sympathetic system will be examined.

7.2 Subjects

All subjects (N = 10) were undergraduate optometry students at Aston University. Mean age of subjects was 22.5 ± 2.8 years (range 21 to 30 years). The cohort consisted of 4 emmetropes, 2 early onset myopes and 4 late onset myopes. Subjects had normal visual acuity, correctable to at least 6/6 and were free of abnormal ocular conditions. Owing to

the slight risk of cardiovascular side-effects from systemic absorption of a sympathomimetic agent, any history of cardiac abnormalities was emphasised as a subject exclusion criterion (Hopkins and Pearson, 1998). No subjects reported any such general health problems. All subjects taking part in this experiment were also participants in the dynamic accommodation trials of Chapter 6, and had acted as subjects for the autonomic profiling study (Chapter 3).

7.3 Methods

Subjects observed a high contrast Maltese cross target monocularly via a +5 DS Badal optometer. The Maltese cross target was mounted on the carriage of a Lloyd PL3 X-Y plotter to facilitate movement of the stimulus along the visual axis. A Thandar TG501 function generator was used to control the position and speed of the plotter carriage. The function generation was adjusted to provide sinusoidal movement of the Maltese cross target at temporal frequencies between 0.05 and 0.5 Hz. The accommodative demand of the task ranged from 2 to 4 D. A stationary target position was set within the Badal optometer to provide a 3 D stimulus to accommodation; this position being used for the 3 minute adaptation task. Accommodation responses were recorded continuously using a modified Shin-Nippon SRW-5000 infra-red autorefractor (Mallen *et al.*, 2001; Wolffsohn *et al.*, 2001) at a sampling rate of 42 Hz. All measurements were conducted on the right eye.

Experimental trials consisted of the randomised allocation of the following treatment conditions:

- Instillation of 1 drop (approximately 26 μl; Hopkins and Pearson, 1998) of 0.9% saline (*Minims,* Chauvin Pharmaceuticals, Romford, Essex, UK), followed by a dynamic tracking task.
- Instillation of 1 drop of 0.9% saline. Conduction of a static, 3-minute, passive observation task of 3 D accommodative demand, followed immediately by a dynamic tracking task.
- Instillation of 1 drop (approximately 26 μl; Hopkins and Pearson, 1998) of 2.5% phenylephrine hydrochloride (*Minims,* Chauvin Pharmaceuticals, Romford, Essex, UK), followed by a dynamic tracking task.

- Instillation of 1 drop of 2.5% phenylephrine hydrochloride Conduction of a static, 3-minute, passive observation task of 3 D accommodative demand, followed immediately by a dynamic tracking task.

One drop of the topical anaesthetic proxymetacaine hydrochloride (0.5%, *Minims,* Chauvin Pharmaceuticals, Romford, Essex, UK) was instilled into both eyes of each subject prior to the instillation of saline or phenylephrine to inhibit reflex blinking and lacrimation, and to aid passage of phenylephrine though the cornea.

Under all conditions, the 2 to 4 D dynamic tracking task was carried out in separate trials at temporal frequencies of 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 Hz. The order of temporal frequencies was randomised. Accommodative responses to the dynamic tracking task were recorded for sufficient time to provide 6 consecutive sinusoidal target cycles.

Myopic subjects were fitted with *1 Day Acuvue* soft disposable contact lenses to correct refractive error. Contact lenses were fitted following an anterior eye examination to assess suitability for lens wear. Following insertion, the contact lenses were allowed to settle for at least 20 minutes before the recording of accommodative response data. Visual acuity of 6/6 or better was achieved by all subjects following contact lens fitting.

7.4 Results

Accommodative response gain and phase lag were calculated for each temporal frequency and task/drug combination according to the method adopted by Kruger and Pola (1986). Mean and standard deviation gain and phase lag values for the whole subject cohort were calculated. Results are presented graphically in bode plots. Group mean accommodative gain and phase lag plots have a linear axis for gain and phase lag, and a logarithmic axis for temporal frequency. Gain and phase lag plots for individual subjects can be found in Appendix 9.

7.4.1 Accommodative gain

Mean accommodative gain results prior to the 3-minute adaptation task under saline and phenylephrine conditions are presented in figure 7.1, with gain values (± 1 SD) shown in table 7.1. Error bars in figure 7.1 indicate 1 standard deviation of the mean data at each point. Figure 7.2 shows the effect of the 3-minute adaptation task on accommodative gain.

Group mean accommodative gain at each temporal frequency prior to the adaptation task (filled squares – Phenylephrine 1) and immediately following the adaptation task (open squares – Phenylephrine 2) are compared.

Figure 7.1. Mean accommodative gain results – saline 1 vs phenylephrine 1.

Figure 7.2. Mean accommodative gain results – phenylephrine 1 vs phenylephrine 2.

Frequency (Hz)	Saline 1 (Gain)	Saline 2	Phenylephrine 1	Phenylephrine 2
0.05	0.82±0.06	0.87±0.07	0.85±0.07	0.83±0.08
0.1	0.80±0.08	0.83±0.07	0.83±0.10	0.84±0.10
0.2	0.69±0.09	0.71±0.10	0.73±0.11	0.72±0.11
0.3	0.62±0.09	0.66±0.08	0.64±0.09	0.66±0.09
0.4	0.55±0.10	0.56±0.09	0.52±0.08	0.52±0.10
0.5	0.50±0.09	0.51±0.09	0.52±0.09	0.50±0.08

Table 7.1. Mean accommodative gain against drug and task.

Factorial ANOVA and Scheffe's *post-hoc* test showed that increasing the temporal frequency of target oscillation reduced the overall accommodative gain significantly ($p = <0.0001$), however, gain values were not significantly different between frequencies of 0.05 and 0.1 Hz ($p = 0.80$) and 0.4 and 0.5 Hz ($p = 0.37$). Instillation of phenylephrine produced a small increase in accommodative gain, but this effect was not significant ($p = 0.70$). The overall effect of the 3 minute adaptation task was also not significant ($p = 0.10$) following the instillation of phenylephrine.

7.4.2 Phase lag

Figure 7.3 shows the mean group effect of phenylephrine on dynamic accommodative response phase lag. Group mean results for saline (Saline 1) and phenylephrine (Phenylephrine 1) prior to the 3-minute adaptation task are shown. Group mean values at each data point are also shown in table 7.2. The effect of the 3-minute adaptation task on phase lag is shown in figure 7.4. Group mean phase lag at each temporal frequency prior to the adaptation task (filled squares – Phenylephrine 1) and immediately following the adaptation task (open squares – Phenylephrine 2) are compared.
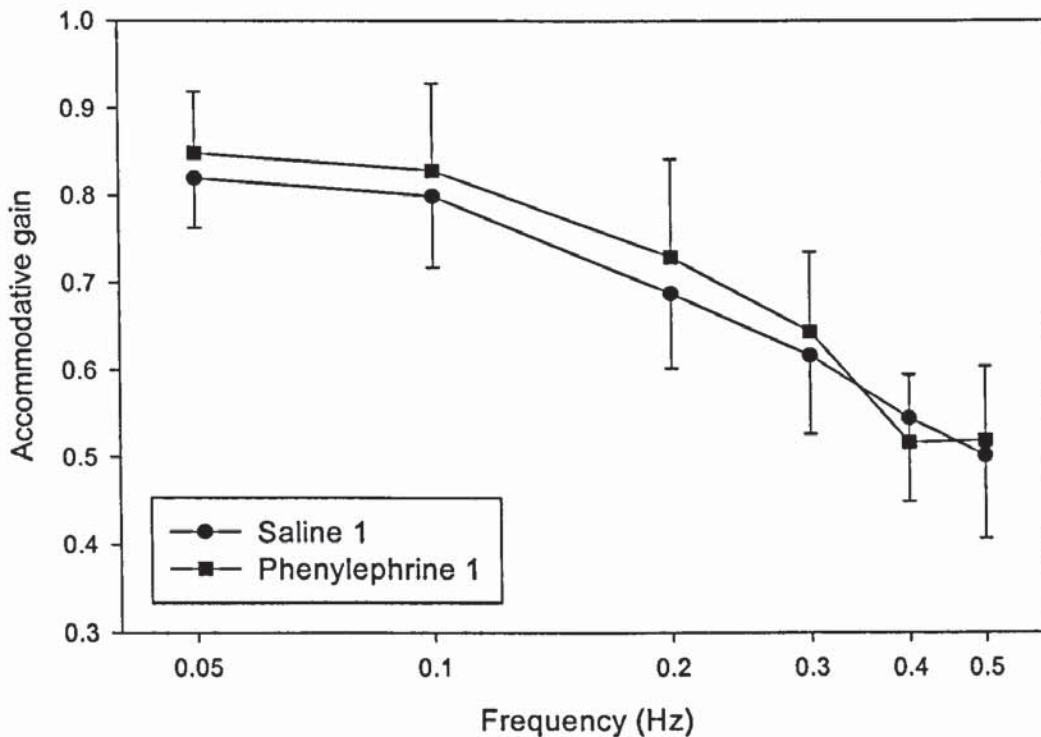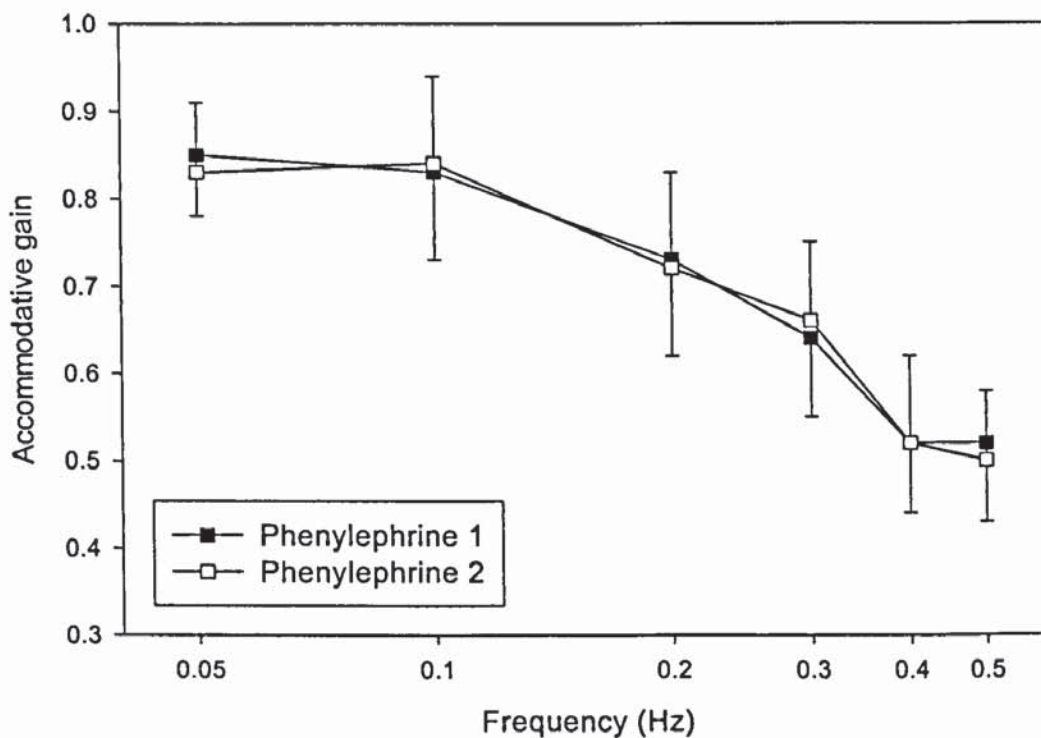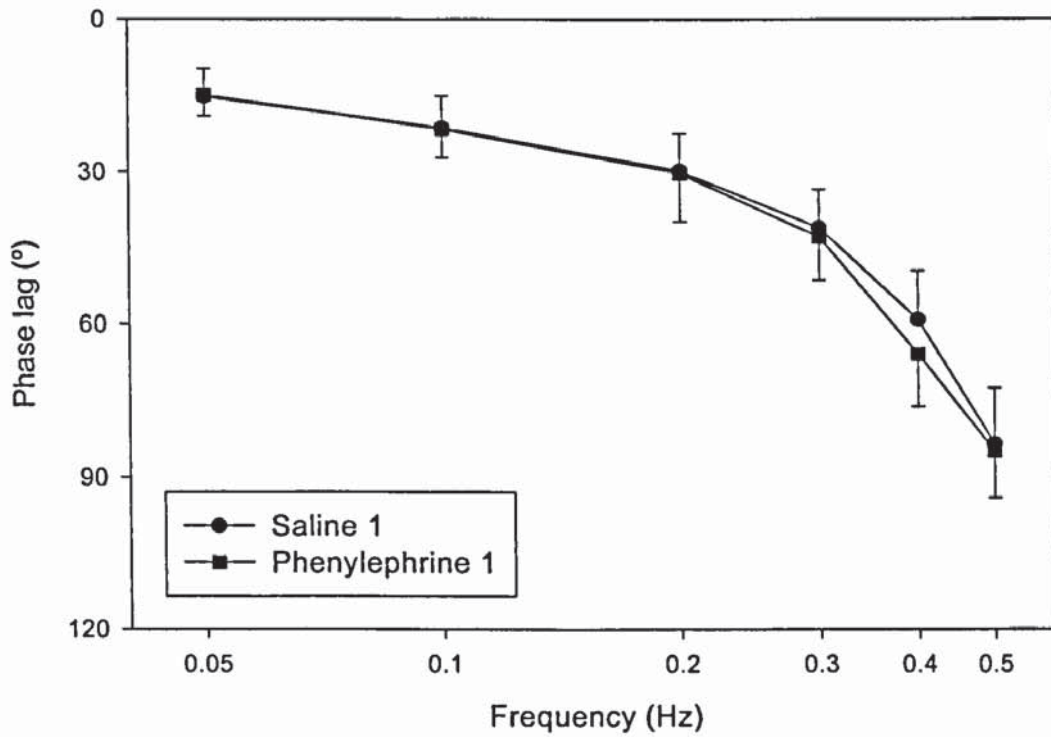
Figure 7.3. Mean phase lag – saline 1 vs phenylephrine 1.
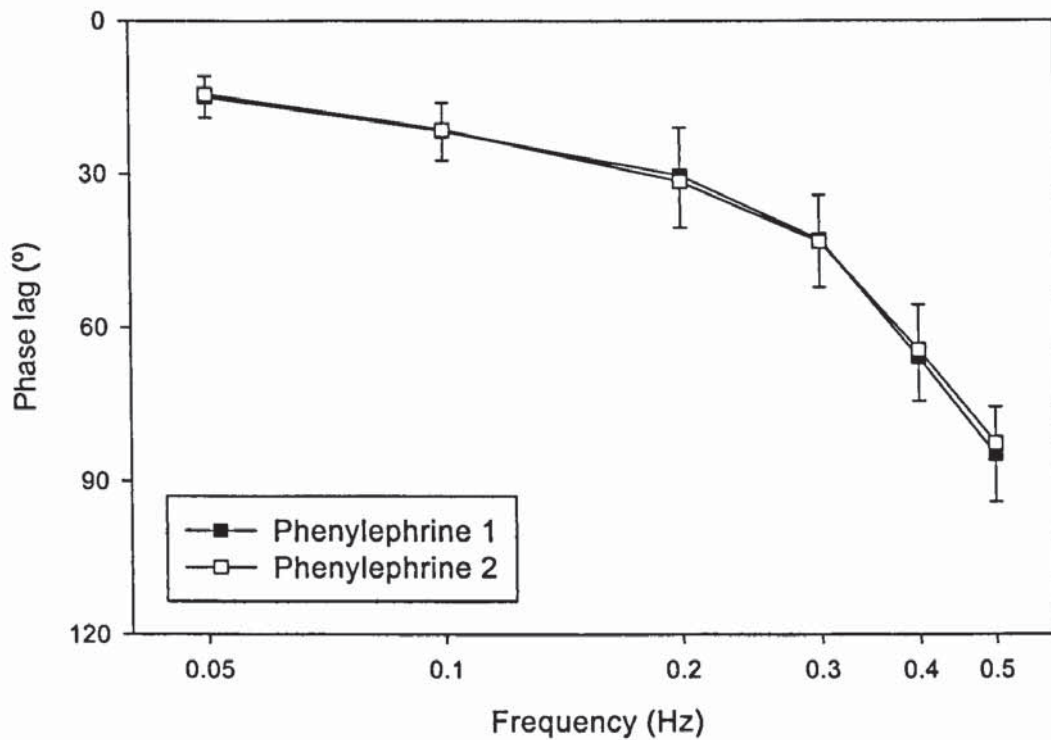
Figure 7.4. Mean phase lag – phenylephrine 1 vs phenylephrine 2.

Frequency (Hz)	Saline 1 (Lag°)	Saline 2	Phenylephrine 1	Phenylephrine 2
0.05	15.3±5.4	13.7±6.1	15.0±4.1	14.4±4.6
0.1	21.4±6.3	19.9±7.0	21.7±5.6	21.4±6.0
0.2	29.9±7.3	30.1±8.0	30.4±9.4	31.6±9.0
0.3	41.1±7.5	40.7±7.8	42.9±8.6	43.4±8.9
0.4	59.2±9.6	59.4±9.0	65.9±10.3	64.4±10.1
0.5	83.6±11.0	82.9±10.0	84.9±9.2	82.6±11.5

Table 7.2. Mean accommodative phase lag against drug and task.

Factorial ANOVA and Scheffe's *post-hoc* test showed a significant overall effect of frequency on phase lag ($p = <0.0001$), a significant increase in phase lag was observed at each increnemtal frequency increase. A small, but statistically significant overall reduction in phase lag of 1.78° was observed following instillation of phenylephrine ($p = 0.04$).

7.5 Discussion

As shown in previous studies (Kruger and Pola, 1986; Culhane *et al.*, 1999), the accuracy of the dynamic accommodation response declines in terms of a reduction in overall response gain and increased response phase lag as the temporal frequency of closed-loop stimulus oscillation is increased. The group mean accommodative gain values under non-adapted saline conditions obtained from the current study were similar to those found by Culhane *et al.* (1999), with a similar rate of decline in accommodative gain as a function of stimulus frequency increase being observed.

Augmentation of the α_1 adrenergic system following the topical administration of phenylephrine hydrochloride has produced smaller effects on closed-loop accommodative gain that those observed in previous studies (Culhane *et al.*, 1999). Culhane *et al.* (1999) noted increases in accommodative gain of 0.3 to 0.4 at stimulus frequencies of 0.05 to 0.3 Hz following the administration of phenylephrine; the work reported here provides an intriguing contrast to these results. The high temporal and dioptric resolution of the continuous recording system employed has enabled the application of rigorous statistical tests, which have failed in most cases to reveal significant effects of phenylephrine on closed-loop accommodation responses. As noted in Chapter 6, all participants used in this study have been shown not to have access to sympathetic inhibition of accommodation. As

phenylephrine hydrochloride acts principally as an agonist to the α_1 sub-class of receptors within the sympathetic branch of the ANS, the observed results from this experiment suggest a link between the presence of α_1 and β_2 receptors in human subjects. The results obtained suggest that subjects without access to sympathetic facility mediated by β_2 receptors (i.e. subjects failing to show a differential open-loop response subsequent to a sustained near-task following the administration of timolol maleate) also fail to demonstrate an α_1 mediated sympathetic response. Further work should now be conducted to compare the effects of α_1 stimulation and β_2 blockade in subject groups with, and without access to sympathetic inhibitory facility. This work has also failed to show any significant effect of concurrent α_1 pharmacological simulation and sustained near vision activity on the human dynamic accommodation response.

It would be interesting to investigate the dose effect of phenylephrine by carrying out a further experiment to compare the effects of the 2.5% and 10% concentrations of this agent. Also of interest would be the effect of the α_1 antagonist thymoxamine (Shah *et al.*, 1989) on the dynamic accommodation response. A three way experimental protocol could be implemented to compare the agonist/antagonist pharmacological treatments against each other, and against the effect of sustained accommodation. Further, it may also be possible to examine differential effects between two subject cohorts grouped according to autonomic profile, i.e. a group demonstrating active sympathetic inhibitory facility as shown by prior autonomic profiling, and a group with deficient sympathetic system.

CHAPTER 8

THE EFFECT OF COGNITIVE DEMAND ON NEARWORK INDUCED TRANSIENT MYOPIA

8.1 Introduction

Nearwork induced transient myopia (NITM) describes the short-term inward shift of the far-point plane following a near task (Lancaster and Williams, 1914). The magnitude of transient myopic shifts following nearwork has received considerable attention in the literature, with far-point changes from 0.12 D (Rosenfield *et al.*, 1992a) to 1.30 D (Lancaster and Williams, 1914) being reported. Although these effects are transient in nature and generally decay within a number of seconds (Ciuffreda *et al.*, 1996) to several minutes (Ciuffreda and Ordonez, 1995) following completion of the task, the small post-task retinal blur induced may be sufficient to stimulate axial elongation and thus generate permanent myopic change (Irving *et al.*, 1991; Schaeffel and Howland, 1991; Smith *et al.*, 1999). Propensity for NITM has been shown to differ according to refractive error by a number of workers. Most recently, Ciuffreda and Lee (2002) have demonstrated increased levels of post-task NITM in early and late onset myopes compared to emmetropes and hyperopes.

Ciuffreda and Wallis (1998) examined magnitude and decay of NITM in myopes (N = 24), emmetropes (N = 11) and hyperopes (N = 9) following a 10 minute binocular task of 5 D accommodative demand. Myopic subjects were further classified in term of age of onset (early onset myopes (EOM), N = 13, onset before 15 years of age; late onset myopes (LOM), N = 11, onset after 15 years of age). Group averaged results showed greater post-task accommodative after-effects in the myopic groups compared to emmetropes and hyperopes. Although the magnitude of NITM was similar (0.35 D) between early- and late-onset groups, the time course of NITM decay was greater in late-onset myopes compared to early-onset myopes (63 seconds and 35 seconds respectively). Deficiency in sympathetic input to accommodative control was suggested as a possible cause of the protracted decay of NITM in LOMs.

Vera-Diaz *et al.* (2002) have recently conducted a similar study to Ciuffreda and Wallis (1998), but classified myopic subjects in terms of refractive stability (stable myopes, SM (N = 14); progressing myopes, PM (N = 13)) rather than age of onset. The near task carried

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out in this study was also different (i.e. 4 D monocular task of 10 minutes duration). Greater NITM was found in progressing myopes. The NITM observed was found following a monocular task, indicating that the post-task after-effects occurred principally as a result of blur-driven accommodative inaccuracy, with no input from the vergence system. Interestingly, emmetropic (N = 14) and SM subjects exhibited similar post-task accommodative responses. This study shows, therefore, that myopes are more susceptible to nearwork induced accommodative after-effects during the progressive phase of myopia.

An adaptation model of NITM (Hung and Ciuffreda, 1999) has laid down a theoretical basis for the differential nearwork-induced after-effects observed between refractive groups. This theory is based on the dual-interactive model of accommodation and vergence (Hung and Semmlow, 1980). Variation in 'adaptive gain' (K_A) of the accommodative branch of the model was shown to affect the time course of NITM decay. A comparison between mathematical modelling of NITM decay and actual NITM decay observed in human experimental work showed that low values of K_A were associated with hypermetropia and emmetropia. Higher values of K_A were evident in early- and late-onset myopia. Hung and Ciuffreda (1999) conclude that the adaptive gain element of accommodative control may be a factor in the time course of NITM, and consequently may contribute to chronic retinal blur at distance following nearwork. It follows therefore, that high levels of adaptive gain may be associated with a greater propensity for the development of late onset myopia when intense nearwork tasks are undertaken.

It has been demonstrated that mental effort influences the within-task closed loop accommodation response. Winn *et al.* (1991) measured closed-loop accommodation responses to passive observation of a matrix of reduced Snellen letters at near (3.5D stimulus to accommodation). Further within-task measurements were carried out with the subjects (10 young emmetropes) searching the letter matrix for a specific letter (the stimulus-dependent task) or observing the letters while counting backwards in sevens (the stimulus-independent task). A statistically significant increase in the mean accommodative response of 0.17 D was found during the stimulus dependent task compared to the passive observation task. The response to the stimulus independent task was not significantly different from the passive observation task.

The effect of cognitive input on post-task refractive hysteresis was examined by Rosenfield and Ciuffreda (1994). Twelve young adult subjects carried out a monocular, 10 minute, 5 D task at three levels of cognitive demand: a low cognitive task requiring N6 sized numbers to be read out loud; a moderate cognitive task consisting of mental arithmetic of pairs of N6 sized numbers; and a high cognitive task of adding four pairs of numbers. The results showed a mean post-task closed-loop myopic shift of 0.25D. NITM decay was complete within 40 seconds following task completion. No statistically significant difference in post-task transient myopic effects was observed between the cognitive levels employed, indicating that NITM observed under post-task closed-loop conditions is independent of within-task cognitive input.

The purpose of this work was to measure the effect of cognitive demand on the magnitude and time course (decay) of post-task transient myopia induced by a sustained near task. Of particular interest will be the evaluation of any differences in magnitude and duration of NITM between emmetropes, early-onset and late onset myopes.

8.2 Subjects

All subjects (N = 18) were undergraduate and postgraduate students at Aston University. Age range of subjects was 18-35 years. Visual acuity of subjects was correctable to at least 6/6, and all subjects were free of abnormal ocular conditions. Subjects were categorized in terms of refractive error into three groups: emmetropes (N = 6, spherical refraction ±0.25 DS, mean age 22.9 years), early onset myopes (EOM) (N = 6, mean spherical refraction −4.42 ± 3.32 DS, mean age of myopic onset 10.8 years, mean age 23.7 years) and late onset myopes (LOM) (N = 6, mean spherical refraction −2.04 ± 0.75 DS, mean age of myopic onset 20 years, mean age 23.2 years). Subjects were given a full explanation of the procedures involved, and gave informed consent to act as participants in the study under the terms of the Declaration of Helsinki.

8.3 Methods

Ametropic subjects were fitted with ultra-thin soft contact lenses (*1-Day Acuvue, Johnson and Johnson*) to correct fully their refractive error. A full slit lamp examination of the anterior segment was carried out prior to contact lens fitting. A patch was fitted to occlude the left eye, all measurements being made on the right eye.

Accommodative responses were continuously recorded using the modified Shin-Nippon SRW-5000 infra-red autorefractor described in Chapter 2. The stimulus to accommodation was a 5x4cm liquid crystal display (LCD) unit. The unit was mounted on the carriage of an X-Y plotter (see Chapter 2) to allow the LCD to be moved within a +5 DS Badal arrangement. A switching system facilitated the movement of the LCD within the Badal system to provide accommodative stimuli of 0 D (optical infinity) or 4.50 D. Change of stimulus vergence was complete within ~500 ms.

A second computer equipped with *LabView* software was programmed to drive the LCD device. The LCD acted as both an observation target and a cognitive target. The observation target consisted of a single numeric digit between 0 and 9 of size approximately equivalent to 6/9 Snellen. The subject was required simply to look at the number and keep it clearly in focus for the observation task. For the cognitive task *LabView* was programmed to display a pair of numbers (also 6/9 equivalent in size) which were summed together. The 'answer' to this sum was displayed immediately beneath the pair of numbers. Random programming of the system was used to make the answer to the sum either correct, or incorrect by 1. The subject was required to indicate incorrect answers by clicking a mouse button. A different sum was displayed every 5 seconds. The accuracy of subject responses was logged during the trials as a measure of concentration.

The experimental procedure for each subject consisted of 4 separate 10-minute trials, the order of which was balanced throughout the subject groups. The trials are listed below:

1. Passive observation of a near (4.50 D) target for five minutes, immediately followed by passive observation of a distance (0 D) target for a further five minutes.

2. Performance of a cognitive summing task at near for five minutes, immediately followed by passive observation of a distance target for a further five minutes.

3. Performance of a cognitive summing task at near for five minutes, immediately followed by performance of a cognitive summing task at distance for a further five minutes.

4. Passive observation of a near (4.50 D) target for five minutes, immediately followed by performance of a cognitive summing task at distance for a further five minutes.

Trials were separated by a five-minute rest period to minimize subject fatigue and to allow full decay of transient myopic effects (Rosenfield *et al.*, 1992a).

8.4 Results

Accommodative response data, together with time and stimulus synchronisation signals were automatically saved to an *Excel* spreadsheet. The accommodation signal was filtered to eliminate blink artefacts by removing data points lying outside of the range −2 D to +6 D. Figure 8.1 shows an example plot of unfiltered raw accommodative response for subject RU to a passive observation task at near and distance. The vertical dashed line indicates the transition between the near task and the far task.
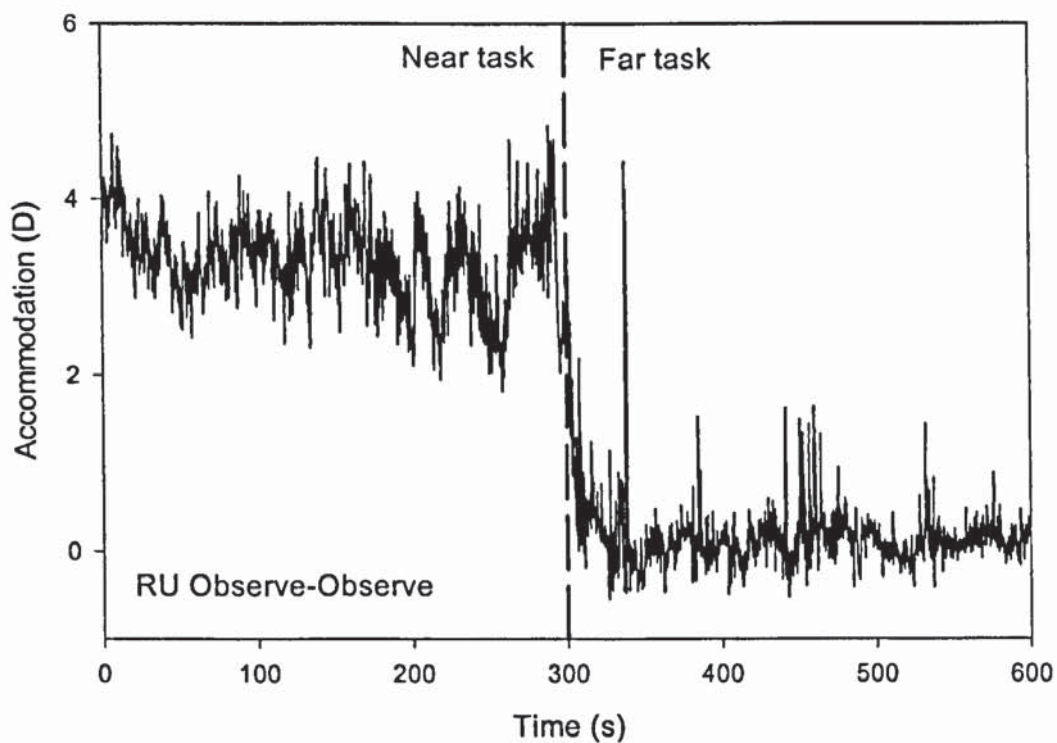
Figure 8.1. Accommodation response for subject RU. Observe-Observe trial.

Data were grouped according to refractive error (EMM, EOM and LOM) for statistical analysis by ANOVA and Scheffe's *post-hoc* test. The mean sampling rate of the Shin-Nippon continuous recording system was 42 Hz, giving in excess of 25,000 data points for each experimental trial. To simplify management of data analysis, accommodation measurements were averaged to 10 second points. Table 8.1 shows group mean accommodative responses (± SD) to the 5 minute near (4.50 D) task at each cognitive load combination; table 8.2 shows corresponding accommodative response values to the

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subsequent 5 minute distance (0 D) task. The 'cognitive combination' column indicates the level of cognitive demand for the 'near' and 'far' sections of each trial, e.g. 'Cognition-Observe' denotes a cognitive task at near, followed by passive observation at distance.

Cognitive combination	Emmetropes	Early onset myopes	Late onset myopes
Observe-Observe	3.60±0.73 D	3.37±0.82 D	3.12±1.12 D
Cognition-Cognition	3.59±0.72 D	3.46±0.62 D	3.12±1.20 D
Cognition-Observe	3.44±0.79 D	3.72±0.65 D	3.36±1.36 D
Observe-Cognition	3.39±0.72 D	3.13±1.01 D	3.65±1.18 D

Table 8.1. Mean accommodative response at near.

For the near task (table 8.1), cognitive combination failed to have a significant effect on group mean accommodative response. Scheffe's *post-hoc* test with respect to refractive group showed that the mean accommodative response of the LOM group was significantly less than the response of the emmetropic group (mean difference −0.19 D, $p = 0.005$). Other comparisons according to refractive group were not significant. (EOM vs LOM: mean difference +0.11 D, $p = 0.08$; EOM vs EMM: mean difference −0.08 D, $p = 0.26$). Accommodative responses to the near task are represented graphically in figure 8.2. Data are grouped according to refractive category and combination of cognitive/observation task trials. Error bars show 1 standard error of the mean (SEM) of the group mean response for each category.

Cognitive combination	Emmetropes	Early onset myopes	Late onset myopes
Observe-Observe	0.25±0.36 D	0.86±0.93 D	0.46±0.51 D
Cognition-Cognition	0.16±0.32 D	0.52±0.59 D	0.62±0.64 D
Cognition-Observe	0.10±0.41 D	0.89±0.96 D	0.67±0.58 D
Observe-Cognition	0.03±0.29 D	0.54±0.50 D	0.71±0.70 D

Table 8.2. Mean accommodative response (NITM) at distance.

For the subsequent distance task (table 8.2), accommodative responses were significantly different between refractive groups (Scheffe's *post-hoc* test: EOM vs LOM, $p = 0.03$; EOM vs EMM $p = < 0.0001$; LOM vs EMM $p = < 0.0001$), with myopic groups showing greatest NITM (group mean NITM: EMM 0.14 D, EOM 0.70 D, LOM 0.62 D). Post-task closed-loop NITM is represented graphically in figure 8.3. Again, data are grouped

according to refractive category and combination of cognitive/observation task trials. Error bars show 1 standard error of the mean (SEM) of the group mean response for each category.
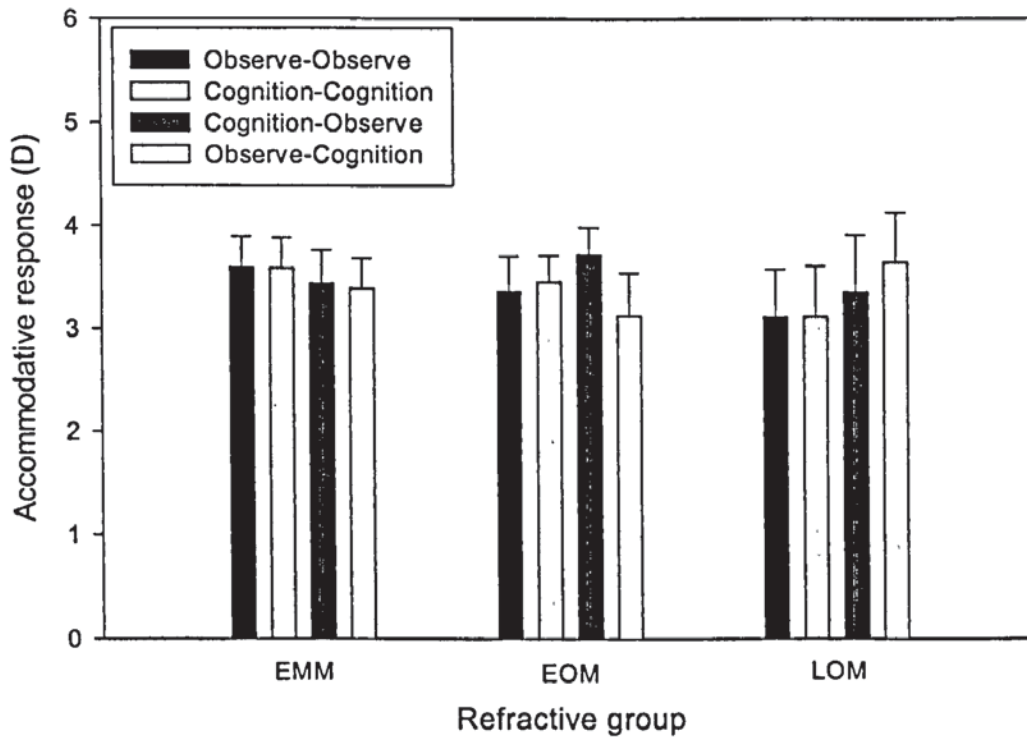
Figure 8.2. Group averaged accommodative response to near tasks.
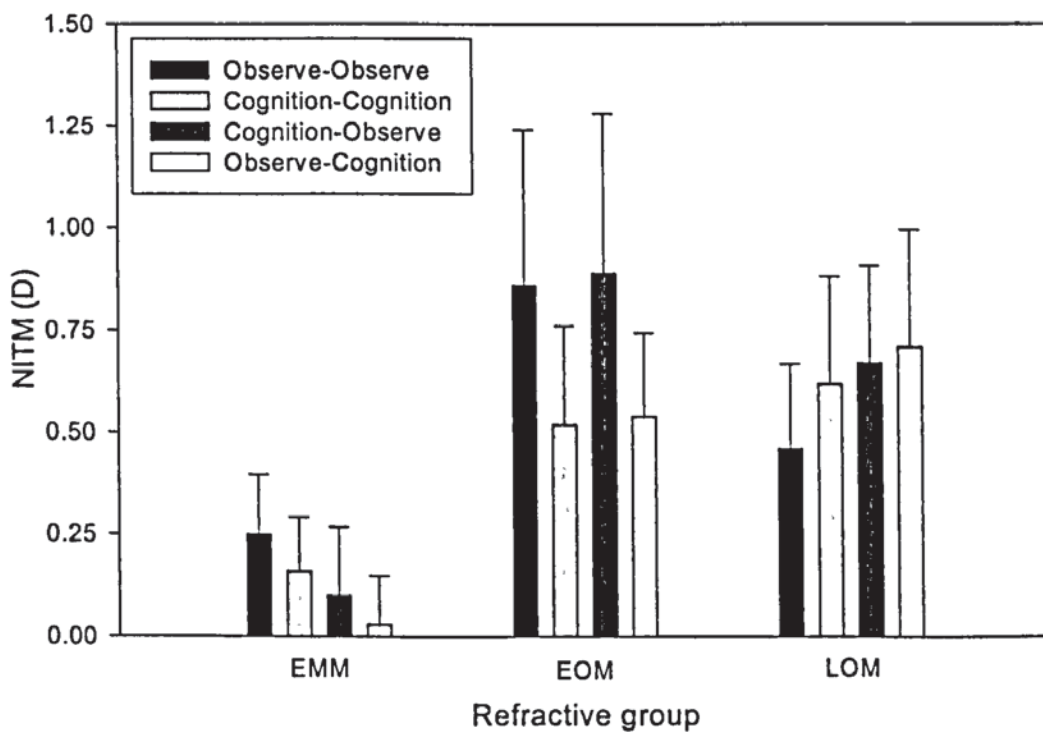
Figure 8.3. NITM as a function of refractive group and cognitive combination.

The group averaged closed-loop accommodative (near) task and distance task responses for emmetropes, early-onset myopes and late-onset myopes against time are shown in figures 8.4, 8.5 and 8.6 respectively. Representation of the data in this format allows the differential accommodative regression functions between refractive groups and cognitive levels to be visualized. Error bars indicate 1 standard deviation from the group mean (10 second) response for each cognitive combination. The change in target distance occurred at the 300 second time point in each case.
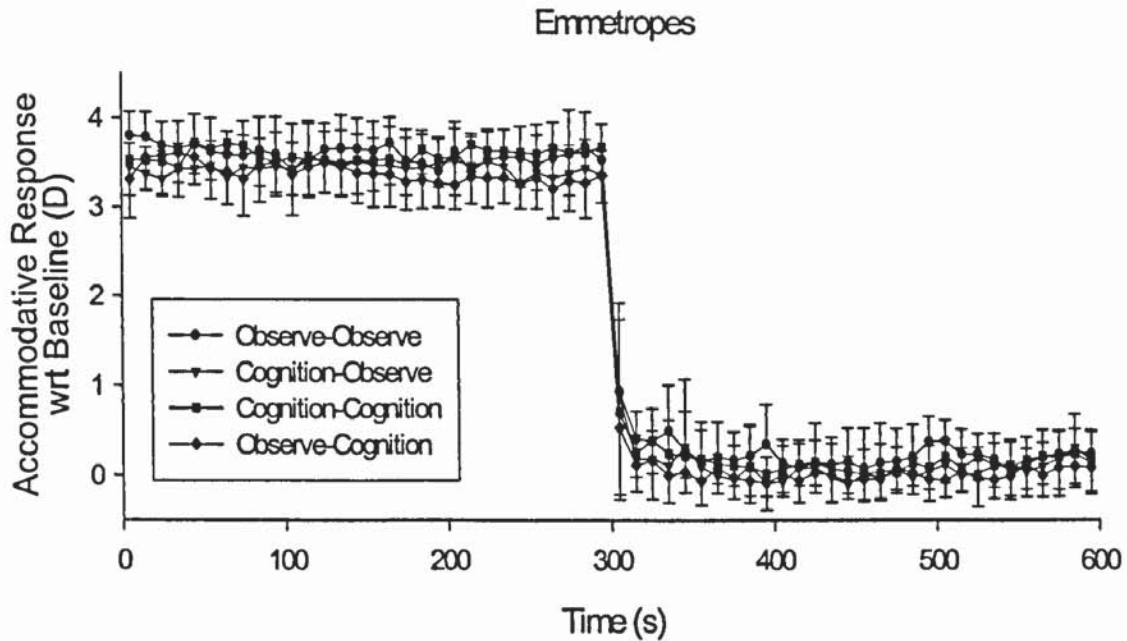
Figure 8.4. Mean response/NITM plots for emmetropes.
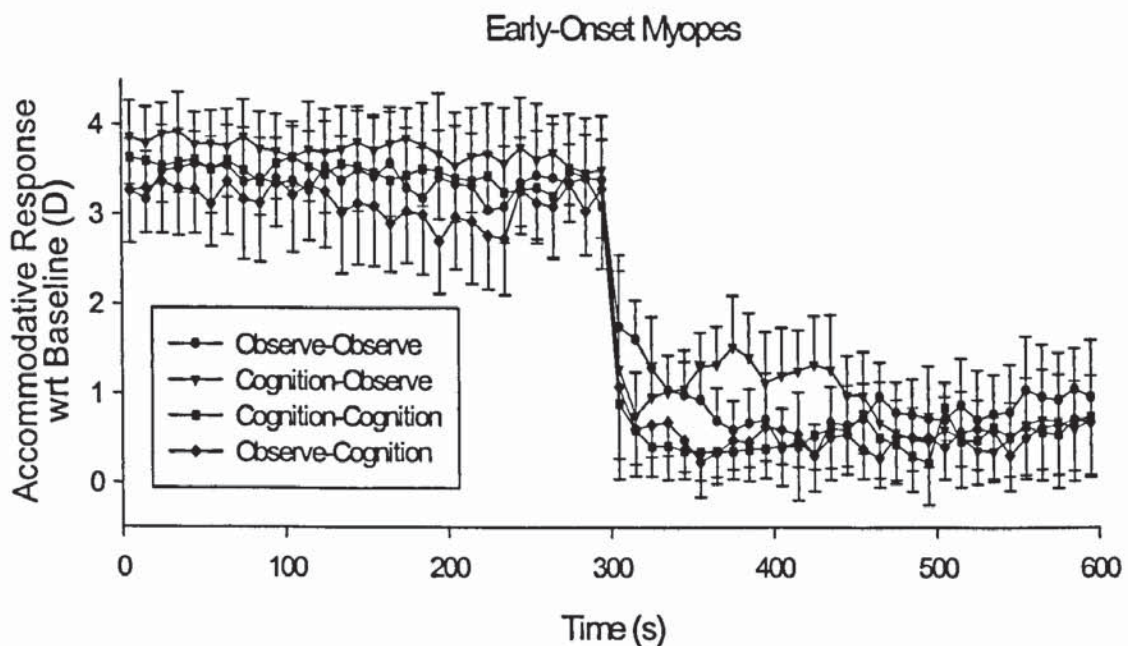
Figure 8.5. Mean response/NITM plots for early-onset myopes.
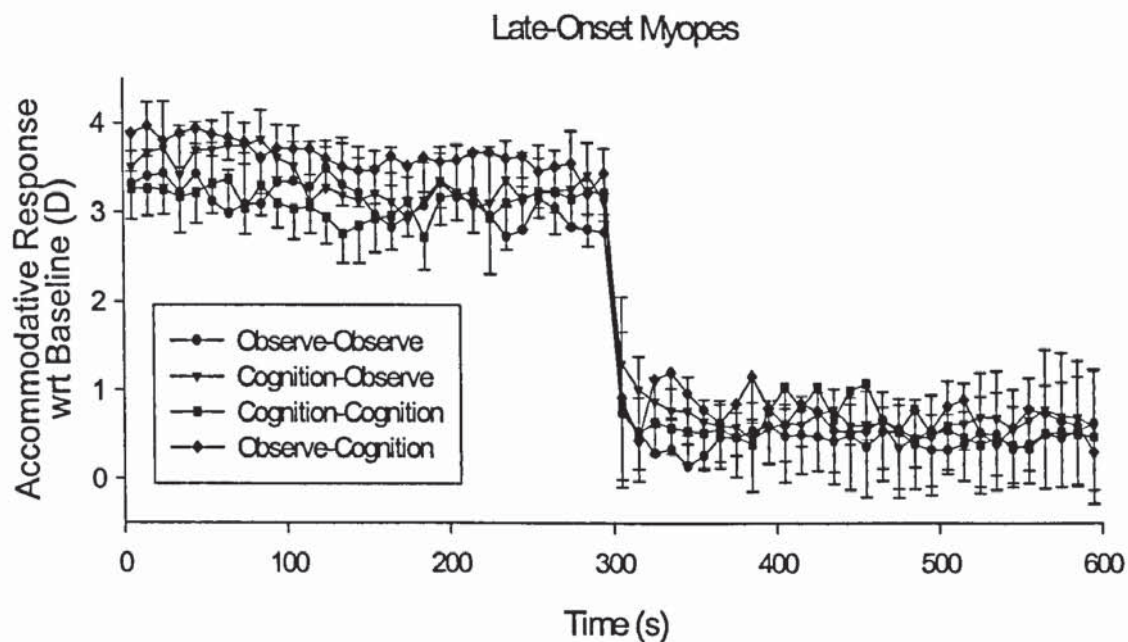
Figure 8.6. Mean response/NITM plots for late-onset myopes.

Table 8.3 shows the time course of NITM decay (seconds) according to refractive group and cognitive/passive observational task combination. NITM duration was defined as the time taken for the post-task accommodative response to fall to the pre-task closed-loop distance response level. Decay values were averaged for each refractive group and task combination.

TASK	EMM	EOM	LOM
Observe-Observe	20	270	120
Cognitive-Observe	10	260	260
Cognitive-Cognitive	10	150	220
Observe-Cognitive	10	200	260

Table 8.3. Time course of NITM decay (s) according to refractive group and cognitive task.

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8.5 Discussion

This study has employed an experimental design to examine the effect of a cognitive task on post-task closed-loop NITM. A four way design encompassing the possible permutations of cognitive and non-cognitive (observation) task at near, followed by observation or cognitive task at optical infinity was used. Continuous recording of accommodation responses were obtained for 'near' and 'far' sections of each experimental trial. Cognitive load was fixed for all subjects. Subjects used in this experimental work were not part of the main cohort used for previous work in this thesis; as a result, it was not possible to carry out cross-correlation between NITM, refractive stability and innervation of ciliary smooth muscle. A different subject cohort was used in this work mainly due to time constraints of the project and the availability of volunteers. It would be interesting to evaluate NITM dynamics in a subject cohort of known autonomic profile to determine the effect of sympathetic facility on magnitude and decay time constants.

Time course of NITM decay was greater in both myopic groups compared to the emmetropic group. Overall, little difference in NITM decay time constant was observed between early-onset and late-onset myopes. It would be interesting to repeat this experimental protocol to compare duration of NITM decay on early-onset and late-onset myopes with 'stable' and 'progressing' refractive error. From the recent work of Vera-Diaz *et al.* (2002), greater NITM decay times would be expected in the 'progressing' myopic subjects. The addition of varying cognitive load in this experimental protocol may yield some useful results.

Cognitive level failed to have a significant effect on the accommodative response at near (within task response). Both myopic subject groups exhibited greater lags of accommodation to the near task than the emmetropic group, but this difference was only statistically significant between late onset myopes and emmetropes. When compared to emmetropes, early- and late-onset myopic subjects showed significant transient myopic shifts in refraction under closed-loop conditions at distance, following the near task. The introduction of cognitive load to the near and/or distance tasks failed to show any consistent pattern of effects on NITM. From the results obtained it appears that myopes are able to tolerate greater amounts of blur than emmetropes, as noted by Gwiazda *et al.* (1993a) in children. This suggests that retinal blur is less efficient as a stimulus to accommodation in myopes compared to emmetropes. The results are also strongly

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indicative of the adaptive nature of the accommodation response in myopic individuals (Hung and Ciuffreda, 1999). Post-near task accommodative responses following the near task clearly demonstrate the greater adaptive effects in myopic subjects.

From inspection of figure 8.5 it can be seen that the magnitude and decay duration of NITM in early-onset myopes is greatest when a passive observation task at distance follows a sustained cognitive task at near. Again, this area should be explored further to evaluate the effect of refractive stability. It is interesting to note that reduced accommodative after-effects were noted in this group when an active cognitive task at distance followed a cognitive task at near. Extended NITM duration was also seen when a passive distance task followed a passive near task. These findings suggest that it may be the passive nature of the distance task that increases the time course of NITM decay. The users of visual display units have been advised to take regular rest periods during prolonged work sessions. The work presented here suggests that the nature of the visual 'task' undertaken during the rest period may have important implications with regard to NITM. The results suggest, particularly for the early-onset myope, that an active visual task carried out at distance during the rest period may actually reduce the time course of NITM effects.

Abbott *et al.* (1998) have shown that accommodative inaccuracy is more apparent during the progression of myopia, with stable myopes showing similar stimulus/response curves to emmetropes. For the current study, no reliable data was available with regard to the stability of refractive error of the subject cohort. It was therefore not possible to conduct analyses between 'stable' and 'progressing' myopic subgroups. The significantly greater lag of accommodation observed in the LOM group during the near task does suggest that a proportion of these subjects may be progressing myopes. Further work is therefore suggested to examine the combined effects of accommodative and cognitive demand on NITM between stable and progressing myopic subjects.

The results of this study have shown that myopes are more susceptible to transient post-task myopic effects than emmetropes, thus supporting the findings of previous workers (Hung and Ciuffreda, 1999; Ciuffreda and Lee, 2002). Variation in post-task accommodative hysteresis as a result of cognitive demand has revealed no distinct pattern across refractive groups. Post-task myopic shifts in late onset myopes increased when a

cognitive load was imposed; this pattern was not evident in other refractive groups. Further work in this area is recommended using a similar experimental protocol, but with larger sample sizes to achieve greater statistical power.

Acknowledgement

CHAPTER 9
CONCLUSIONS AND PROPOSALS FOR FUTURE WORK

9.1 Conclusions from the present studies

The central experimental work of this thesis has been a longitudinal study of refractive error development in young adults, combined with a concurrent profile of ciliary smooth muscle innervation. Significant levels of late onset myopia developed in a proportion of subjects during the course of the study. Approximately one third of these subjects showed clinical signs indicating the presence of sympathetic inhibitory facility in the control of accommodation. A cross sectional study of autonomic profile of ciliary smooth muscle also revealed the presence of sympathetic facility in approximately one third of the total cohort, with an equal distribution of sympathetic inhibition across refractive error groups. From these findings it can be deduced that a deficiency of sympathetic control of accommodation is not a primary risk factor in the development of myopia. Further, it is suggested that the theoretical links between sympathetic deficit and a propensity to late onset myopia do not hold firm, as noted by Gilmartin and Winfield (1995) in a smaller subject cohort.

A feature of the above work has been the development (in collaboration) of a new system for continuous recording of ocular accommodation responses, based around the Shin-Nippon SRW-5000 open-view infra-red autorefractor and National Instruments *LabView* development software. It has been demonstrated that the system is capable of producing valid and repeatable monocular recordings of the accommodation response and pupil size variation, and provides advances in measurement facility over previous systems. The performance of the system offers considerable technical and operational advances over the Canon R-1 continuous recording system due to the ability to make simultaneous static and continuous measurements. This feature allows a calibration check of the continuous recording system to be carried out at any time. Further development of this system is in progress.

A longitudinal study of ocular biometric factors utilizing new apparatus (Zeiss *IOLMaster*) has confirmed axial length elongation as the primary structural correlate in late onset myopia. Ocular volume was found to correlate with the degree of myopia. During the development of late onset myopia in young emmetropic adult subjects, corneal curvature

and anterior chamber depth remain relatively unchanged. The performance of the Zeiss *IOLMaster* has been evaluated against traditional 'Gold Standard' biometric techniques. The performance of the *IOLMaster* in terms of validity and repeatability was impressive, and it is envisaged that the *IOLMaster* will become the standard instrument for ocular biometry in research laboratories due to its ease of use and non-invasive mode of operation.

In two separate sections of work, the gain and phase lag of the dynamic accommodation response were seen to degrade as temporal frequency of a dynamic stimulus increased. In contrast to previous studies, the instillation of both non-selective, and selective β-adrenoceptor antagonists was seen to reduce accommodative response gain at low to mid temporal frequencies. It may be the case that the accommodation responses of some individuals can be modified by selective β_1 antagonism, indicating an alternative interaction route between drug and oculomotor system. This effect warrants further investigation. The most likely explanation of the effects of both selective and non-selective β-antagonists is the lack of sympathetic inhibitiory facility in the subject group; the small reductions in accommodative gain perhaps being manifest as a result of ocular hypotensive effects. Augmentation of the α-adrenoceptor system induced a small increase in accommodative response gain, but to a lesser extent than previously observed. This increase in accommodative gain was not statistically significant; again, the general absence of sympathetic facility in the subject cohort can explain this finding.

From the work carried out it has been shown that no significant difference in autonomic innervation of ciliary smooth muscle and oculomotor function is apparent in the late onset myopic individual. Structurally, the late onset myopic eye manifests similar dimensional change as the early onset myopic eye. The magnitude of structural recalibration is smaller in LOM compared to EOM. This may be due to the older LOM eye being less amenable to growth than the younger EOM eye, and generally smaller amounts of myopia found in LOM eyes compared with EOM eyes. It is therefore concluded that eyes with a propensity for LOM development are no different from emmetropic eyes in terms of autonomic or oculomotor function. From this, it is suggested that risk factors in LOM may be found in the ergonomics of visual tasks of individuals: near working distance, position of chromatic focus, overall luminance of task, spectral response of task illumination. Further work in

these areas is required. Recommendations for future work in this area are proposed in section 9.3.

An important feature of this work has been the opportunity to carry out cross-correlations between autonomic profile, refractive error, refractive stability, ocular biometry, oculomotor responses and dynamic accommodation responses. The experimental designs employed have allowed examination of the interactive effects of a number of refractive, autonomic, oculomotor and biometric features; as a result it has been possible to formulate a profile of ocular features within emmetropic, early-onset and late-onset myopic groups.

9.2 Critical analysis of experimental work and suggestions for improvement

Ocular biometric measures were conducted using the Zeiss *IOLMaster*, a newly available instrument. The instrument was acquired by the laboratory 15 months into the course of the longitudinal study (Chapter 3). A clinical evaluation of the instrument was carried out immediately, the results of which were published in *British Journal of Ophthalmology*. Had this instrument been available earlier, full biometric measurements could have been made at each refractive error monitoring data point. This would have given the study the added benefit of concurrent refraction and biometric data over the full 30 months of the longitudinal study, rather than the actuality of full biometric data for only 12 months. Ethical constraints at the start of the longitudinal study prevented the use of A-scan ultrasonography due to the reported theoretical risk of transmission of variant Creutzfeld-Jacob disease between subjects following the re-use of devices contacting the ocular surface.

Autonomic profiling of the post-task open-loop accommodation response was also carried out over 1 year after the commencement of the longitudinal study of refractive error change (Chapter 3). The main reason for this delay was the development of the Shin-Nippon SRW-5000 continuous recording optometer system. The original experimental design involved the use of the Shin-Nippon device in static mode, which gave the facility to take measurements of accommodation at 1-second intervals. Interfacing to a personal computer was arranged via serial interface and dedicated computer program (Li and Edwards, 2001). Development of the continuous recording system was instigated by Dr. James Wolffsohn and Dr. Sei-Ichi Tsujimura following their appointments to the department during 2000. It was felt best to delay the taking of autonomic data until the

continuous recording facility was in place due to the significant improvement in temporal and dioptric resolution afforded by the new system. Had the system been in place earlier, a modified experimental strategy would have been used: carry out refractive screening in a group of young adults to identify emmetropic subjects. Profile the autonomic control of accommodation in these subjects. Identify 20 subjects showing a response to timolol maleate (i.e. subjects having sympathetic facility in accommodation control) and 20 subjects showing no response to timolol maleate (i.e. subjects lacking sympathetic inhibition of accommodation). Monitor refractive error in this (N = 40) subject cohort for 2.5 years.

9.3 Proposals for future work

9.3.1 Ocular biometric assessment of nearwork induced transient myopia.

Nearwork induced transient myopia (NITM) is thought to be a manifestation of hysteresis in the ciliary body/crystalline lens apparatus following intense near work (Ong and Ciuffreda, 1997). It would, however, be of interest to investigate the possibility of transient changes in structural dimensions associated with NITM. The Zeiss *IOLMaster* could be utilized to measure axial length, anterior chamber depth and corneal curvature before and after an intense near task. Addition of a beam splitter and Badal type focus stimulator could allow within-task *IOLMaster* measurements. A pilot study has shown that *IOLMaster* measurements are not significantly affected by the inclusion of a beam splitter device within the optical path (see Appendix 3). Advancement in this area will be achieved owing to the improved resolution in axial length measurement afforded by the *IOLMaster* over A-scan ultrasonography (i.e. 0.01 mm compared with 0.1 mm).

9.3.2 Monitoring of ocular biometric change during the onset and progression of late onset myopia.

It would be of interest to study the rate of structural change in a group of progressing late onset myopes. Permanent myopia results from a structural recalibration of the eye, namely an increase in vitreous chamber depth (Wildsoet, 1998). It is not known whether this structural change follows a monotonic progression rate. It may be the case that the rate of change varies according to the nature of visual tasks being carried out. The Zeiss *IOLMaster* is an ideal instrument with which to establish a longitudinal biometric profile of the late onset myopic eye. The instrument is non-invasive and does not require the use of ophthalmic drugs. Full biometric measurements (axial length, corneal curvature and

anterior chamber depth) can be completed on a single subject in less than 5 minutes. Initially, the screening of a potential subject cohort will be required to identify emmetropes. An ideal subject source would be first year undergraduate students at university intake. Refractive error screening by infra-red autorefractor would be carried out at the start of term 1. Ocular biometry and autorefraction would be carried out at 1 month intervals for the entire undergraduate study period (i.e. 3 years).

Also of interest would be the rate of change in refraction with respect to time of year and position in the academic calendar, and to correlate this change with the change in biometric profile. It has been shown in children that the rate of myopic progression is reduced during school vacations when, it is assumed, that less near work is carried out (Fulk and Cyert, 1996). Tan *et al.* (2000) observed an increase in rate of myopia progression in school children in the period immediately following examinations. It would be interesting to observe the rate of myopic change in a young adult university cohort before, during and after examination periods. Based on previous findings from child studies it is proposed that the rate of myopic change would increase following the intense near-work carried out during examinations and the preceeding revision period.

9.3.3 Position of retinal chromatic focus as a function of refractive error

The magnitude of longitudinal chromatic aberration of the human eye is around 1.50 to 2.50 D (Bedford and Wyszecki, 1957; Jenkins, 1963; Gilmartin and Hogan, 1985c; Howarth and Bradley, 1986). Longer wavelengths (red end of the visible spectrum) tend to be in focus during distance vision, and shorter wavelengths (blue end of the visible spectrum) are in closer focus during near vision due to the lead and lag of the accommodation response. The magnitude of the chromatic interval remains fairly constant over a range of accommodative states (Millodot and Sivak, 1973). It would be interesting to explore the possibility of differences in chromatic focus, especially at near, between refractive groups, and to examine whether the position of chromatic focus is altered during the onset and/or progression of late onset myopia.

Cooper and Pease (1988) estimated the position of chromatic focus in the human eye at distance (3 m) and near (40 cm) using a subjective Vernier optometer system. Vernier alignment of the optometer target was adjusted by the observer under 8 discrete illumination wavelengths, produced by a monochromator device. Large variation in the

wavelength in focus on the retina was found between the 14 subjects examined. At 3 m working distance, mean chromatic focus was 518 nm (range 457-593 nm); at 40 cm, mean chromatic focus was 468 nm (range 375-548 nm).

Alternative apparatus for the measurement of chromatic focus could consist of a modified Hartinger coincidence optometer fitted with a variable wavelength light source. The normal incandescent light source of the Hartinger optometer (Henson, 1996) could be replaced with a monochromator device to provide a narrow, variable peak wavelength, illumination system (Freeman, 1990). The optometer could be set to place the focal point of the instrument conjugate with the retina of the subject for the specific working distance employed. The wavelength of the monochromator output could then be adjusted until the position of best retinal focus was obtained. This should give a good estimate of chromatic focus with respect to a specific viewing distance. It would be of considerable interest to examine the position of chromatic focus during distance and near fixation as a function of refractive error; in particular, differences between emmetropes and late onset myopes.

9.3.4 Influence of spectral response of artificial lighting, and chromatic focus on lag of accommodation and late onset myopia.

Incandescent light sources (e.g. tungsten filament lamps) provide a wide, continuous spectrum of luminous output (North, 1993). Over recent years there has been a move away from traditional tungsten sources due to their relatively poor luminous efficiency. Modern gas discharge lamps have higher luminous efficiency than tungsten sources, but a trade off has been narrower output spectrum leading to poor colour rendering; the worst case being low pressure sodium lamps which have a monochromatic output. Also, the peak output wavelength is dependent on the type of source being used.

Longitudinal chromatic aberration of the human eye has been shown to be a powerful factor in the accommodation response (Kruger et al., 1994, 1997). Most recently, Seidemann and Schaeffel (2002a) have shown that reading in short wavelength (blue) light produces a smaller accommodative response when compared to reading in long wavelength (red) light. In the same study, it was seen that the refraction of newly hatched chicks could be manipulated by monochromatic light. Exposure to blue light (peak wavelength 430 nm) produced a hyperopic shift in refraction; conversely, exposure to red light (615 nm) produced a relative myopic shift in refraction. This area of work has a clear

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link with the widespread use of visual display units during near vision tasks. From previous findings it can be seen that the background colour of visual display units may have a powerful influence on the accommodative response. A situation where the peak wavelength of the visual display unit output is different to the chromatic focus of the eye may produce sufficient retinal blur to induce structural recalibration, and consequently myopic change.

A study is proposed in which the lag of accommodation to a near task, and the position of chromatic focus is measured under a variety of light sources. It is suggested that the output spectrum of a light source may have an effect on the magnitude of retinal blur experienced during a near task. Certain light sources may produce less retinal blur during near vision due to the relationship between the chromatic focus of the individual and the peak output wavelength of the light source. Where there is a greater difference between the peak wavelength of the light source and the position of chromatic focus, there will be a greater degree of retinal defocus during near tasks. This proposed effect may act as a contributory factor to the onset of myopic change. This work may have considerable ramifications in the lighting and ergonomic arrangements in the workplace. Consequently, the choice of appropriate light source for the illumination of near tasks may have a limiting effect on the propensity to late onset myopic change.

9.3.5 Measurement of retinal contour during accommodation and vergence.

The direct mechanical effects of the extraocular muscles upon the globe during accommodation and vergence have been suggested as possible myopigenic factors (Greene, 1980, 1991; Greene and McMahon, 1979). Changes in retinal contour have been difficult to measure due to ergonomic considerations and the resolution of measurement devices such as A-scan ultrasonography. The advent of partial coherence interferometric techniques allowed Drexler *et al.* (1998) to measure axial length changes during accommodation in emmetropes and myopes. Axial elongation during accomodation was found to be higher in emmetropes than myopes (12.7 μm and 5.2 μm respectively); this difference between refractive groups was statistically significant (p <0.001). Further work is required to investigate axial length variation between early onset and late onset myopes.

Walker and Mutti (2002) have used a Canon R-1 autorefractor to demonstrate ocular shape change during sustained accommodation. It has been shown that the *IOLMaster* is capable

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of making repeatable measurements of retinal contour (see Appendix 3). This feature could be applied to the measurement of retinal shape during accommodation. High resolution of the *IOLMaster* measurements (0.01mm) should allow detection of more subtle changes in the ocular dimensions occurring as a result of intra- and extraocular muscle forces exerted on the globe during accommodation. Scleral thinning reported in myopia (Wildsoet, 1998) may render the myopic eye more susceptible to ocular shape change during accommodation. These changes, although transient in nature, may contribute to post-task retinal blur following near work.

Additionally, the effects of convergence and gaze direction on transient structural change could be investigated. The tension in the extraocular muscles, and the force they exert on the globe is dependent on the direction of gaze (Greene, 1991). As a consequence, an interaction between accommodation and ocular rotation within the orbit may occur, thus forming a myopigenic force. An experiment is suggested in which the subject observes an accommodative target at a range of distances. Measurements of axial length are then made over time to investigate change in axial dimensions as a result of sustained accommodation.

Concluding statement.

This thesis has addressed a number of questions with regard to the onset and progression of late-onset myopia (LOM). Evidence has been presented to show that deficiency in sympathetic innervation of ciliary muscle is not likely to be associated with a propensity for LOM. A number of recommendations for further investigations in this enthralling area of research are suggested.

REFERENCES

Abbott, M. L., Schmid, K. L. and Strang, N. C. (1998). Differences in the accommodation stimulus response curves of adult myopes and emmetropes. *Ophthalmic and Physiological Optics.* **18,** 13-20.

Abdalla, M. I. And Hamdi, M. (1970). Applanation ocular tension in myopia and emmetropia. *British Journal of Ophthalmology.* **54,** 122-125.

Adams, A. J. (1987). Axial length elongation, not corneal curvature, as a basis of adult onset myopia. *American Journal of Optometry and Physiological Optics.* **64,** 150-152.

Ahlquist, R. P. (1948). A study of adrenotropic receptors. *American Journal of Physiology.* **153,** 586-600.

Armaly, M. F. and Burian, M. L. (1958). Changes in the tonogram during accommodation. *Archives of Ophthalmology.* **60,** 60-69.

Armaly, M. F. and Rubin, M. L. (1961). Accommodation and applanation tonometry. *Archives of Ophthalmology.* **54,** 122-125.

Armstrong, R. A., Slade, S. V. and Eperjesi, F. (2000). An introduction to analysis of variance (ANOVA) with special reference to data from clinical experiments in optometry. *Ophthalmic and Physiological Optics.* **20,** 235-241.

Atchison, D. A., Bradley, A., Thibos, L. N., and Smith, G. (1995). Useful variations of the Badal optometer. *Optometry and Vision Science.* **72,** 279-284.

Bailey, I. L. and Lovie, J. E. (1976). New design principles for visual acuity letter charts. *American Journal of Optometry and Physiological Optics.* **53,** 740-745.

Barrett, B. and McGraw, P. (1998). Clinical assessment of anterior chamber depth. *Ophthalmic and Physiological Optics.* **18,** S32-S39.

Bartlett, J. D., Niemann, K., Houde, B., Allred, T. and Edmondson, M. J. (2000). Safety and tolerability of pirenzipine ophthalmic gel in pediatric myopic patients. *Investigative Ophthalmology and Visual Science (Suppl).* **41,** 303.

Bedford, R. E. and Wyszecki, G. (1957). Axial chromatic aberration of the human eye. *Journal of the Optometric Society of America.* **47,** 564-565.

Bennett, R. and Rabbetts, A. (1998). *Clinical Visual Optics.* Oxford, Butterworth Heinemann.

Bland, J. H. S. and Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* **1,** 307-10.

Buckingham, T. and Young, R. (1986). The rise and fall of intraocular pressure: The influence of physiological factors. *Ophthalmic and Physiological Optics.* **6,** 95-99.

Bullimore, M. A., Fusaro, R. E. and Adams, C. W. (1998). The repeatability of automated and clinical refraction. *Optometry and Vision Science* **75,** 617-622.

Bullimore, M. A., Gilmartin, B. and Royston, J. M. (1992). Steady-state accommodation and ocular biometry in late-onset myopia. *Documenta Ophthalmologica.* **80,** 143-155.

Bullimore, M. A., Reuter, K. S., Jones, L., Mitchell, L., Bottjer, C. and Rah, M. (2002). The study of progression of adult nearsightedness (SPAN). *9th International Conference on Myopia.*

Butcher, J. M. and O'Brien, C. (1991). The reproducibility of biometry and keratometry measurements. *Eye.* **5,** 708-11.

Campbell, F. and Westheimer, G. (1960). Dynamics of the accommodation response of the human eye. *Journal of Physiology (London).* **151,** 285-295.

Charman, W. N. (1982). The accommodative resting point and refractive error. *Ophthalmic Optician.* **21,** 469-473.

Charman, W. N. (1983). The retinal image in the human eye. *Progress in Retinal Research.* **2**, 1-50.

Charman, W. N. and Heron, G. (1988). Fluctuations in accommodation: a review. *Ophthalmic and Physiological Optics.* **8**, 153-164.

Charman, W. N. and Whitefoot, H. (1977). Pupil diameter and the depth-of-focus of the human eye as measured by laser speckle. *Optica Acta.* **24**, 1211-1216.

Cheng, H. M., Singh, O. S., Kwong, K. K., Xiong, J., Woods, B. T. and Brady, T. J. (1992). Shape of the myopic eye as seen with high resolution magnetic resonance imaging. *Optometry and Vision Science.* **9**, 698-701.

Chua, W., Balakrishnan, V. and Chan, Y. (2002) Analysis of safety data for atropine in the treatment of myopia (ATOM) study. *ARVO abstract.* **B313.**

Ciuffreda, K. J. (1998). Accommodation, the pupil, and presbyopia. In: *Borish's Clinical Refraction.* Benjamin W. J. W. B. Saunders Company, Philadelphia.

Ciuffreda, K. J., Colburn, C. and Wallis, D. (1996). Effect of stimulus duration and dioptric demand on transient myopia. *Investigative Ophthalmology and Visual Science (Suppl).* **37**, 164.

Ciuffreda, K. J. and Lee, M. (2002). Differential refractive susceptibility to sustained nearwork. *Ophthalmic and Physiological Optics.* **22**, 372-379.

Ciuffreda, K. J. and Ordonez, X. (1995). Abnormal transient myopia in symptomatic individuals after sustained nearwork. *Optometry and Vision Science.* **72**, 506-510.

Ciuffreda, K. J. and Wallis, D. M. (1998). Myopes show increased susceptibility to nearwork aftereffects. *Investigative Ophthalmology and Visual Science.* **39**, 1797-1803.

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Cogan, D. G. (1937). Accommodation and the Autonomic Nervous System. *Archives of Ophthalmology.* **18,** 739-766.

Cohn, H. (1886). The Hygiene of the Eye in Schools, and English translation. Ed: Turnbull, W. P. Simpkin Marshall, London.

Coleman, D. J. and Trokel, S. (1969). Direct-recorded intraocular pressure variations in a human subject. *Archives of Ophthalmology.* **82,** 637-640.

Collins, C. C., Bach-y-Rita, P. and Loeb, D. R. (1967). Intraocular pressure variation with oculo-rotary muscle tension. *American Journal of Physiology.* **213,** 1039-1043.

Collins, M. J., Davis, B. and Wood, J.M. (1995). Micro-fluctuations of steady-state accommodation and the cardiopulmonary system. *Vision Research.* **35,** 2491-2512.

Cook, R. C. and Glasscock, R. E. (1951). Refractive and ocular findings in the newborn. *American Journal of Ophthalmology.* **34,**1407-1413.

Cooper, D. P. and Pease, P. L. (1988). Longitudinal chromatic aberration of the human eye and wavelength in focus. *American Journal of Optometry and Physiological Optics.* **65,** 99-107.

Culhane, H. M. (1999). Physiological and Perceptual Correlates of the Temporal Accommodation Response. PhD Thesis. Department of Optometry, University of Bradford.

Culhane, H. M. and Winn, B. (1997). Modulation of the temporal closed-loop accommodation response by sympathetic innervation. *Investigative Ophthalmology and Visual Science (Suppl).* **38,** S984.

Culhane, H. M. and Winn, B. (1999). Dynamic accommodation and myopia. *Investigative Ophthalmology and Visual Science.* **40,** 1968-1974.

Culhane, H. M., Winn, B. and Gilmartin, B. (1999). Human dynamic closed-loop accommodation augmented by sympathetic inhibition. *Investigative Ophthalmology and Visual Science.* **40,** 1137-1143.

Curtin, B. J., Iwamoto, T. and Renaldo, D. P. (1979). Normal and staphylomatous sclera of high myopia. *Archives of Ophthalmology.* **97,** 912-921.

David, R., Zangwill, L. M., Tessler, Z. and Yassur, Y. (1985). The correlation between intraocular pressure and refractive status. *Archives of Ophthalmology.* **103,** 1812-1815.

Davis, B., Collins, M. and Atchison, D. (1993). Calibration of the Canon Autoref R-1 for continuous measurement of accommodation. *Ophthalmic and Physiological Optics.* **13,** 191-198.

Davson, H. (1990). *Physiology of the eye.* London, Macmillan Press.

Diekhoff, G. (1992). Statistics for the social and behavioural sciences: Univariate, bivariate, multivariate. Wm. C. Brown Publishers, Dubuque.

Douthwaite, W. A., Hough, T., Edwards, K. and Notay, H. (1999). The eyesys videokeratoscopic assessment of apical radius and p-value in the normal human cornea. *Ophthalmic and Physiological Optics.* **19,** 467-474.

Drexler, W., Findl, O., Schmetterer, L., Hitzenberger, C. K. and Fercher, A. F. (1998). Eye elongation during accommodation in humans: Differences between emmetropes and myopes. *Investigative Ophthalmology and Visual Science.* **39,** 2140-2147.

Drobe, B. and de Saint-André, R. (1995). The pre-myopic syndrome. *Ophthalmic and Physiological Optics.* **15,** 375-378.

Dunne, M. (1995). A computing scheme for determination of retinal contour from peripheral refraction, keratometry and A-scan ultrasonography. *Ophthalmic and Physiological Optics.* **15,** 133-143.

Dunne, M. C. M., Barnes, D. A. and Clement, R. A. (1987). A model for retinal shape changes in ametropia. *Ophthalmic and Physiological Optics.* **7**, 159-160.

Eadie, A. S. and Carlin, P. J. (1995). Evolution of control system models of ocular accommodation, vergence and their interaction. *Medical and Biological Engineering and Computing.* **33**, 517-524.

Edwards, M. H. and Brown, B. (1996). IOP in myopic children: the relationship between increases in IOP and the development of myopia. *Ophthalmic and Physiological Optics.* **16**, 243-246.

Edwards, M. H., Chun, C. Y. and Leung, S. S. F. (1993). Intraocular pressure in an unselected sample of 6- to 7-year-old Chinese children. *Optometry and Vision Science.* **70**, 198-200.

Edwards, M. H., Li, R. W., Lam, C. S., Lew, J. K. and Yu, B. S. (2002). The Hong Kong progressive lens myopia control study: Study design and main findings. *Investigative Ophthalmology and Visual Science.* **43**, 2852-2858.

Ehrlich, D. L. (1987). Near vision stress: Vergence adaptation and accommodative fatigue. *Ophthalmic and Physiological Optics.* **7**, 353-357.

Ferree, C. E., Rand, G. and Hardy, C. (1931). Refraction for the peripheral field of vision. *Archives of Ophthalmology.* **5**, 717-731.

Fisher, S. K., Ciuffreda, K. J. and Levine, S. (1987). Tonic accommodation, accommodative hysteresis and refractive error. *American Journal of Optometry and Physiological Optics.* **64**, 799-809.

Fledelius, H. C. (1995). Adult onset myopia - oculometric features. *Acta Ophthalmologica.* **73**, 397-401.

Flitcroft, D. I. (1998). A model of the contribution of oculomotor and optical factors to emmetropization and myopia. *Vision Research.* **38**, 2869-2879.

Flitcroft, D. I. (1999). The lens paradigm in experimental myopia: Oculomotor, optical and neurophysiological considerations. *Ophthalmic and Physiological Optics.* **19**, 103-111.

Fong, D. S. (1997). Is myopia related to amplitude of accommodation? *American Journal of Ophthalmology.* **123**, 416-418.

Fredrick, D. R. (2002). Myopia. *British Medical Journal.* **324**, 1195-1199.

Freeman, M. H., (1990). Optics. Tenth edition. Butterworth-Heinemann, Oxford.

Fulk, G. W. and Cyert, L. A. (1996). Can bifocals slow myopia progression? *Journal of the American Optometric Association.* **67**, 749-754.

Gawron, V. (1981). Differences among myopes, emmetropes and hyperopes. *American Journal of Optometry and Physiological Optics.* **58**, 753-760.

Giles, G. H. (1965). The principles and practice of refraction and its allied subjects. Second edition. Hammond, Hammond & Company Ltd. London.

Gilmartin, B. (1986). A review of the role of sympathetic innervation of the ciliary muscle in ocular accommodation. *Ophthalmic and Physiological Optics.* **6**, 23-37.

Gilmartin, B. (1998). Autonomic correlates of near-vision in emmetropia and myopia. In: *Myopia and Nearwork.* Eds: M. Rosenfield and B. Gilmartin. Butterworth-Heinemann, Oxford. pp 117-146.

Gilmartin, B. and Bullimore, M. A. (1987). Sustained near-vision augments sympathetic innervation of the ciliary muscle. *Clinical Vision Science.* **1**, 197-208.

Gilmartin, B. and Bullimore, M. A. (1991). Adaptation of tonic accommodation to sustained visual tasks in emmetropia and late-onset myopia. *Optometry and Vision Science.* **68**, 22-26.

Gilmartin, B., Bullimore, M. A., Rosenfield, M., Winn, B. and Owens, H. (1992). Pharmacological effects on accommodative adaptation. *Optometry and Vision Science.* **69**, 276-282.

Gilmartin, B. and Hogan, R. E. (1985). The role of the sympathetic nervous system in ocular accommodation and ametropia. *Ophthalmic and Physiological Optics.* **5**, 91-93.

Gilmartin, B. and Hogan, R. E. (1985b). The relationship between tonic accommodation and ciliary muscle innervation. *Investigative Ophthalmology and Visual Science.* **26**, 1024-1028.

Gilmartin, B. and Hogan, R. E. (1985c). The magnitude of longitudinal chromatic aberration of the human eye between 458 and 633 nm. *Vision Research.* **25**, 1747-1753.

Gilmartin, B., Logan, N. S. and Wildsoet, C. F. (2002a). Posterior retinal contours in Taiwanese Chinese and Caucasian Anisomyopia. 19th International Conference on Myopia.

Gilmartin, B., Mallen, E. A. H. and Wolffsohn, J. S. (2002b). Sympathetic control of accommodation: evidence for inter-subject variation. *Ophthalmic and Physiological Optics* **22**, 366-371.

Gilmartin, B. and Winfield, N. R. (1995). The effect of topical beta-adrenoceptor antagonists on accommodation in emmetropia and myopia. *Vision Research.* **35**, 1305-1312.

Goss, D. A. (1986). Effect of bifocal lenses on the rate of childhood myopia progression. *American Journal of Optometry and Physiological Optics.* **63**, 135-141.

Goss, D. A. (1991). Clinical accommodation and heterophoria findings preceding juvenile onset of myopia. *Optometry and Vision Science.* **68**, 110-116.

Goss, D. A. and Caffey, T. W. (1999). Clinical findings before the onset of myopia in youth: 5. Intraocular pressure. *Optometry and Vision Science.* **76**, 286-291.

Goss, D. A., Cox, V. D., Herrin-Lawson, G. A., Neilson, E. D. and Dolton, W. A. (1990). Refractive error, axial length, and height as a function of age in young myopes. *Optometry and Vision Science.* **67,** 332-338.

Goss, D. A. and Grosvenor, T. (1990). Rates of childhood myopia progression with bifocals as a function of nearpoint phoria: consistency of three studies. *Optometry and Vision Science.* **67,** 637-640.

Goss, D. A. and Jackson, T. W. (1995). Clinical findings before the onset of myopia in youth: 1 Ocular optical components. *Optometry and Vision Science* **72,** 870-878.

Goss, D. A. and Jackson, T. W. (1996a). Clinical findings before the onset of myopia in youth: 3. Heterophoria. *Optometry and Vision Science.* **73,** 269-278.

Goss, D. A. and Jackson, T. W. (1996b). Clinical findings before the onset of myopia in youth: 4. Parental history of myopia. *Optometry and Vision Science.* **73,** 279-282.

Goss, D. A. and Rosenfield, M. (1998). Vergence and Myopia. In: *Myopia and Nearwork.* Eds: M. Rosenfield and B. Gilmartin. Butterworth-Heinemann, Oxford. pp 147-161.

Goss, D. A. and Winkler, R. L. (1983). Progression of myopia in youth: age of cessation. *American Journal of Optometry and Physiological Optics.* **60,** 651-658.

Goss, D. A. and Zhai, H. (1994). Clinical and laboratory investigations of the relationship of accommodation and convergence function with refractive error. *Documenta Ophthalmologica.* **86,** 349-380.

Gottlieb, M. D., Fugate-Wentzek, L. A. and Wallman, J. (1987). Different visual deprivations produce different ametropias and different eye shapes. *Investigative Ophthalmology and Visual Science.* **28,** 1225-1235.

Gray, L. S., Winn, B. and Gilmartin, B. (1993). Accommodative microfluctuations and pupil diameter. *Vision Research.* **33,** 2083-2090.

Greene, P. R. (1980). Mechanical considerations in myopia: relative effects of accommodation, convergence, intraocular pressure, and the extraocular muscles. *American Journal of Optometry and Physiological Optics.* **57**, 902-914.

Greene, P. R. (1991). Mechanical considerations in myopia. In: *Refractive Anomolies. Research and Clinical Applications.* (Eds: T. Grosvenor and M.C. Flom). Butterworth-Heinemann, pp 287-300.

Greene, P. R. and McMahon, T. A. (1979). Scleral creep vs temperature and pressure in vitro. *Experimental Eye Research.* **29**, 527-537.

Grosvenor, T. (1988). High axial length/corneal radius as a risk factor in the development of myopia. *American Journal of Optometry and Physiological Optics.* **65**, 689-696.

Grosvenor, T., Perrigin, D. M., Perrigin, J. and Maslovtz, B. (1987) Houston myopia control study: a randomised clinical trial. Part II. Final report by the patient care team. *American Journal of Optometry and Physiological Optics.* **63**, 482-98.

Grosvenor, T. and Scott, R. (1991). Comparison of refractive components in youth-onset and early adult-onset myopia. *Optometry and Vision Science.* **68**, 204-209.

Grosvenor, T. and Scott, R. (1993). Three-year changes in refraction and its components in youth-onset and early adult onset myopia. *Optometry and Vision Science* **70**, 677-683.

Grosvenor, T. and Scott, R. (1994). Role of the axial length/corneal radius ratio in determining the refractive state of the eye. *Optometry and Vision Science* **71**, 573-579.

Guggenheim, J. A. and McBrien, N. A. (1996). Form-deprivation myopia induces activation of scleral matrix metalloproteinase-2 in tree shrew. *Investigative Ophthalmology and Visual Science.* **37**, 1380-1395.

Gustafsson, J., Terenius, E., Buchheiser, J. and Unsbo, P. (2001). Peripheral astigmatism in emmetropic eyes. *Ophthalmic and Physiological Optics* **21**, 393-400.

Gwiazda, J., Bauer, J., Thorn, F. and Held, R. (1995). A dynamic relationship between myopia and blur-driven accommodation in school-aged children. *Vision Research.* **35**, 1299-1304.

Gwiazda, J., Grice, K. and Thorn, F. (1999). Response AC/A ratios are elevated in myopic children. *Ophthalmic and Physiological Optics* **19**, 173-179.

Gwiazda, J., Thorn, F., Bauer, J. and Held, R. (1993a). Myopic children show insufficient accommodative response to blur. *Investigative Ophthalmology and Visual Science.* **34**, 690-694.

Gwiazda, J., Thorn, F., Bauer, J. and Held, R. (1993b). Emmetropization and the progression of manifest refraction in children followed from infancy to puberty. *Clinical Vision Science.* **8**, 337-344.

Haigis, W., Lege, B., Miller, N. and Schneider, B. (2000). Comparison of immersion ultrasound biometry and partial coherence interferometry for intraocular lens calculation according to Haigis. *Graefe's Archives of Clinical and Experimental Ophthalmology.* **238**, 765-773.

Hammond, C. J., Sneider, H., Gilbert, C. E. and Spector, T. D. (2001). Genes and environment in refractive error: the twin eye study. *Investigative Ophthalmology and Visual Science.* **42**, 1232-1236.

Harper, J. (2001). Ocular biometric correlates of early- and late-onset myopia. Ph.D thesis. Aston University, Birmingham.

Henson, D. B. (1996). Optometric Instrumentation. Second Edition. Butterworth-Heinemann, Oxford.

Hepsen, I. F., Evereklioglu, C. and Bayramlar, H. (2001). The effect of reading and near-work on the development of myopia in emmetropic boys: a prospective, controlled, three-year follow-up study. *Vision Research.* **41**, 2511-2520.

Heron, G. and Winn, B. (1989). Binocular accommodation reaction and response times for normal observers. *Ophthalmic and Physiological Optics*. **9**, 176-183.

Hitzenberger, C. (1991). Optical measurement of the axial eye length by laser dopler interferometry. *Investigative Ophthalmology and Visual Science*. **32**, 616-624.

Hogan, R. (1985). Aspects of Tonic Accommodation and Tonic Vergence. Ph.D thesis. Vision Sciences. University of Aston. Birmingham.

Hogan, R. and Gilmartin, B. (1984). The choice of laser speckle exposure duration in the measurement of tonic accommodation. *Ophthalmic and Physiological Optics*. **9**, 431-436.

Hopkins, G. and Pearson, R. (1998) O'Connor Davies's Ophthalmic Drugs: Diagnostic and Therapeutic Uses. Butterworth-Heinemann, Oxford.

Howarth, P. A. and Bradley, A. (1986). The longitudinal chromatic aberration of the human eye, and its correction. *Vision Research*. **26**, 361-366.

Hung, G. K. and Ciuffreda, K. J. (1999). Adaptation model of nearwork-induced transient myopia. *Ophthalmic and Physiological Optics*. **19**, 151-158.

Hung, G. K., Ciuffreda, K. J. and Rosenfield, M. (1996). Proximal contribution to a linear static model of accommodation and vergence. *Ophthalmic and Physiological Optics*. **16**, 31-41.

Hung, G. K. and Semmlow, J. L. (1980). Static behaviour of accommodation and vergence: computer simulation of an interactive dual-feedback system. *IEEE Transactions on Biomedical Engineering*. **27**, 439-447.

Hurwitz, B., Davidowitz, J., Chin, N. B. and Breinin, G. M. (1972a). The effects of the sympathetic nervous system on accommodation: 1. Beta sympathetic nervous system. *Archives of Ophthalmology*. **87**, 668-678.

Hurwitz, B., Davidowitz, J., Chin, N. B. and Breinin, G. M. (1972b). The effects of the sympathetic nervous system on accommodation: 2. Alpha sympathetic nervous system. *Archives of Ophthalmology* **87**, 675-678.

Hyman, L., Gwiazda, J., Marsh-Tootle, W., Norton, T. and the COMET Group. (2001). The correction of myopia evaluation trial (COMET): Design and baseline characteristics. *Controlled Clinical Trials.* **22**, 573-592.

Irving, E. L., Callender, M. G. and Sivak, J. G. (1991). Inducing myopia, hyperopia, and astigmatism in chicks. *Optometry and Vision Science.* **68**, 364-368.

Irving, E. L., Sivak, J. G. and Callender, M. G. (1992). Refractive plasticity of the developing chick eye. *Ophthalmic and Physiological Optics.* **12**, 448-456.

Jenkins, T. C. A. (1963). Aberrations of the eye and their effects on vision: Part II. *British Journal of Physiological Optics.* **20**, 161-201.

Jiang, B. C. (1995). Parameters of accommodative and vergence systems and the development of late-onset myopia. *Investigative Ophthalmology and Visual Science.* **36**, 1737-1742.

Jiang, B. C. and Morse, S. E. (1999). Oculomotor functions and late-onset myopia. *Ophthalmic and Physiological Optics.* **19**, 165-172.

Jiang, B. C. and Woessner, W. M. (1996). Vitreous chamber elongation is responsible for myopia development in a young adult. *Optometry and Vision Science.* **73**, 231-234.

Kaufman, P. L. (1992). Accommodation and presbyopia: neuro-muscular and biophysical aspects. *Adler's physiology of the eye.* M. H. Hart. St Louis, Mosby Year Books.

Kikkawa, Y. and Sato, T. (1963). Elastic properties of the lens. *Experimental Eye Research.* **2**, 210-215.

206

Kotulak, J. C. and Schor, C. M. (1987). The effects of optical vergence, contrast and luminance on the accommodative response to spatially bandpass filtered targets. *Vision Research* **27**, 1797-1806.

Kruger, P. B., Mathews, S., Katz, M., Aggarwala, K. R. and Nowbotsing, S. (1997). Accommodation without feedback suggests directional signals specify ocular focus. *Vision Research.* **37**, 2511-2526.

Kruger, P. B., Mathews, S., Kruger, E. S. and Aggarwala, K. R. (1994). Accommodation responds to changing contrast of the red, green and blue components of the retinal image. *Investigative Ophthalmology and Visual Science (Suppl).* **35**, 1281.

Kruger, P. B. and Pola, J. (1986). Stimuli for accommodation: Blur, chromatic aberration and size. *Vision Research.* **26**, 957-971.

Krumholz, D. M., Fox, R. S. and Ciuffreda, K. J. (1986). Short-term changes in tonic accommodation. *Investigative Ophthalmology and Visual Science.* **27**, 552-557.

Lam, A. K. C., Chan, R. and Pang, P. C. K. (2001). The repeatability and accuracy of axial length and anterior chamber depth measurements from the IOLMaster. *Ophthalmic and Physiological Optics.* **21**, 477-483.

Lancaster, W. and Williams, E. (1914). New light on the theory of accommodation, with practical applications. *Transactions of the Amerian Acadademy of Ophthalmology and Oto-Laryng.* **19**, 170-195.

Leech, E. M., Cottriall, C. L. and McBrien, N. A. (1995). Pirenzipine prevents form deprivation myopia in a dose dependent manner. *Ophthalmic and Physiological Optics.* **15**, 351-356.

Leibowitz, H. W. and Owens, D. A. (1978). New evidence for the intermediate position of relaxed accommodation. *Documenta Ophthalmologica.* **46**, 133-147.

Li, R. W. H. and Edwards, M. H. (2001). Interfacing the Shin-Nippon autorefractor SRW-5000 with a personal computer. *Ophthalmic and Physiological Optics.* **21**, 114-116.

Liu, H. K., Chiou, G. C. Y. and Garg, L. C. (1980). Ocular hypotensive effects of timolol in cats eyes. *Archives of Ophthalmology.* **98**, 1467-1469.

Logan, N. S. (1997). Ocular Biometric Investigation of Anisometropia. Ph.D. thesis. Vision Sciences, Aston University, Birmingham.

Logan, N. S., Gilmartin, B. and Dunne, M. C. M. (1995). Computation of retinal contour in anisomyopia. *Ophthalmic and Physiological Optics.* **15**, 363-366.

Love, J., Gilmartin. B. and Dunne, M. C. M. (2000). Relative peripheral refractive error in adult myopia and emmetropia. *Investigative Ophthalmology and Visual Science (Suppl).* **41**, S302.

Mallen, E. A. H., Wolffsohn, J. S., Gilmartin, B. and Tsujimura, S. (2001). Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in adults. *Ophthalmic and Physiological Optics.* **21**, 101-107.

Mauger, R. R., Likens, C. P. and Applebaum, M. (1984). Effects of accommodation and repeated applanation tonometry on intraocular pressure. *American Journal of Physiological Optics.* **61**, 28-30.

McBrien, N. A. and Adams, D. W. (1997). A longitudinal investigation of adult-onset and adult-progression of myopia in an occupational group. Refractive and biometric findings. *Investigative Ophthalmology and Visual Science.* **38**, 321-333.

McBrien, N. A. and Barnes, D. A. (1984). A review and evaluation of theories of refractive error development. *Ophthalmic and Physiological Optics* **4**, 201-213.

McBrien, N. A. and Millodot, M. (1985). Clinical evaluation of the Canon Autoref R-1. *American Journal of Optometry and Physiological Optics.* **62**, 786-792.

McBrien, N. A. and Millodot, M. (1986a). Amplitude of accommodation and refractive error. *Investigative Ophthalmology and Visual Science.* **27**, 1187-1190,

McBrien, N. A. and Millodot, M. (1986b). The effect of refractive error on the accommodative response gradient. *Ophthalmic and Physiological Optics* **6**, 145-149.

McBrien, N. A. and Millodot, M. (1987a). The relationship between tonic accommodation and refractive error. *Investigative Ophthalmology and Visual Science.* **28**, 997-1004.

McBrien, N. A. and Millodot, M. (1987b). Biometric investigation of late-onset myopic eyes. *Acta Ophthalmologica.* **65**, 461-468.

McBrien, N. A. and Millodot, M. (1988). Differences in adaptation of tonic accommodation with refractive state. *Investigative Ophthalmology and Visual Science.* **29**, 460-469.

Medina, A. and Fariza, E. (1993). Emmetropization as a first order feedback system. *Vision Research.* **33**, 21-26.

Midelfart, A. M., Aamo, B., Sjohaug, K. A. and Dysthe, B. E. (1992). Myopia among medical students in Norway. *Acta Ophthalmologica* **70**, 317-322.

Millodot, M. (1981). Effect of ametropia on peripheral refraction. *American Journal of Optometry and Physiological Optics.* **58**, 691-695.

Millodot, M. and Sivak, J. (1973). Influence of accommodation on the chromatic aberration of the eye. *British Journal of Physiological Optics.* **28**, 169-174.

Miwa, T. and Tokoro, T. (1993). Accommodative hysteresis of refractive errors in light and dark fields. *Optometry and Vision Science* **70**, 323-327.

Morse, S. and Smith, E. (1993). Long-term adaptational aftereffects of accommodation are associated with distal dark focus and not with late onset myopia. *Investigative Ophthalmology and Visual Science (Suppl).* **34**, 1308.

Mutti, D. O., Jones, L. A., Mitchell, G. L., Moeschberger, M. L. and Zadnik, K. (2002). Excess accommodative lag accompanies but does not precede the onset of myopia. *ARVO abstract.* **B522.**

Mutti, D. O., Jones, L. A., Moeschberger, M. L. and Zadnik, K. (2000a). AC/A ratio, age and refractive error in children. *Investigative Ophthalmology and Visual Science.* **41,** 2469-2478.

Mutti, D. O., Sholtz, R. I., Friedman, N. E. and Zadnik, K. (1997). Peripheral refraction and ocular shape in children. *Investigative Ophthalmology and Visual Science (Suppl).* **38,** S1157.

Mutti, D. O., Sholtz, R. I., Friedman, N. E. and Zadnik, K. (2000b). Peripheral refraction and ocular shape in children. *Investigative Ophthalmology and Visual Science.* **41,** 1022-1030.

Mutti, D. and Zadnik, K. (1997). Refractive error. *The Ocular Examination.* K. Zadnik. Philadelphia, WB Saunders.

Ni, J., and Smith, E. L. (1989). Effects of chronic optical defocus on the kitten's refractive status. *Vision Research.* **29,** 929-938.

North, R. V. (1993). Lamps and lighting. In: Work and the eye. Butterworth-Heinemann. Oxford.

O'Neal, M. R. and Connon, T. R. (1987). Refractive error change at the United States Air Force academy - Class of 1985. *American Journal of Optometry and Physiological Optics.* **64,** 344-354.

Ong, E. and Ciuffreda, K. J. (1995). Nearwork-induced transient myopia- a critical review. *Documenta Ophthalmologica.* **91,** 57-85.

Ong, E. and Ciuffreda, K. J. (1997). Nearwork-induced transient myopia. *In:* Accommodation, Myopia and Nearwork. Optometric Extension Program Foundation, Santa Ana.

Ong, E., Ciuffreda, K. J. and Rosenfield, M. (1994). Accommodation, vergence and nearwork-induced transient myopia. *Optometry and Vision Science (suppl).* **71,** 129.

Ong, E., Ciuffreda, K. and Rosenfield, M. (1995). Effect of target proximity on transient myopia induced by equidioptic stimuli. *Optometry and Vision Science.* **72,** 502-505.

Ong, E., Grice, K., Held, R., Thorn, F. and Gwiazda, J. (1999). Effects of spectacle intervention on the progression of myopia in children. *Optometry and Vision Science.* **76,** 363-369.

Ostberg, O. (1980). Accommodation and visual fatigue in display work. *Ergonomic aspects of Visual Display Terminals.* E. Grandjean and E. Vigliani. Taylor and Francis, London. 41-52.

Owens, D. A. and Wolf-Kelly, K. (1987). Near work, visual fatigue and variations of oculomotor tonus. *Investigative Ophthalmology and Visual Science.* **28,** 743-749.

Pacella, R., McClellan, J., Grice, K., Del Bono, E. A., Wiggs, J. L. and Gwiazda, J. E. (1999). Role of genetic factors in the etiology of juvenile-onset myopia based on a longitudinal study of refractive error. *Optometry and Vision Science.* **76,** 381-386.

Portello, J. K., Rosenfield, M. and O'Dwyer, M. (1997). Clinical characteristics of pre-myopic individuals. *Optometry and Vision Science (Suppl).* **74,** 176.

Post, R. B., Johnson, C. A. and Tsuetaki, T. K. (1984). Comparison of laser and infrared techniques for the measurement of the resting focus of accommodation: mean differences and long-term variability. *Ophthalmic and Physiological Optics.* **4,** 327-332.

Pruett, R. C. (1988). Progressive myopia and intraocular pressure, what is the linkage? A literature review. *Acta Ophthalmological (Suppl.).* **185,** 117-129.

Pugh, J. R., Eadie, A. S., Winn, B. and Heron, G. (1987). Power spectrum analysis in the study of ocular mechanisms. *Ophthalmic and Physiological Optics.* **7**, 321-324.

Pugh, J. R. and Winn, B. (1988). Modification of the Canon Auto Ref R-1 for use as a continuously recording infra-red optometer. *Ophthalmic and Physiological Optics.* **8**, 460-464.

Pugh, J. R. and Winn, B. (1989). A procedural guide to the modification of the Canon Autoref R-1 for use as a continuously recording optometer. *Ophthalmic and Physiological Optics.* **9**, 451-454.

Raj, P. S., Ilango, B. and Watson, A. (1998). Measurement of axial length in the calculation of intraocular lens power. *Eye.* *12*, 227-229.

Ramsdale, C. and Charman, W. (1989). A longitudinal study of the changes in the static accommodation response. *Ophthalmic and Physiological Optics.* **9**, 255-263.

Ray, W. A. and O'Day, D. M. (1985). Statistical analysis of multi-eye data in ophthalmic research. *Investigative Ophthalmology and Visual Science.* **26**, 1186-1188.

Rempt, F., Hoogerheide, J. and Hoogenboom, W. P. H. (1971). Peripheral retinoscopy and the skiagram. *Ophthalmologica.* **162**, 1-10.

Reuter, K. S., Jones, L. A., Mitchell, G., Rah, M. and Bullimore, M. A. (2002). The Study of Progression of Adult Nearsightedness (SPAN): Pilot study results. *ARVO Abstract.* **B519**.

Robinson, D. A. (1964). The mechanism of human saccadic eye movement. *Journal of Physiology.* **174**, 245-264.

Rosenfield, M. (1997). Accommodation. *The Ocular Examination.* K. Zadnik. Philadelphia, W.B.Saunders Company.

Rosenfield, M. (1998). Accommodation and myopia. In: Myopia and Nearwork. Eds: M. Rosenfield and B. Gilmartin. Butterworth Heinemann, Oxford.

Rosenfield, M. and Abraham-Cohen, J. A. (1999). Blur sensitivity in myopes. *Optometry and Vision Science.* **76,** 303-307.

Rosenfield, M. and Baker, F. J. (1998). Testing the gradient AC/A ratio with plus or minus lenses: Does it matter? *Optometry and Vision Science.* **75 (Suppl),** 257.

Rosenfield, M. and Ciuffreda, K. J. (1994). Cognitive demand and transient nearwork-induced myopia. *Optometry and Vision Science.* **71,** 381-385.

Rosenfield, M., Ciuffreda, K. J., Hung, G. K. and Gilmartin, B. (1993). Tonic accommodation: a review. 1. Basic aspects. *Ophthalmic and Physiological Optics.* **13,** 266-284.

Rosenfield, M., Ciuffreda, K. J. and Novogrodsky, L. (1992a). Contribution of accommodation and disparity-vergence to transient nearwork-induced myopic shifts. *Ophthalmic and Physiological Optics.* **12,** 433-436.

Rosenfield, M., Ciuffreda, K. J., Novogrosky, L., Yu, A. and Gillard, M. (1992b). Sustained near vision does indeed induce myopia! *Investigative Ophthalmology and Visual Science (Suppl).* **33,** 710.

Rosenfield, M. and Gilmartin, B. (1987). Effect of a near-vision task on the response AC/A of a myopia population. *Ophthalmic and Physiological Optics.* **7,** 225-233.

Rosenfield, M. and Gilmartin, B. (1988). Disparity-induced accommodation in late-onset myopia. *Ophthalmic and Physiological Optics* **8,** 353-355.

Rosenfield, M. and Gilmartin, B. (1989). Temporal aspects of accommodative adaptation. *Optometry and Vision Science.* **66,** 229-234.

Rosenfield, M. and Gilmartin, B. (1998). Myopia and nearwork: causation or merely association. In: *Myopia and Nearwork.* Eds: M. Rosenfield and B. Gilmartin. Butterworth Heinemann, Oxford.

Rosenfield, M. and Gilmartin, B. (1999). Accommodative error, adaptation and myopia. *Ophthalmic and Physiological Optics.* **19,**159-164.

Rosner, J. and Rosner, J. (1989). Relation between clinically measured tonic accommodation and refractive status in 6 to 14 year old children. *Optometry and Vision Science.* **66,** 436-439.

Ruskell, G. L. (1973). Sympathetic innervation of the ciliary muscle in monkeys. *Experimental Eye Research.* **16,** 183-190.

Ruskell, G. L. (1990). Accommodation and the nerve pathway to the ciliary muscle: a review. *Ophthalmic and Physiological Optics.* **10,** 239-242.

Santodomingo-Rubido, J., Mallen, E. A. H., Gilmartin, B. and Wolffsohn, J. S. (2002). A new non-contact optical device for ocular biometry. *British Journal of Ophthalmology.* **86,** 458-462.

Saude, T. (1993). *Ocular anatomy and physiology.* London, Blackwell Scientific Publications.

Saw, S. M., Gazzard, G., Au Eong, K-G. and Tan, D. T. H. (2002). Myopia: attempts to arrest progression. *British Journal of Ophthalmology.* **86,** 1306-1311.

Saw, S. M., Katz, J., Schein, O. D., Chew, S. J. and Chan, T. K. (1996). Epidemiology of myopia. *Epidemiologic Reviews.* **18,** 175-187.

Saw, S. M., Wu, H. M., Seet, B., Wong, T. Y., Yap, E., Chia, K. S., Stone, R. A. and Lee, L. (2001). Academic achievement, close up work parameters, and myopia in Singapore military conscripts. *British Journal of Ophthalmology.* **85,** 855-860.

Schaeffel, F. and Howland, H. (1991). Properties of the feedback loops controlling eye growth and refractive state in the chicken. *Vision Research.* **31,** 717-734.

Schor, C. M. (1992). A dynamic model of cross-coupling between accommodation and convergence: Simulations of step and frequency responses. *Optometry and Vision Science.* **69,** 258-269.

Schor, C. M., Johnson, C. A. and Post, R. B. (1984). Adaptation of tonic accommodation. *Ophthalmic and Physiological Optics.* **4,** 133-137.

Schor, C. M., Kotulak, J. C. and Tsuetaki, T. (1986). Adaptation of tonic accommodation reduces accommodative lag and is masked in darkness. *Investigative Ophthalmology and Visual Science.* **27,** 820-827.

Seidemann, A. and Schaeffel, F. (2002a). Effects of longitudinal chromatic aberration on accommodation and emmetropization. *Vision Research.* **42,** 2409-2417.

Seidemann, A. and Schaeffel, F. (2002b). Factors influencing the measurement of lag of accommodation. *9th International Conference on Myopia.*

Shah, B., Hubbard, B., Stewart-Jones, J. H. and Edgar, D. F. (1989). Influence of thymoxamine eye-drops on the mydriatic effect of tropicamide and phenylephrine alone and in combination. *Ophthalmic and Physiological Optics.* **9,** 153-155.

Smith, E. L. (1998). Environmentally induced refractive errors in animals. In: Myopia and Nearwork. Eds: Rosenfield, M., and Gilmartin, B. Butterworth-Heinemann. Oxford.

Smith, E. L., Bradley, D. V., Fernandes, A. and Boothe, R. G. (1999). Form deprivation in adolescent monkeys. *Optometry and Vision Science.* **76,** 428-432.

Snell, R. and Lemp, M. (1989). *Clinical Anatomy of the Eye.* Boston, Blackwell Scientific Publications.

Sorsby, A., Leary, G. A. and Richards, M. J. (1962a). The optical components in anisometropia. *Vision Research.* **2,** 43-51.

Sorsby, A., Leary, G. A. and Richards, M. J. (1962b). Correlation ametropia and component ametropia. *Vision Research.* **2,** 309-313.

Sorsby, A., Sheridan, M. and Leary G. A. (1960). Vision, visual acuity and ocular refraction of young men. *British Medical Journal.* **1,** 1394-1398.

Sperduto, R. D., Seigel, D., Roberts, J. and Rowland, M. (1983). Prevalence of myopia in the United States. *Archives of ophthalmology* **101,** 405-407.

Stark, L. R. and Atchison, D. A. (1994). Subject instructions and methods of target presentation in accommodation research. *Investigative Ophthalmology and Visual Science.* **35,** 528-537.

Stenstrom, S. (1948). Investigation of the variation and the correlation of the optical elements of human eyes (translated by D. Woolf). *American Journal of optometry and Archives of the American Academy of Optometry.* **25,** 218-232, 286-299, 340-350, 388-397, 438-451, 496-505.

Stewart, R. H., Kimbrough, R. L. and Ward, R. L. (1986). Betaxolol vs timolol: a six month double-blind comparison. *Archives of Ophthalmology.* **104,** 46-48.

Storey, J. K. (1982). Measurement of the eye with ultrasound. *Ophthalmic Optician.* **22,** 150-160.

Strang, N. C. (1995). Modulation of Foveal Image Quality in Myopia: Investigation of Spatiotopic and Retinotopic Factors. PhD thesis. Department of Vision Sciences. Glasgow Caledonian University.

Strang, N. C., Gilmartin, B., Gray, L. S., Winfield, N. R. and Winn, B. (2000). Open-loop accommodation in emmetropia and myopia. *Current Eye Research.* **20,** 190-194.

216

Strang, N. C., Winn, B. and Gilmartin, B. (1994). Repeatability of post-task regression of accommodation in emmetropia and late-onset myopia. *Ophthalmic and Physiological Optics* **14**, 88-91.

Subbaram, M. V. and Bullimore, M. A. (2002). Visual acuity and the accuracy of the accommodative response. *Ophthalmic and Physiological Optics*. **22**, 312-318.

Sutton, M. R. and Ditmars, D. L. (1970). Vision problems at West Point. *Journal of the American Optometric Association*. **41**, 263-265.

Takei, K., Sekine, Y., Okamoto, F. and Hommura, S. (2002). Measurement of axial length of eyes with incomplete filling of silicone oil in the vitreous cavity using X-ray computed tomography. *British Journal of Ophthalmology*. **86**, 47-50.

Tan, N. W. H., Saw, S. M., Lam, D. S. C., Cheng, H. M., Rajan, U. and Chew, S. J. (2000). Temporal variations in myopia progression in Singaporean children within an academic year. *Optometry and Vision Science*. **77**, 465-472.

Tan, R. K. T. and O'Leary, D. J. (1988). Accommodation characteristics before and after near work. *Clinical and Experimental Optometry*. **71**, 165-169.

Thibos, L. N., Wheeler, W. and Horner, D. (1997). Power vectors: an application of fourier analysis to the description and statistical analysis of refractive error. *Optometry and Vision Science*. **74**, 367-374.

Tigges, M., Iuvone, M., Fernandes, A., Sugrue, M. F., Mallorga, P. J. Laties, A. M. and Stone, R. A. (1999). Effects of muscarinic cholonergic receptor antagonists on postnatal eye growth of rhesus monkeys. *Optometry and Vision Science*. **76**, 397-407.

Tomlinson, A. and Phillips, C. I. (1970). Applanation tension and axial length of the eyeball. *British Journal of Ophthalmology*. **54**, 548-553.

Tomlinson, A. and Phillips, C. I. (1972). Unequal axial length of eyeball and ocular tension. *Acta Ophthalmologica*. **50**, 872-876.

Törnqvist, G. (1966). Effect of cervical sympathetic stimulation on accommodation in monkeys. *Acta Physiol Scand.* **67**, 363-372.

Törnqvist, G. (1967). The relative importance of the parasympathetic and sympathetic nervous systems for accommodation in monkeys. *Investigative Ophthalmology.* **6**, 612-617.

van Alphen, G. W. H. M. (1961). On emmetropia and ametropia. *Acta Ophthalmologica.* (Suppl). 1-92.

van Alphen, G. W. H. M. (1976). The adrenergic receptors of the intraocular muscles of the human eye. *Investigative Ophthalmology.* **15**, 502-505.

Vera-Diaz, F. A., Strang, N. C. and Winn, B. (2002). Nearwork induced transient myopia during myopia progression. *Current Eye Research.* **24**, 289-295.

Walker, T. W. and Mutti, D. O. (2002). The effect of accommodation on ocular shape. *Optometry and Vision Science.* **79**, 424-430.

Walline, J. J., Mutti, D. O., Jones, L. A., Rah, M. J., Nichols, K. K., Watson, R. and Zadnik, K. (2001). The contact lens and myopia progression (CLAMP) study: Design and baseline data. *Optometry and Vision Science.* **78**, 223-233.

Wax, M. B. and Molinoff, P. B. (1987). Distribution and properties of beta-adrenergic receptors in human iris-ciliary body. *Investigative Ophthalmology and Visual Science.* **28**, 420-430.

Weber, J., Tuinenburg, A. E. and van der Heijde, G. L. (1989). Effect of timolol on the amplitude and dynamics of accommodation. *Documenta Ophthalmologica.* **72**, 341-347.

Wiesel, T. N. and Raviola, E. (1979). Increase in axial length of the macaque monkey eye after corneal opacification. *Investigative Ophthalmology and Visual Science.* **18**, 1232-1236.

Wildsoet, C. (1998). Structural correlates of myopia. *Myopia and Nearwork*. Rosenfield, M and Gilmartin, B. Oxford, Butterworth-Heinemann: 31-56.

Wilson, S. E., Verity, S. M. and Congert, D. L. (1992). Accuracy and precision of the Corneal Analysis System and the Topographic Modelling System. *Cornea*. **11**, 28-35.

Winn, B. and Culhane, H. M. (1998). Autonomic control of accommodation. *Investigative Ophthalmology and Visual Science (Suppl)*. **39**, S1049

Winn, B., Culhane, H. M., Gilmartin, B. and Strang, N. C. (2002). Effect of β-adrenoceptor antagonists on autonomic control of ciliary smooth muscle. *Ophthalmic and Physiological Optics*. **22**, 359-365.

Winn, B. and Gilmartin, B. (1992). Current perspective on microfluctuations of accommodation. *Ophthalmic and Physiological Optics*. **12**, 252-256.

Winn, B., Gilmartin, B., Mortimer, L. C. and Edwards, N. R. (1991). The effect of mental effort on open- and closed-loop accommodation. *Ophthalmic and Physiological Optics*. **11**, 335-339.

Winn, B., Pugh, J. R., Gilmartin, B. and Owens, H. (1990). Arterial pulse modulates steady-state ocular accommodation. *Current Eye Research*. **9**, 971-975.

Wolffsohn, J. S., Gilmartin, B., Mallen, E. A. H. and Tsujimura, S. (2001). Continuous recording of accommodation and pupil size using the Shin-Nippon SRW-5000 autorefractor. *Ophthalmic and Physiological Optics*. **21**, 108-113.

Wolffsohn, J. S., Hunt, O. A. and Gilmartin, B. (2002). Continuous measurement of accommodation in human factor applications. *Ophthalmic and Physiological Optics*. **22**, 380-384.

Woung, L. C., Ukai, K., Tsuchiya, K. and Ishikawa, S. (1993). Accommodative adaptation and age of onset of myopia. *Ophthalmic and Physiological Optics*. **13**, 366-370.

Wu, M. M. M. and Edwards, M. H. (1999). The effect of having myopic parents: An analysis of myopia in three generations. *Optometry and Vision Science.* **76,** 387-392.

Wu, H. M., Seet, B., Yap, E. P. H., Saw, S. M., Lim, T. H. and Chia, K. S. (2001). Does education explain ethnic differences in myopia prevalence? A population-based study of young adult males in Singapore. *Optometry and Vision Science.* **78,** 234-239.

Young, F. A. (1961). The effect of restricted visual space on the primate eye. *American Journal of Ophthalmology.* **52,** 799-806.

Young, F. A. (1963). The effect of restricted visual space on the refractive error of the young monkey eye. *Investigative Ophthalmology.* **2,** 571-577.

Zadnik, K. and Mutti, D. O. (1987) Refractive error changes in Law students. *American Journal of Optometry and Physiological Optics.* **64,** 558-61.

Zadnik, K., Mutti, D. O. and Adams, A. J. (1995). Longitudinal evidence of crystalline lens thinning in children. *Investigative Ophthalmology and Visual Science.* **36,** 1581-1587.

Zetterstrom, C. and Hahnenberger, R. (1988). Pharmacological characterization of human ciliary muscle adrenoceptors in vitro. *Experimental Eye Research.* **46,** 421-430.

APPENDIX 1

ADDITIONAL APPARATUS

The following devices were designed and constructed during postgraduate registration for use in other research projects. Digital images and diagrams are included where appropriate.

A1.1 Disparometer for the measurement of fixation disparity.

This device was designed and constructed in collaboration with Dr. F. Baker for use in a final year elective study project examining the effect of accommodative demand and near working distance on fixation disparity. The intention was to measure fixation disparity at five distances.

Two back illuminated, polarized Nonius bars are viewed by the subject via a polarized visor. The position of the upper Nonius bar can be adjusted by a lead screw arrangement. A dial gauge reports the position of the upper Nonius bar to a precision of 0.01 mm. The lower Nonius bar is fixed. The device is internally illuminated by a pair of 12 volt incandescent lamps. Five separate sets of Nonius bar masks were made to ensure correct angular subtense of the Nonius bar at each viewing distance.
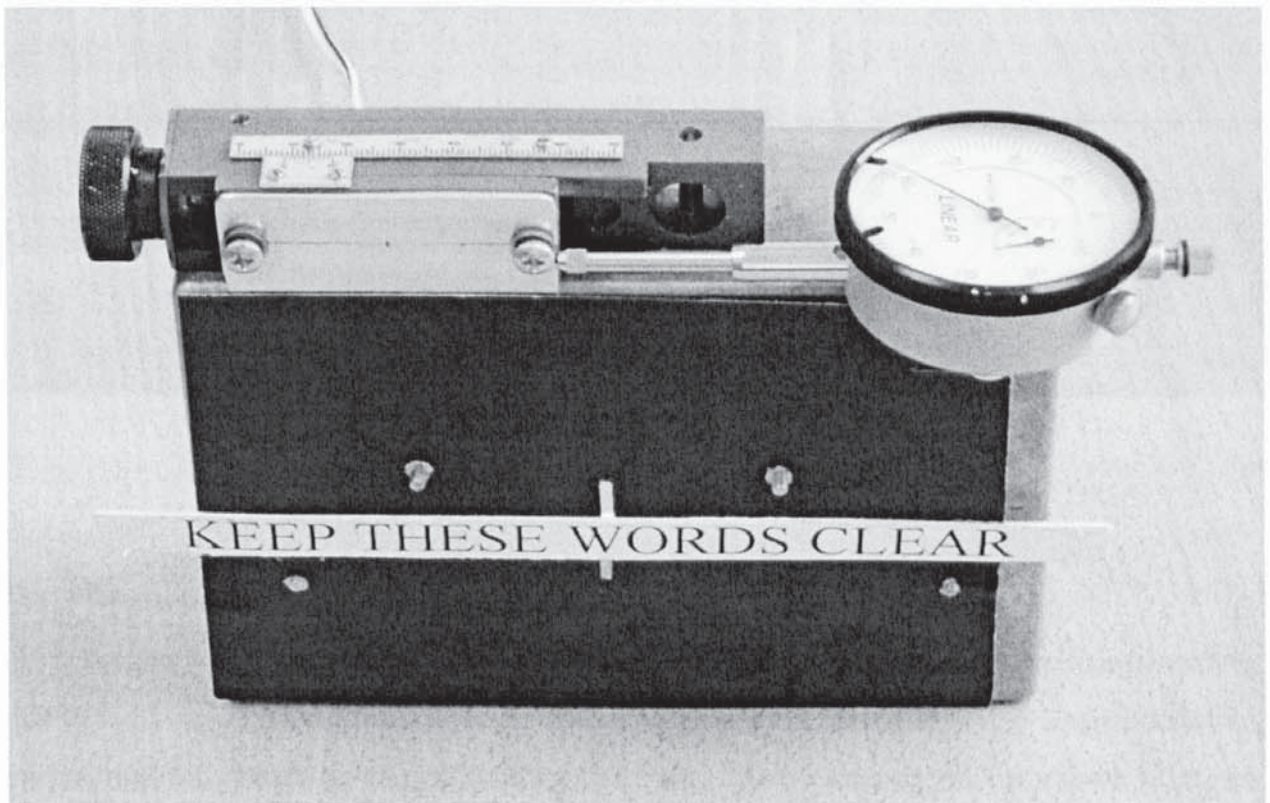
Figure A1.1 Disparometer.

A1.2 Peripheral refraction fixation arc for Canon Autoref R-1.

This piece of apparatus was constructed for Dr. J. Harper to enable accurate and repeatable eccentric fixation positions when measuring peripheral refraction with the Canon Autoref R-1 autorefractor.

A semi-circle of medium density fibre board (radius 70 cm) with a curved back board 5 cm in height was constructed. Fifteen red light emitting diodes (LED) were set into the back board. LEDs were positioned at 5° intervals, thus providing targets for peripheral refraction in the primary position, and out to 35° nasally and temporally. A control unit powers the LEDs individually, illuminating them one at a time.
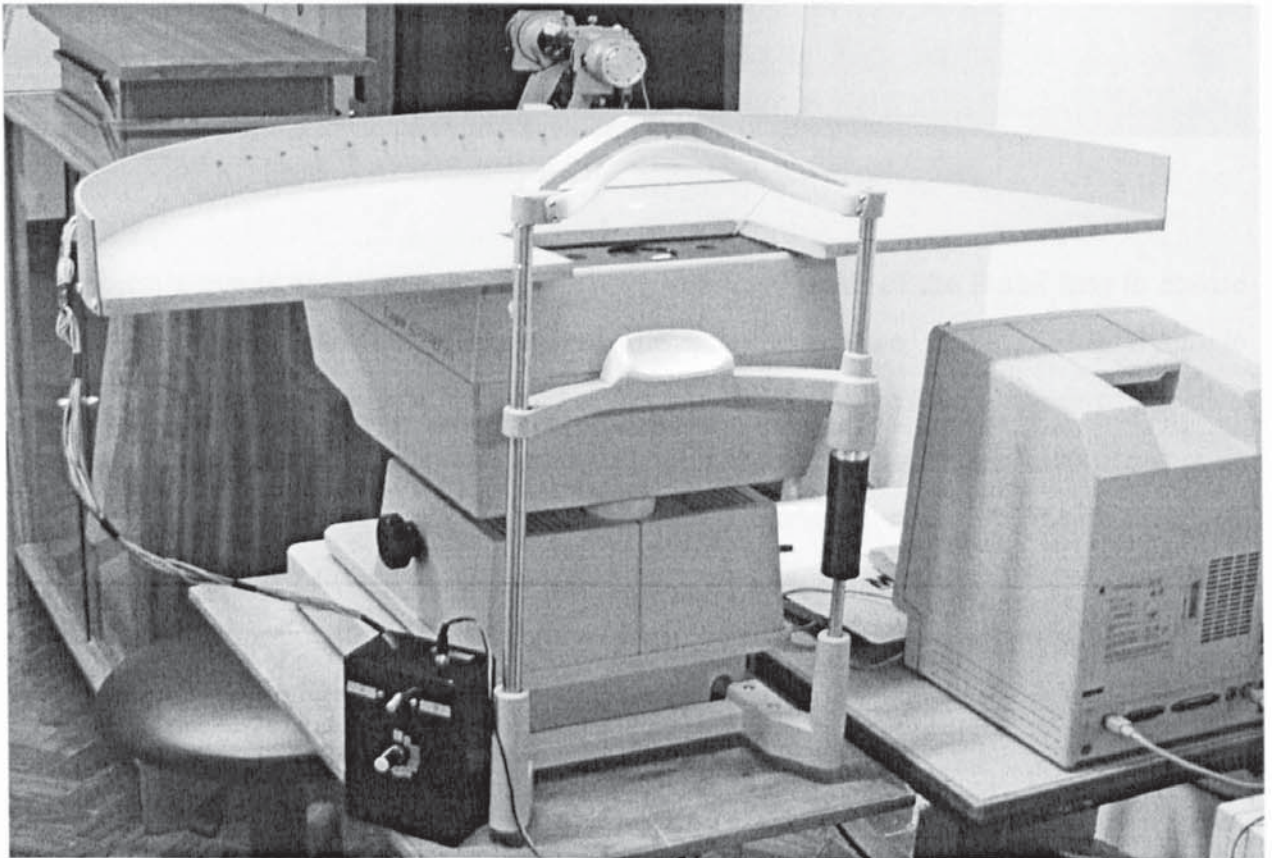
Figure A1.2. Peripheral refraction fixation arc for Canon Autoref R-1.

A1.3 Motorized dynamic accommodation stimulus track.

This system was designed and constructed for Prof. G. Harding. The system comprises two parts: the motorized aluminium track with attachment for Badal lens and accommodative target, and the electronic control unit for the track. The motorized track is shown in figure A1.3.
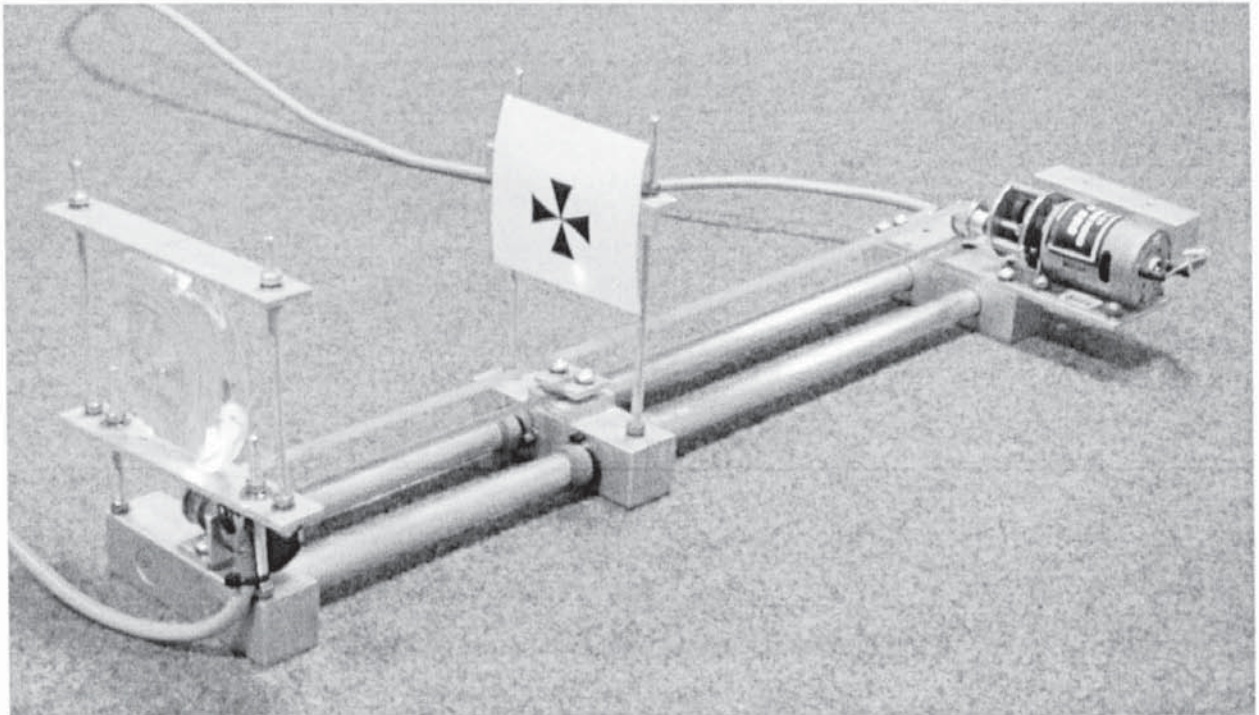
Figure A1.3 Motorized dynamic accommodation stimulus track.

The subject's eye is positioned at the first principal focal point of the Badal lens to ensure constant luminance and magnification of the accommodative target during dynamic stimulation. The target carriage is moved relative to the Badal lens along a pair of polished aluminium rails. A d.c. motor and gearbox drive the target carriage. Motive power is transmitted to the target carriage via a synchronous toothed drive belt. A 10-turn precision potentiometer is also driven by the toothed belt. Output voltage of the potentiometer is proportional to the position of the target carriage on the track. Consequently, the dioptric level of the accommodative stimulus can be continuously monitored. The potentiometer voltage provides a negative feedback signal to the servo control circuit, thus enabling motor drive in the appropriate direction.

Figure A1.4 shows the control unit for the track. This device was purpose built for the project. Three present controls for track position, together with a speed control are built into the unit. An external input signal can be connected via a BNC connector to enable control of the track from a function generator. A voltage signal indicating track position is available via a BNC connector to enable synchronization with external devices, e.g. *LabView*. The operating principle of the track is based around a d.c. servo system. Figure A1.5 shows a block diagram of the purpose-designed circuit for this system.
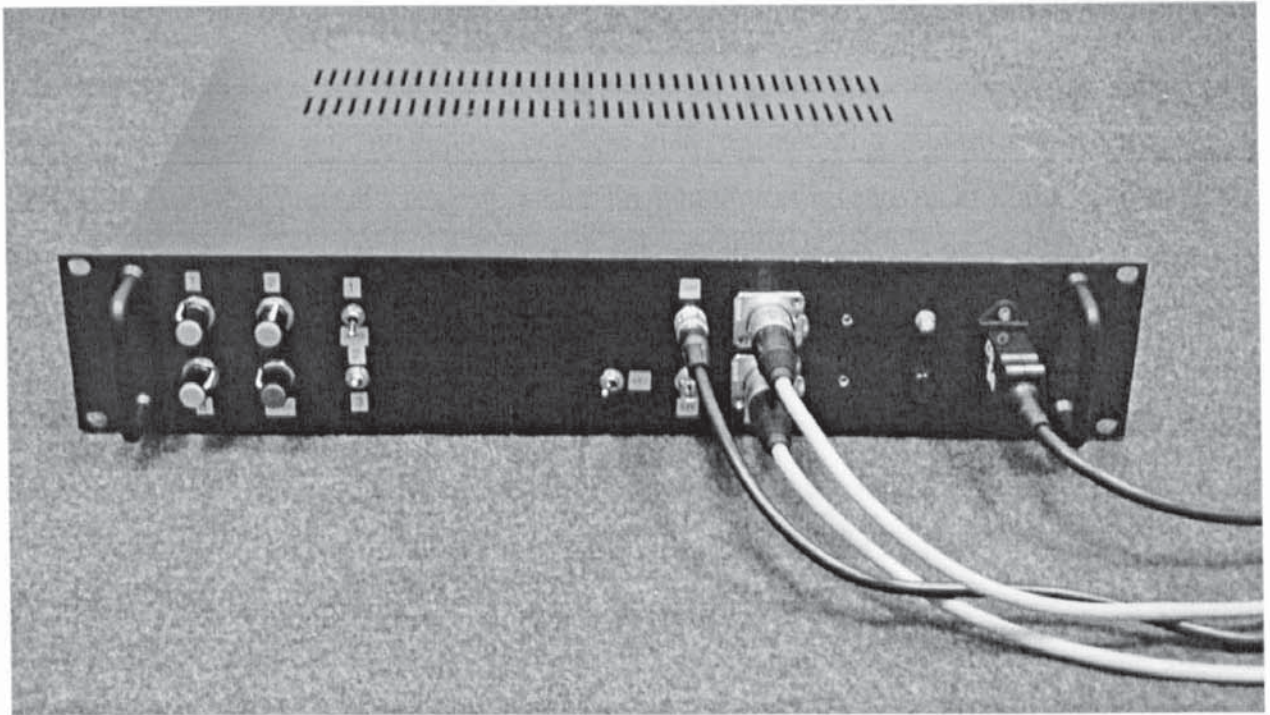
Figure A1.4. Control unit for the track.
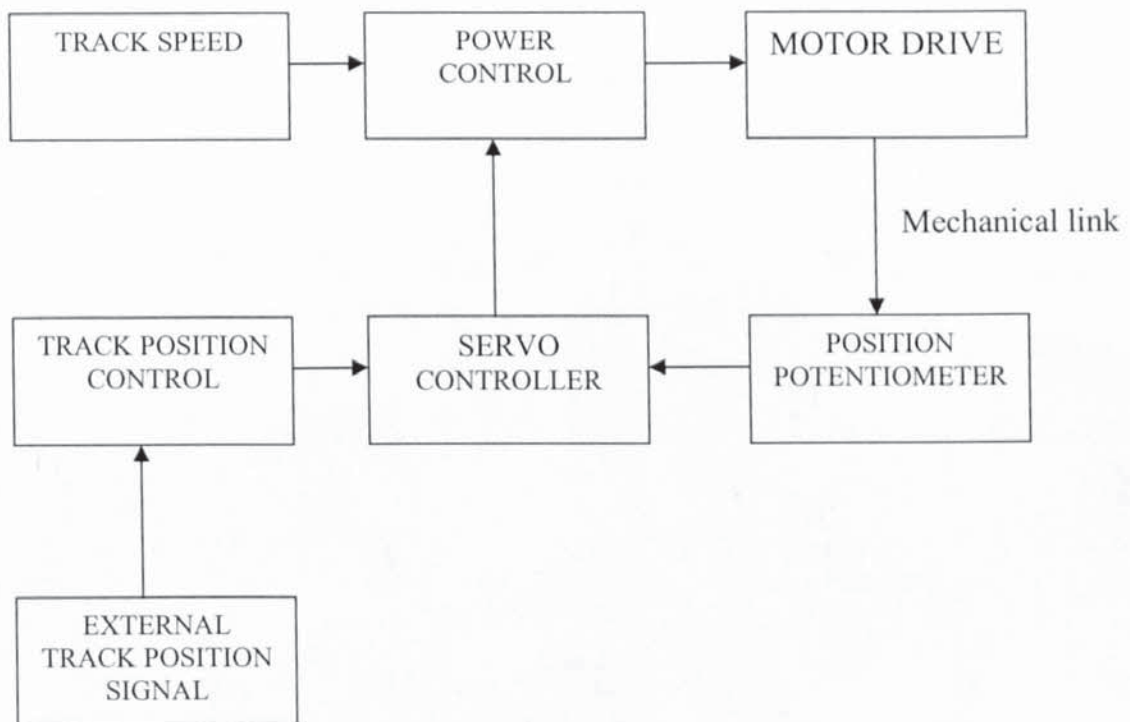
Figure A1.5. Block diagram of servo control system.

A1.4 Stepwise accommodative stimulus apparatus.

This device was designed and constructed for Prof. G. Harding. A project measuring the accommodative response to stepwise changes in accommodative stimuli was being carried out. A device was required to give a near instantaneous change is stimulus vergence to simulate distance to near and near to distance fixation changes.

The system consisted of a +5 DS Badal lens holder, fixed Maltese cross target (the distance target) and a second Maltese cross target (the near target) mounted on a 12 volt rotary solenoid arm. A power supply and control unit was constructed to energize the solenoid. Energizing the solenoid rotates the arm by 95°, and places the near target outside the exit pupil of the Badal system, and thus out of the subject's field of view. An external voltage signal is produced on energizing the solenoid to enable the change in stimulus to be logged by the continuous recording system. The device was mounted on a 50 cm optical bench system and placed on a gantry in front of a Shin-Nippon SRW-5000 autorefractor adapted for continuous recording of accommodation (Mallen *et al.*, 2001).
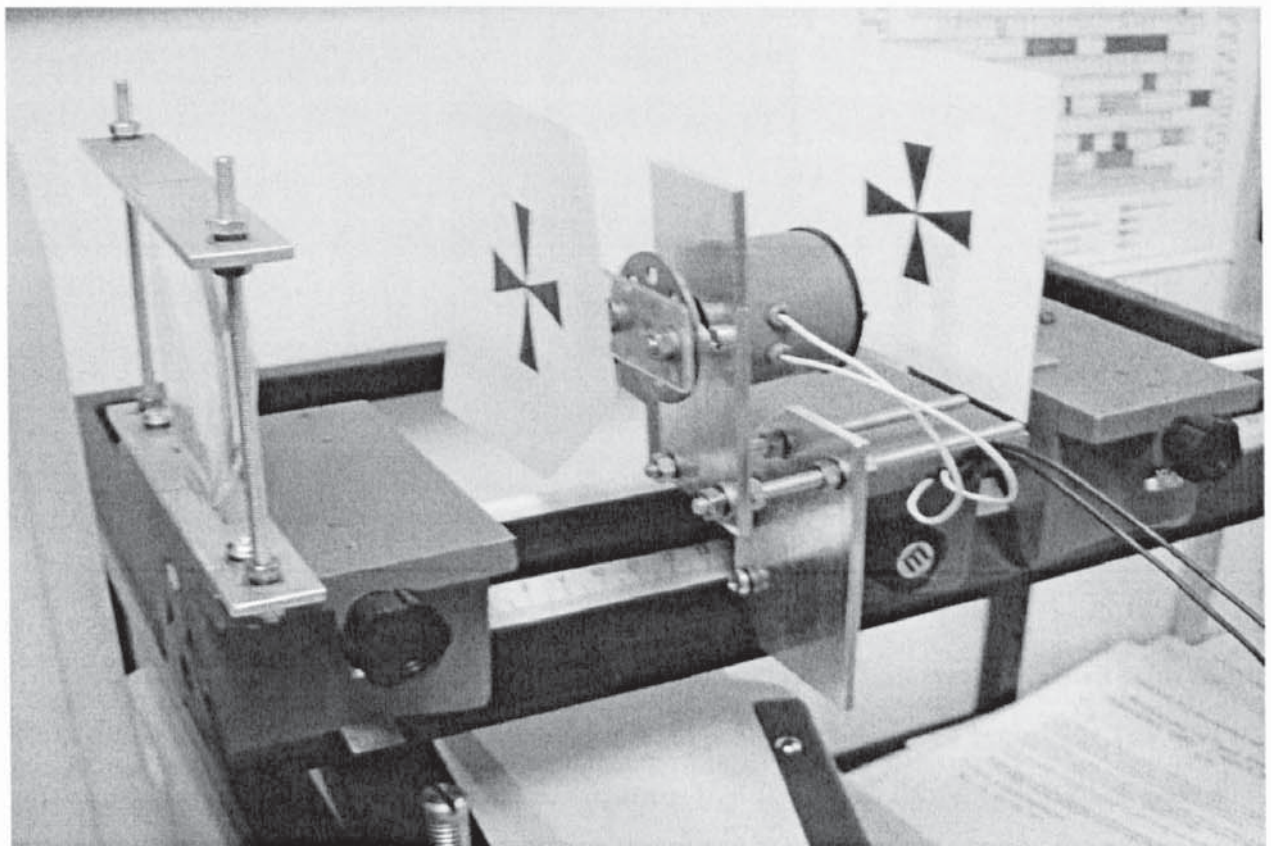
Figure A1.6. Stepwise accommodative stimulus apparatus.

A1.5 Badal system and target for Shin-Nippon SRW-5000 autorefractor.

This system was designed and constructed for Dr. F. Baker. The device allows a Badal lens system and accommodative target to be accurately aligned with the visual axis of a subject and the optical system of a Shin-Nippon SRW-5000 autorefractor. The 5 D Badal lens can be adjusted to place the back vertex at the required distance from the corneal plane (20 cm for a +5 D lens). The target (a Maltese cross target as shown in figure A1.7) can also be adjusted to vary accommodative demand from 0 D to 4.5 D.

The device was used in a project to measure changes in ocular astigmatism during varying states of accommodative demand. Continuous recording of accommodation was carried out in 16 meridians using a modified Shin-Nippon SRW-5000 continuous recording system.
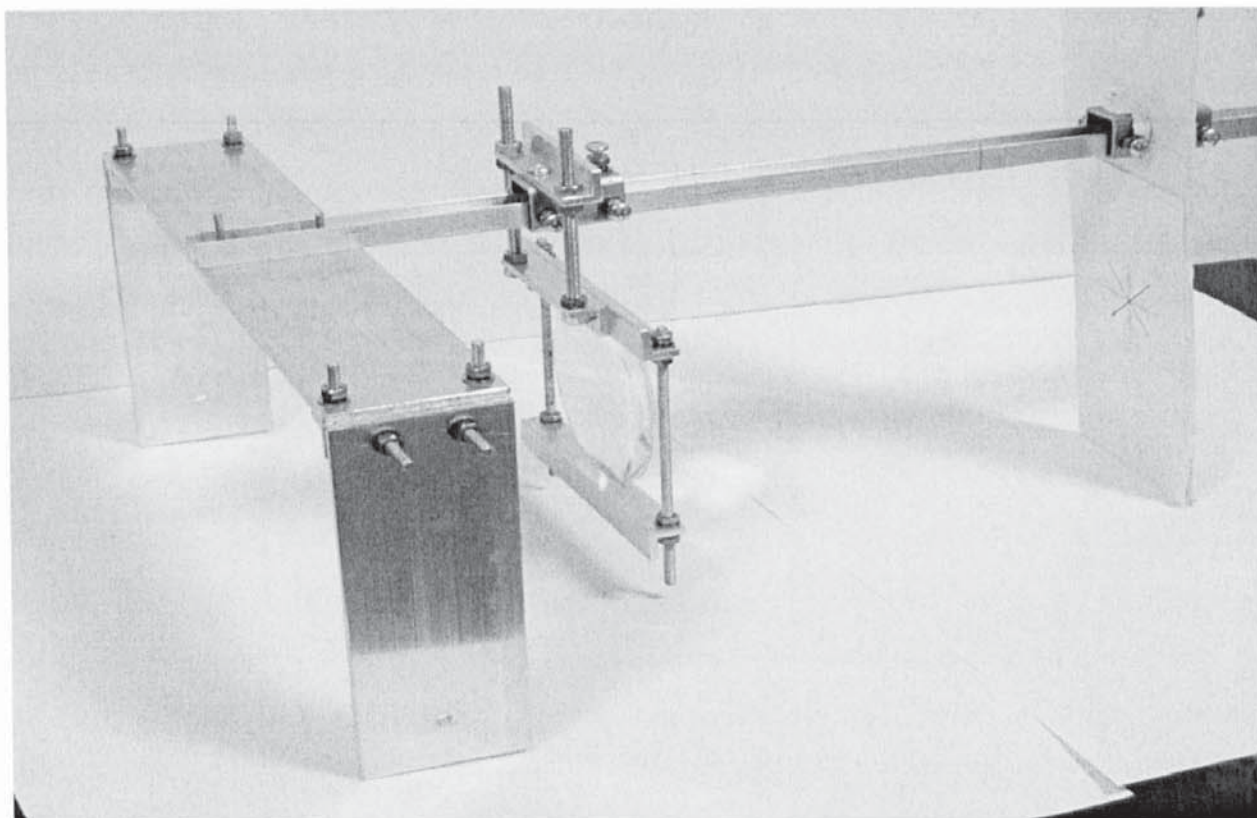
Figure A1.7 Badal system and target for Shin-Nippon SRW-5000 autorefractor.

To attach the apparatus to the SRW-5000 to is necessary to remove the brown trim strip from the head unit. Three M3 set screws are revealed, which must be removed. The unit is placed onto the autorefractor head unit, ensuring that the three fixing holes align with the threaded holes. The unit is secured using three M3 x 16mm set screws (note that set screws longer than 16mm must not be used, as the internal parts of the SRW-5000 will be fouled).

A1.6 Amplifier for finger pulse transducer.

A bioamplification device was designed and constructed to act as an interface between a finger pulse transducer, and the National Instruments PCI 6024E card and BNC 2090 16 channel analogue and digital input/output device. The BNC 2090 device will read analogue signals between ±0.5 and ±10 volts. The output of the pulse transducer device was less than 50 millivolts. A voltage gain of at least 100 times was required to obtain a suitable input signal for the National Instruments hardware. A voltage amplifier based on LM324 bipolar operational amplifiers was constructed. A 2 channel amplifier design was implemented in differential configuration. A differential amplifier can be used to amplify a single signal in phase or anti-phase, or provide the differential output of two input signals. For the purpose of amplifying a single signal, one input is connected to ground.
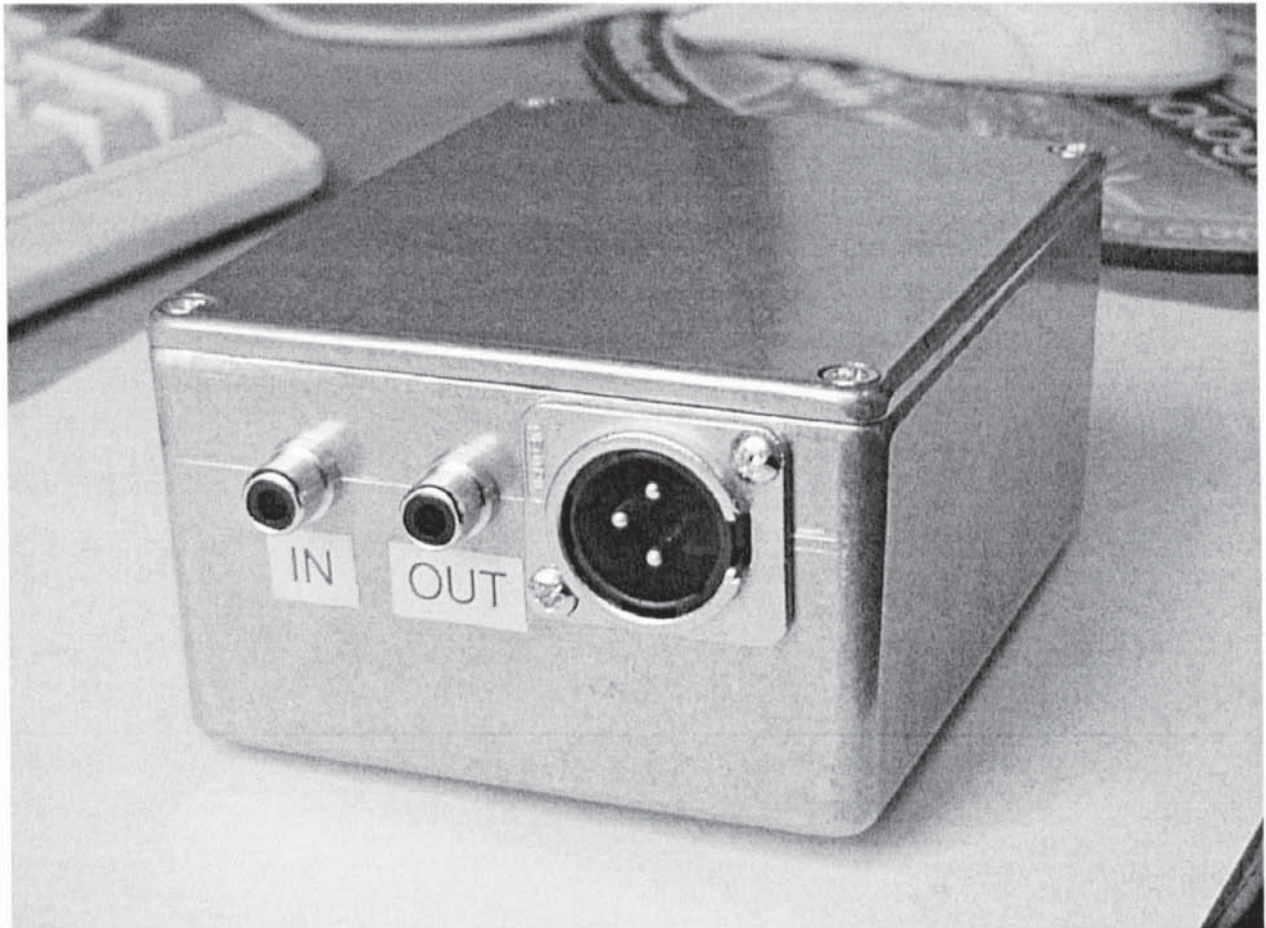
Figure A1.8 Amplifier for finger pulse transducer.
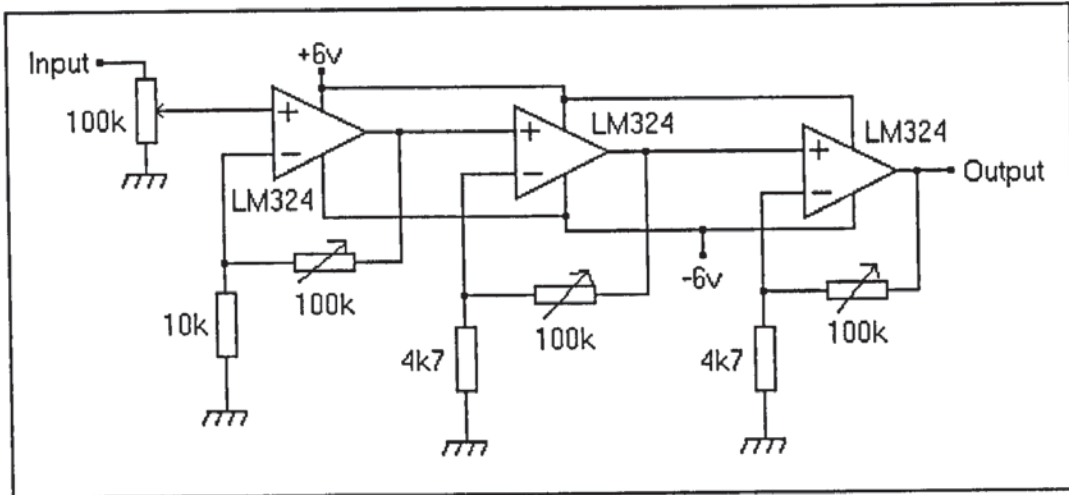
Figure A1.9 Circuit diagram of finger pulse transducer amplifier.

APPENDIX 2

DISTRIBUTION OF REFRACTIVE AND BIOMETRIC FACTORS IN UNIVERSITY STUDENTS AT INTAKE

A2.1 Purpose.

The purpose of this collaborative work was to initially screen a large number of the 2001 Aston University intake students with a view to recruiting suitable subjects for longitudinal studies in myopia and anisometropia. Screening consisted of the measurement of refractive error, axial length (AL), corneal curvature (CC) and anterior chamber depth (ACD) in a large sample of young adult subjects. As a consequence of this screening programme it was possible to determine the range of refractive and biometric values in a university intake group, and establish correlations between biometric factors and refractive error.

A2.2 Subjects.

All subjects (N = 167) were first year undergraduate students of Aston University. Subjects in this study were not used in the other studies in this thesis, and thus form a separate cohort. Gender split of the subject group was 71:97 male:female. Mean age of subjects (± SD) was 20.50 (± 4.97) years. All subjects gave informed consent under the Declaration of Helsinki before taking part in the study.

A2.3 Methods.

Refractive error. Static distance refractive error was measured by Shin-Nippon SRW-5000 autorefraction. The subject was instructed to fixate on a Maltese cross target at a distance of 6 metres. Five readings were taken on each eye, and an average estimate of refractive error was produced by the instrument.

Ocular biometry. The Zeiss *IOLMaster* was used to make all biometric measurements. Three measurements of axial length, three measurements of corneal curvature and five measurements of anterior chamber depth were taken on each eye. The subject was instructed to observe the internal fixation target of the *IOLMaster* during measurements.

A2.4 Results.

The mean spherical refractive error (MRE) of subjects was −0.74 ± 1.97 D (range +3.62 to −9.12 DS). Table A2.1 gives a summary of refractive and biometric results.

	Spherical error (DS)	Cylindrical error (DC)	MRE (DS)	Mean CC (mm)	ACD (mm)	AL (mm)	AL:CC ratio
Mean	-0.43	-0.62	-0.74	7.74	3.59	23.88	3.09
SD	1.92	0.54	1.97	0.34	0.29	1.06	0.17
Maximum	3.97	-3.87	3.62	8.52	4.18	28.04	3.45
Minimum	-8.67	0	-9.12	7.03	2.17	20.83	2.71
Range	12.64	3.87	12.74	1.50	2.01	7.21	0.74

Table A2.1. Summary of refractive and biometric results

Figures A2.1 and A2.2 show histogram distributions of spherical refractive error and mean refractive error respectively. Mean refractive error = Sphere power + (Cylinder power / 2).
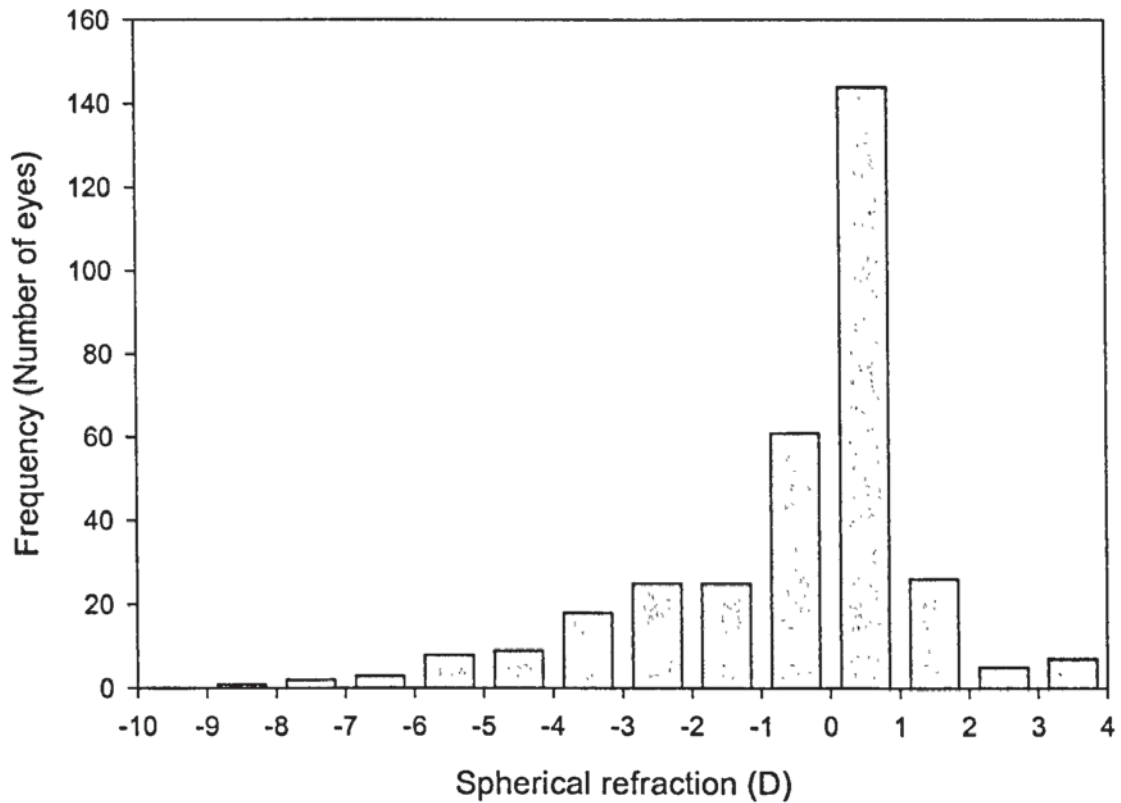
Figure A2.1. Distribution of spherical refractive error.
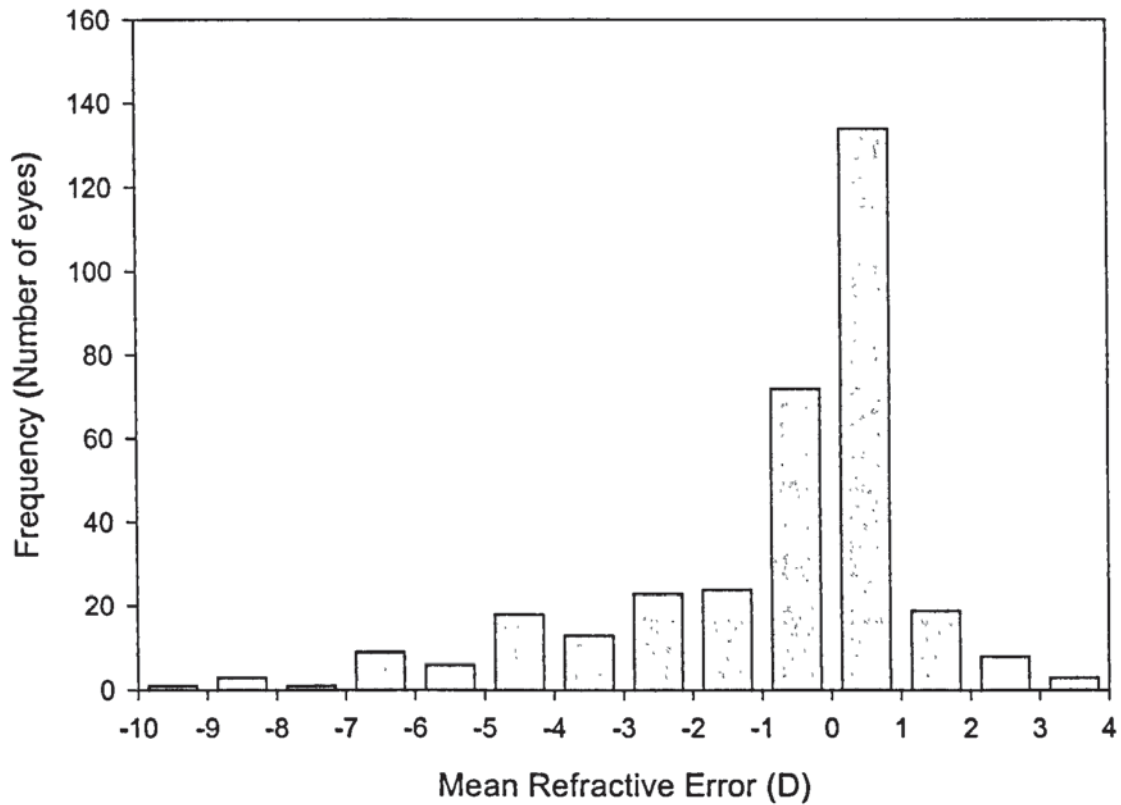
Figure A2.2. Distribution of mean refractive error.

Figures A2.3 and A2.4 show the relationship and linear regression of mean corneal curvature against spherical refraction and mean spherical error respectively. Mean corneal radius was defined as the arithmetic mean corneal radius from the two principal meridians. Figures A2.5 and A2.6 represent linear regression between anterior chamber depth, spherical refractive error and mean refractive error. Figures A2.7 and A2.8 show the correlations between axial length and refraction. Finally, figures A2.9 and A2.10 show the relationship between axial length to corneal curvature radius and refraction.
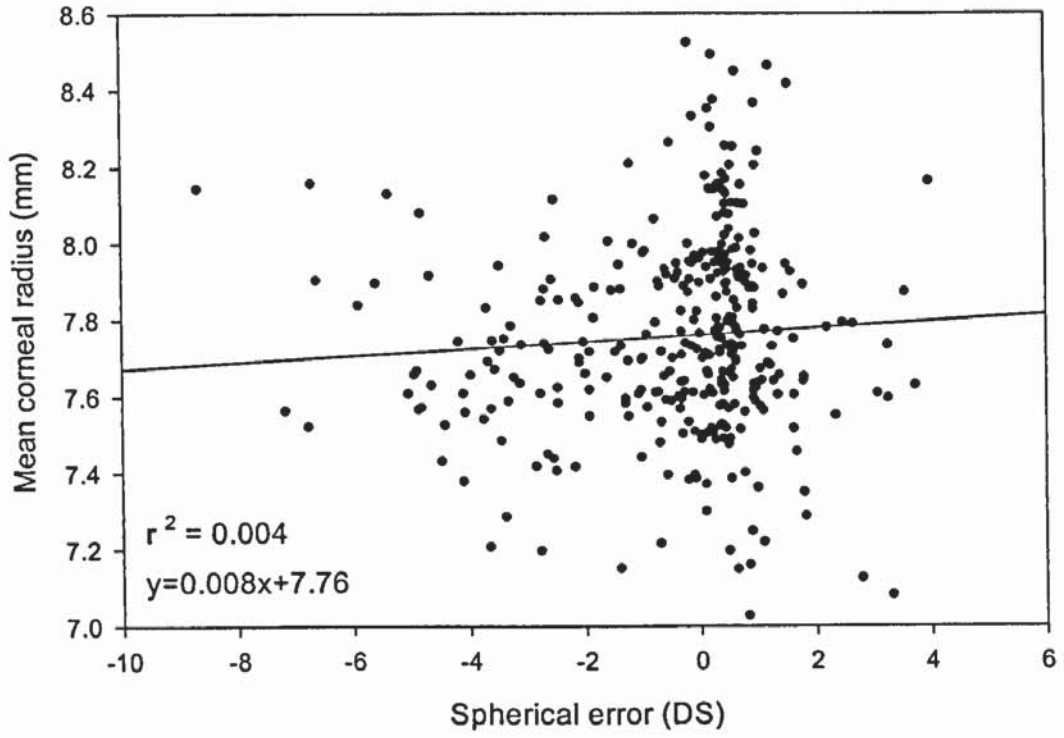
Figure A2.3. Mean corneal radius against spherical refractive error.
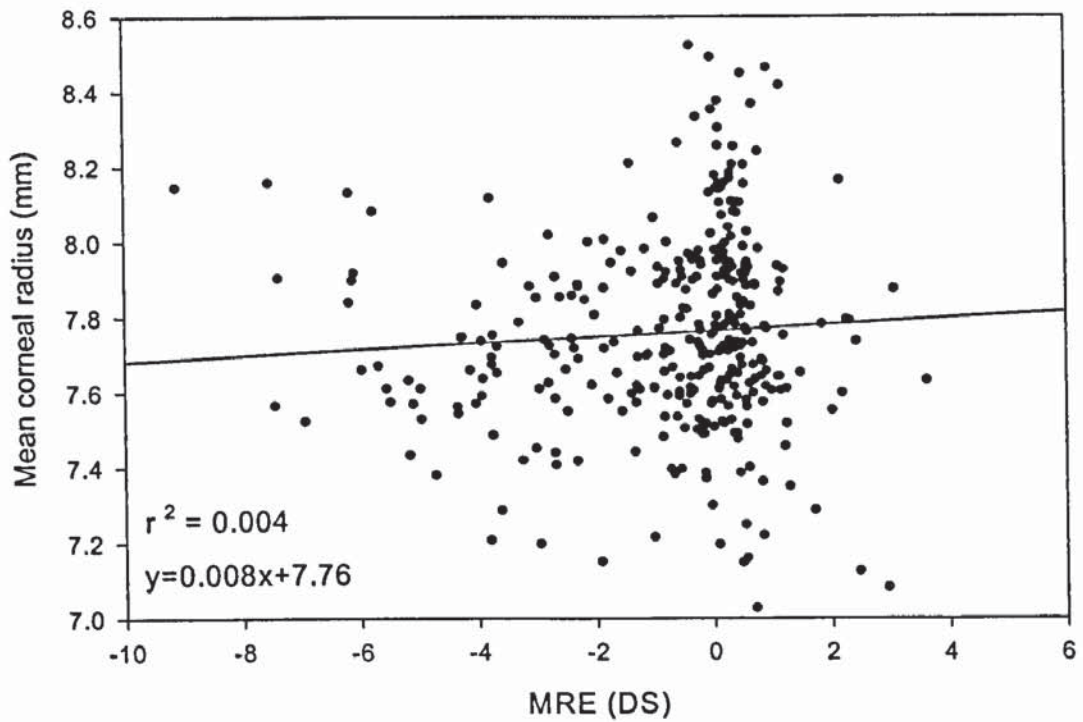
Figure A2.4. Mean corneal radius against mean spherical error.

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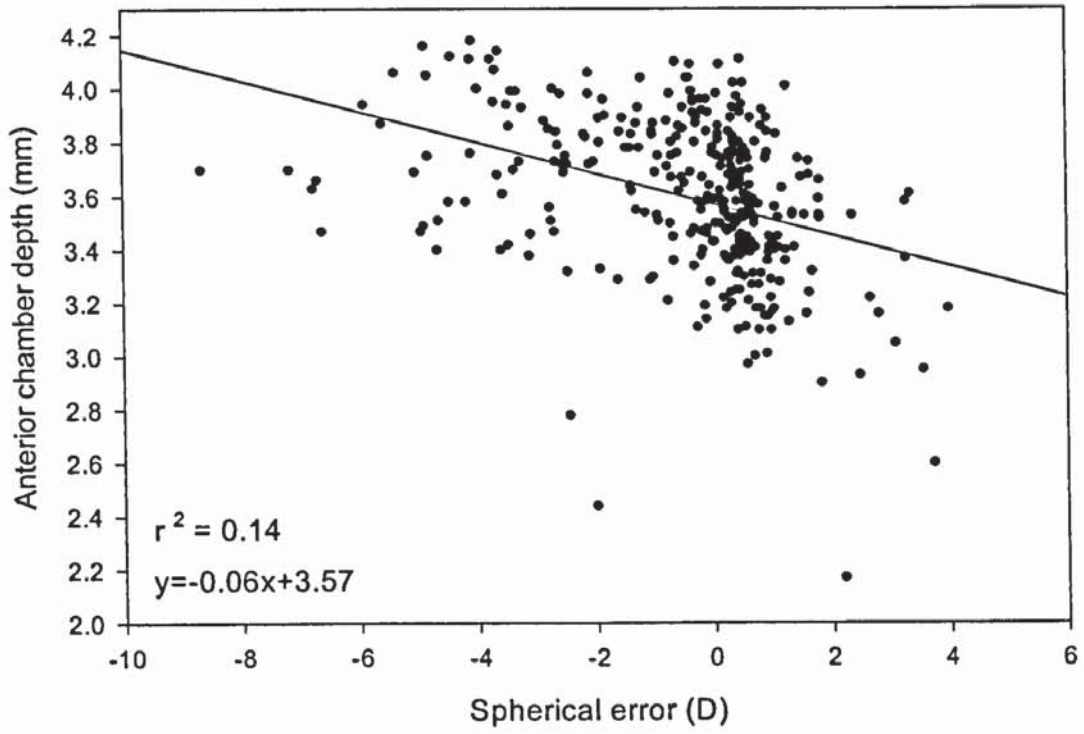
Figure A2.5. Anterior chamber depth against spherical refractive error.
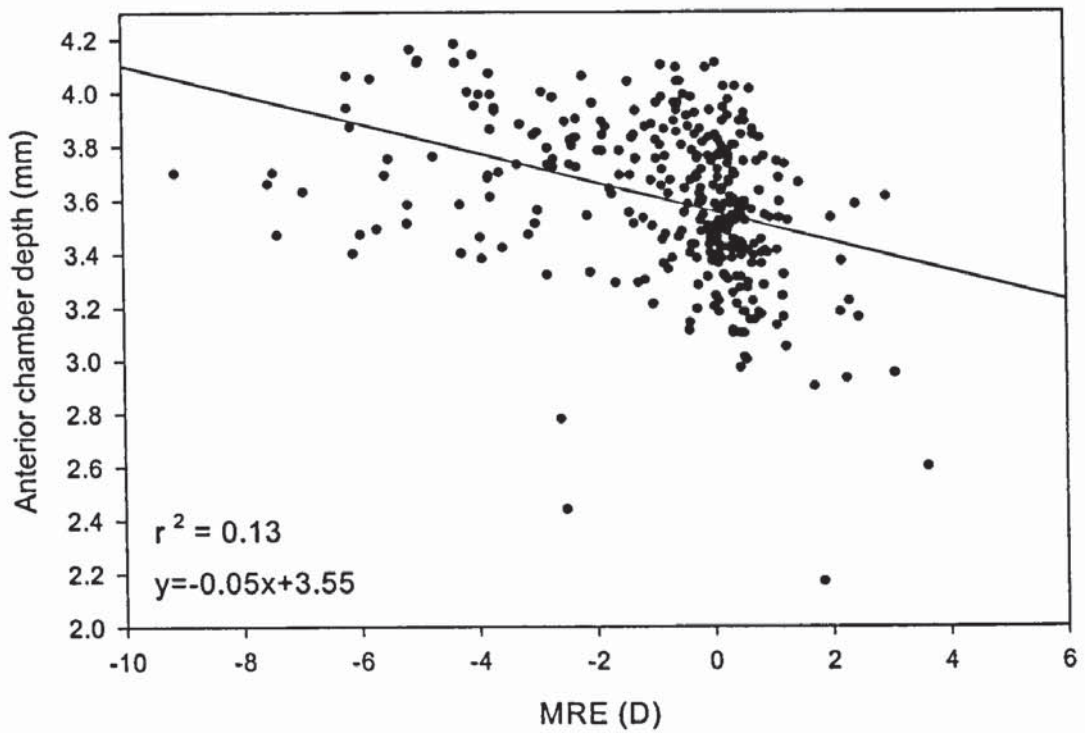

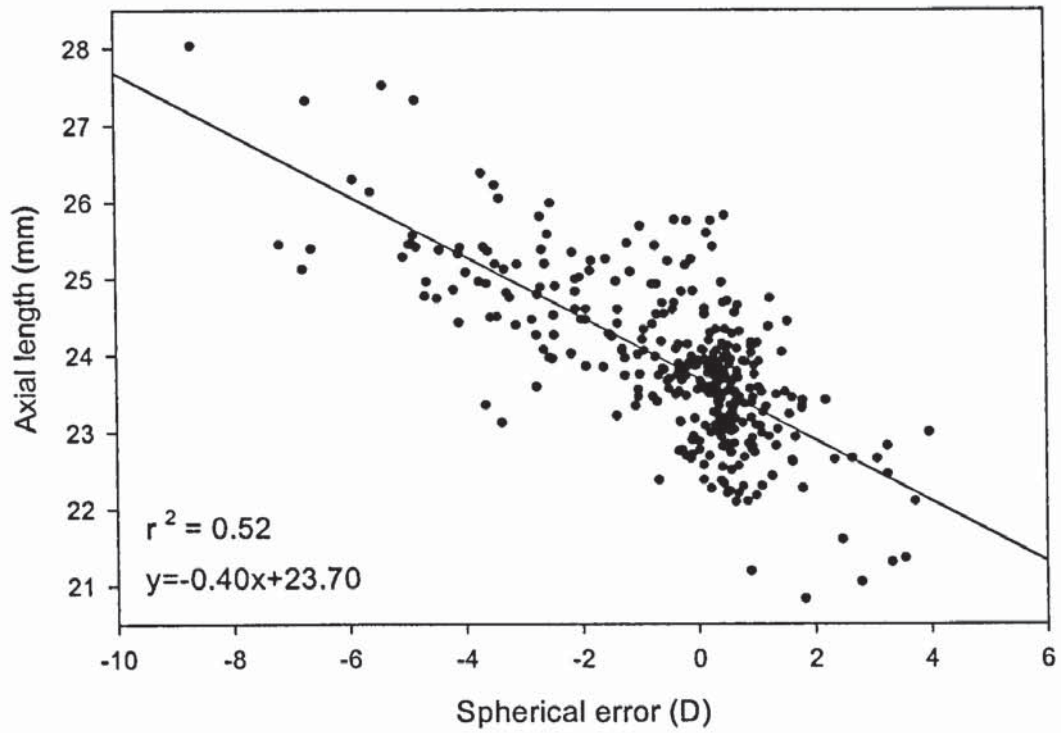Figure A2.6. Mean spherical error against anterior chamber depth

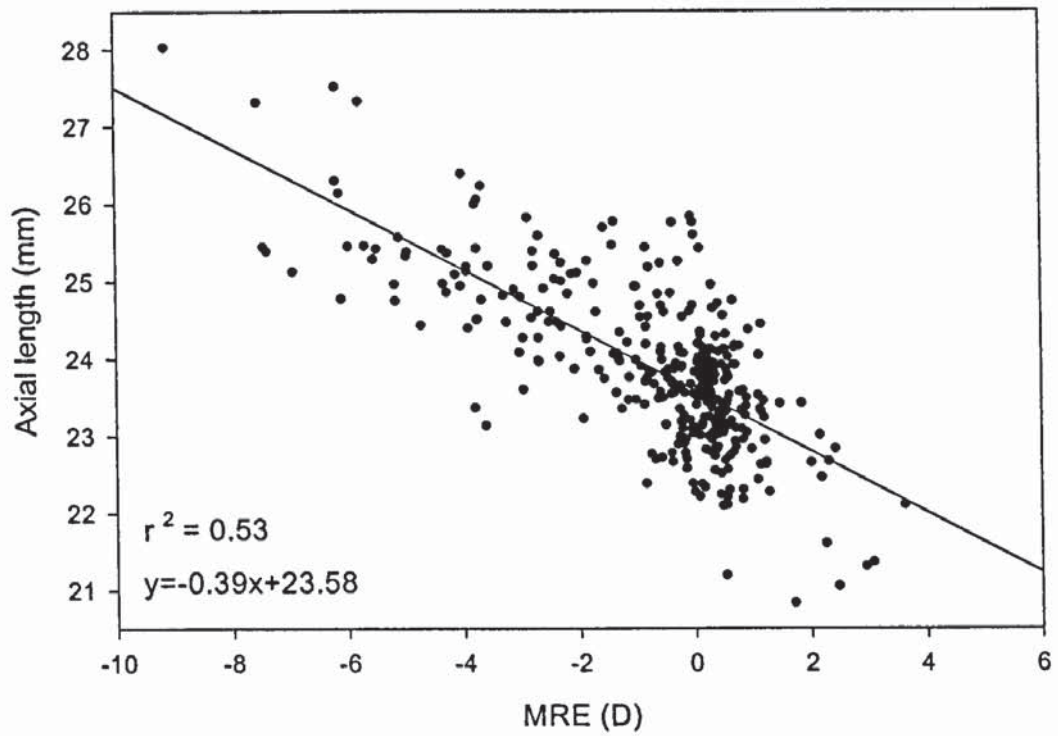Figure A2.7. Axial length against spherical refractive error.

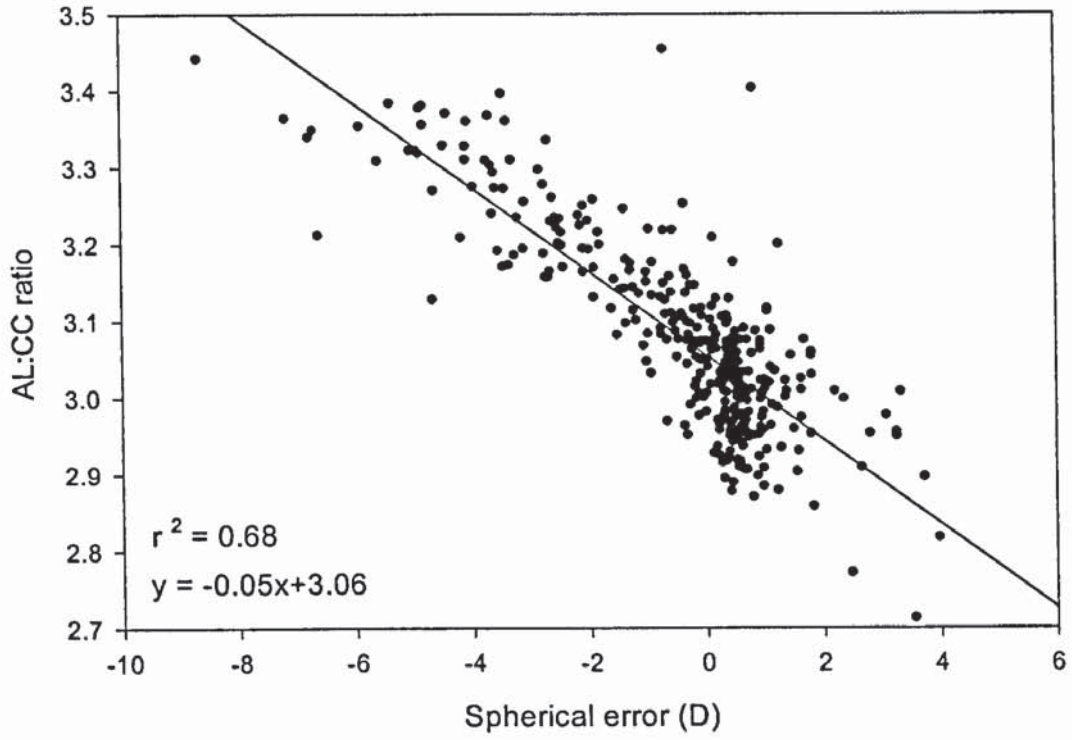Figure A2.8. Axial length against mean spherical refractive error.

Figure A2.9. Axial length:corneal curvature ratio against spherical refractive error.
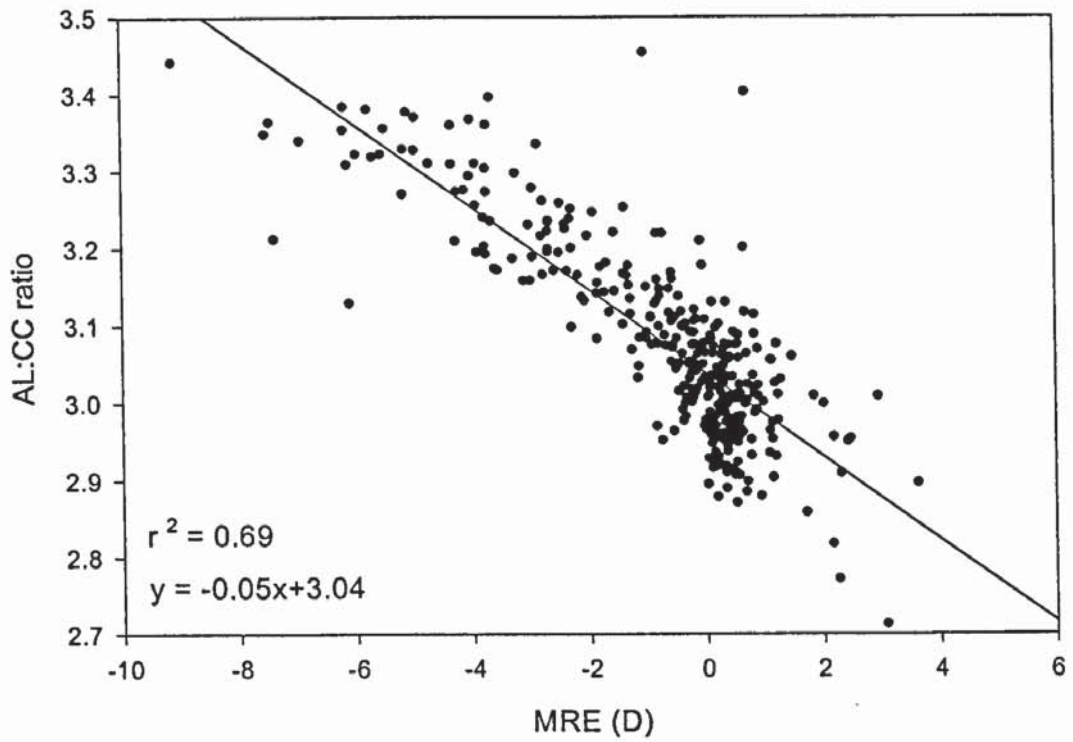

Figure A2.10. Axial length:corneal curvature ratio against mean spherical refractive error.

A2.5 Discussion.

The distributions of spherical refraction and mean refractive error show a strong leptokurtotic profile, indicating a non-normal distribution. Linear regression analysis showed that the biometric factor exhibiting the tightest correlation to refractive error was axial length to corneal curvature ratio. No correlation was observed between mean corneal radius and refractive error. As expected, a strong negative correlation was found between axial length and refraction. Anterior chamber depth showed a weaker negative correlation with spherical error and mean spherical error.

APPENDIX 3

REPEATABILITY OF RETINAL CONTOUR MEASUREMENTS USING THE ZEISS IOLMASTER

A3.1 Purpose

To design and implement a method of assessing retinal contour in human subjects, based on the Zeiss *IOLMaster*. Also, to assess the effects of a beam splitter device placed in the optical path of the instrument on axial length measurements.

A3.2 Instrumentation

The technique utilized a standard Zeiss *IOLMaster* partial coherence interferometer. A novel fixation target was constructed to allow the eyes of the subject to be rotated by specific amounts to measure peripheral length dimensions of the globe.
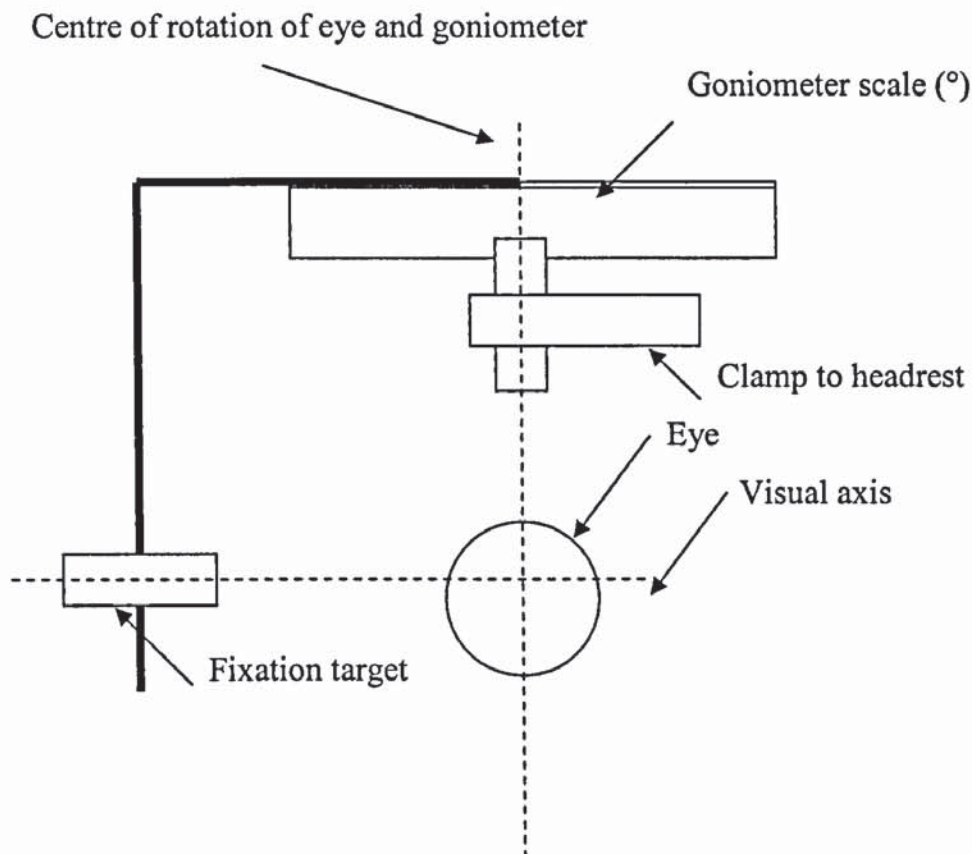

Figure A3.1. Variable angle fixation target

A3.3 Subjects

The subject for the repeatability study was a 29-year-old female subject. The refractive error of the subject was   R –2.75/-0.50 x 40

                                      L –3.75/-0.25 x 30

Assessment of the effects of a beam splitter within the optical path of the instrument was carried out on 3 young adult subjects: 20 year old female emmetrope (RE MRE +0.25 DS), 24 year old male (RE MRE –2.25 DS) and 26 year old male (RE MRE -6.50 DS).

A3.4 Method

The chin rest of the *IOLMaster* was adjusted to suit the subject. The subject was instructed to view the red fixation target of the *IOLMaster* with the right eye. A single measurement of axial length was taken. This represented the 0° (straight ahead) reading. The *IOLMaster* measurement head was locked in place. The moveable fixation target (yellow LED) was aligned with the red fixation light in the *IOLMaster*. The subject was instructed to observe the yellow fixation LED for the remainder of the measurements on the right eye. The yellow fixation LED was rotated along the horizontal axis to a position 10° temporal to fixation. A measurement was taken in this position to measure globe length at a point 10° from fixation on the temporal retina. Subsequent measurements were taken at 15, 20, 25, 30, 35 and 40° Following this, the nasal retina was measured to an eccentricity of 30°. Peripheral measurements to the nasal side were limited to 30° by facial features. Peripheral lengths of the left eye were measured in the same fashion following relocation of the fixation LED before the left eye. The entire measurement procedure was repeated on another day. All measurements and adjustments were made by the same clinician.

Effects of a beam splitter on measurement accuracy was assessed as follows. Six readings of axial length were made on the right eye of each subject. A 1mm thick beam splitter (10% reflectance, 90% transmittance) was mounted on a flexible arm arrangement such that the measurement beam of the *IOLMaster* passed through its centre. Six further axial length measurements were made. The experimental procedure was repeated on a subsequent day, with the order of trials reversed (i.e. measurements with the beam splitter in place made first).

A3.5 Results

Table A3.1 shows averaged results of retinal contour measurements taken on both days.

Eccentricity (°)	RE Day 1 (mm)	RE Day 2 (mm)	LE Day 1 (mm)	LE Day 2 (mm)
40 T	21.93	21.94	21.96	21.99
35 T	22.22	21.98	22.14	22.13
30 T	22.37	22.10	22.25	22.32
25 T	22.58	22.32	22.57	22.55
20 T	22.51	22.37	22.63	22.59
15 T	23.08	22.68	22.84	22.94
10T	23.26	23.15	23.54	23.16
0	23.25	23.27	23.63	23.72
10 N	22.82	23.00	23.33	23.51
15 N	22.97	22.90	23.36	23.35
20 N	22.90	22.58	23.22	22.99
25 N	22.73	22.63	23.02	22.95
30 N	22.63	22.40	22.81	22.67

Table A3.1. Repeated measurements of retinal contour.

Averaged measurements (±SD) of axial length made on both occasions with and without the beam splitter in place are shown in table A3.2.

	Subject 1 (mm)	Subject 2 (mm)	Subject 3 (mm)
RE	25.60±0.02	28.04±0.04	26.31±0.04
RE beam splitter	25.59±0.02	28.05±0.02	26.27±0.02
LE	25.08±0.01	27.26±0.02	26.39±0.03
LE beam splitter	25.09±0.02	27.27±0.02	26.29±0.13

Table A3.2. Axial length measurements with and without beam splitter in light path.

Analysis of variance showed that axial length measurements did not differ significantly following the inclusion of a beam splitter in the light path ($p = 0.95$). It will thus be possible to take axial length measurements while a subject carries out an accommodative task, perhaps via a Badal arrangement.

APPENDIX 4

THE EFFECT OF EXERCISE ON INTRAOCULAR PRESSURE

A4.1 Purpose.

Vigorous exercise produces a fall in intraocular pressure (IOP). Buckingham and Young (1986) found a mean fall in IOP of 4.3 mmHg immediately following 2 minutes of vigorous exercise (running up stairs). IOP returned to baseline after 65 minutes. The purpose of this work was to measure the fall in IOP following an intense, sustained period of exercise, and determine the duration of the fall in IOP. It is important to ascertain the time course of the exercise induced fall in IOP when conducting experimental work which utilizes β-blocker eye drops, as potentially hazardous hypotensive effects may occur if drops are instilled immediately following strenuous exercise.

A4.2 Methods.

A single healthy male subject (age 28 years) was used in this experiment. Baseline intraocular pressure measurement was made on the right eye (average of 4 readings) using a Keeler *Pulsair 2000* non-contact tonometer. Following this the exercise task was commenced. The task consisted of a 3km cycle on an exercise bike (*Techno-gym*) for a duration of 10 minutes. After completion of the exercise task, further IOP measurements were made at 5 minute intervals for a period of 30 minutes.

A4.3 Results.

Pre-task baseline IOP was 12.5 ± 0.71 mmHg. Figure A4.1 shows change in IOP of the right eye following completion of the exercise task. Error bars show 1 standard deviation of mean IOP at each data point. Similar results were found for the left eye.
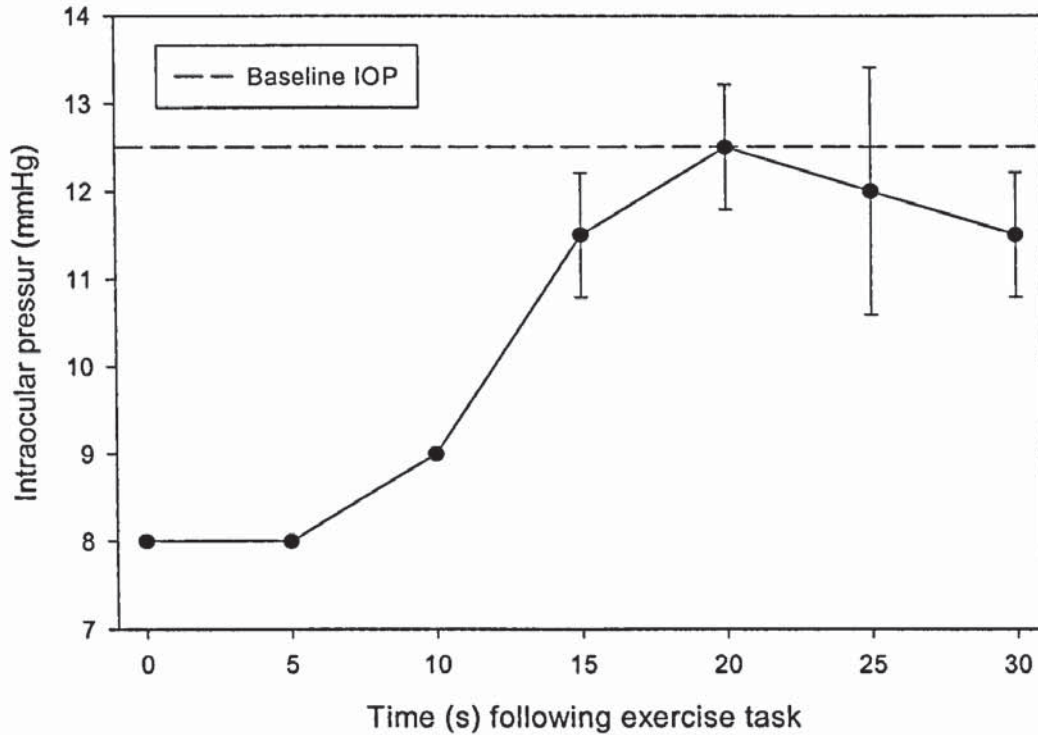
Figure A4.1. Change in IOP following exercise.

A4.4 Discussion.

A reduction in intraocular pressure of 4.5 mmHg was observed as a result of the exercise task. This finding is in agreement with the study by Buckingham and Young (1986). Subsequent rise in IOP following completion of the exercise task occurred more rapidly in this work, compared to the Buckingham and Young (1986) study, i.e. 20 minutes compared to 65 minutes.

Subjects for future experimental work involving the topical use of timolol and betaxolol hydrochloride should be instructed to cease vigorous exercise at least 20 minutes prior to the instillation of the agents. There will be an inbuilt safety factor due to the absorption time of the drug (approximately 20 minutes – see Appendix 5).

APPENDIX 5

TIME COURSE OF THE EFFECTS OF TOPICAL β-ANTAGONISTIC AGENTS

A5.1 Purpose.

The purpose of this study was to determine the time taken for β-adrenoceptor agents to take effect within the eye following topical instillation. When carrying out experimental work on the accommodation response utilizing concurrent pharmacological intervention, it is important to allow sufficient time following instillation for the agent to pass through the cornea and aqueous humour to the binding site. If an insufficient time is allowed following instillation the full effect of the drug will not materialize until some time into the experimental trial. Allowing an excessive period of time post-instillation will unnecessarily protract the experimental protocol and thus reduce subject throughput.

The agents in question, timolol maleate and betaxolol hydrochloride, are beta-blockers and are mainly used to reduce intraocular pressure (IOP) in the treatment of chronic open angle glaucoma. The mode of action of beta-blocking eye drops is to reduce aqueous secretion by binding to receptors in the ciliary body (Liu *et al.*, 1980). Therefore, if IOP is monitored following instillation of the beta-blocking drops, a reduced and stabilized IOP level will indicate that the drug has bound to receptor sites at the ciliary body.

A5.2 Method.

Intraocular pressure (IOP) was measured in 5 young healthy subjects (mean age 27 years, range 24 to 32 years). An average of 4 IOP measurements from the Keeler *Pulsair 3000* non-contact tonometer was recorded prior to installation of the β-antagonistic agents to establish a baseline (pre-drug) pressure. One drop of the topical anaesthetic proxymetacaine hydrochloride was instilled into each eye to aid passage of subsequent agent through the cornea and to control reflex lacrimation. One drop of timolol maleate (0.5%) or two drops of betaxolol hydrochloride (0.5%) was instilled into each eye. A control trial was also carried out with one drop of normal (0.9%) saline solution being instilled into each eye. IOP was measured at 5-minute intervals on each eye for the first 30 minutes after instillation, then at 10-minute intervals for the next 30 minutes. The average of 4 individual readings was taken as the IOP at each time point.

Subjects with a baseline IOP of less than 12 mmHg, or mean spherical refractive error greater than −5 D were excluded from the trial due to the increased risk of retinal detachment in an eye with a relatively long axial length placed in an ocular hypotensive state.

A5.3 Results.

Figures A5.1 to A5.3 show group mean IOP against time following drug instillation for timolol maleate, betaxolol hydrochloride and saline respectively. Error bars show 1 standard deviation at each data point.
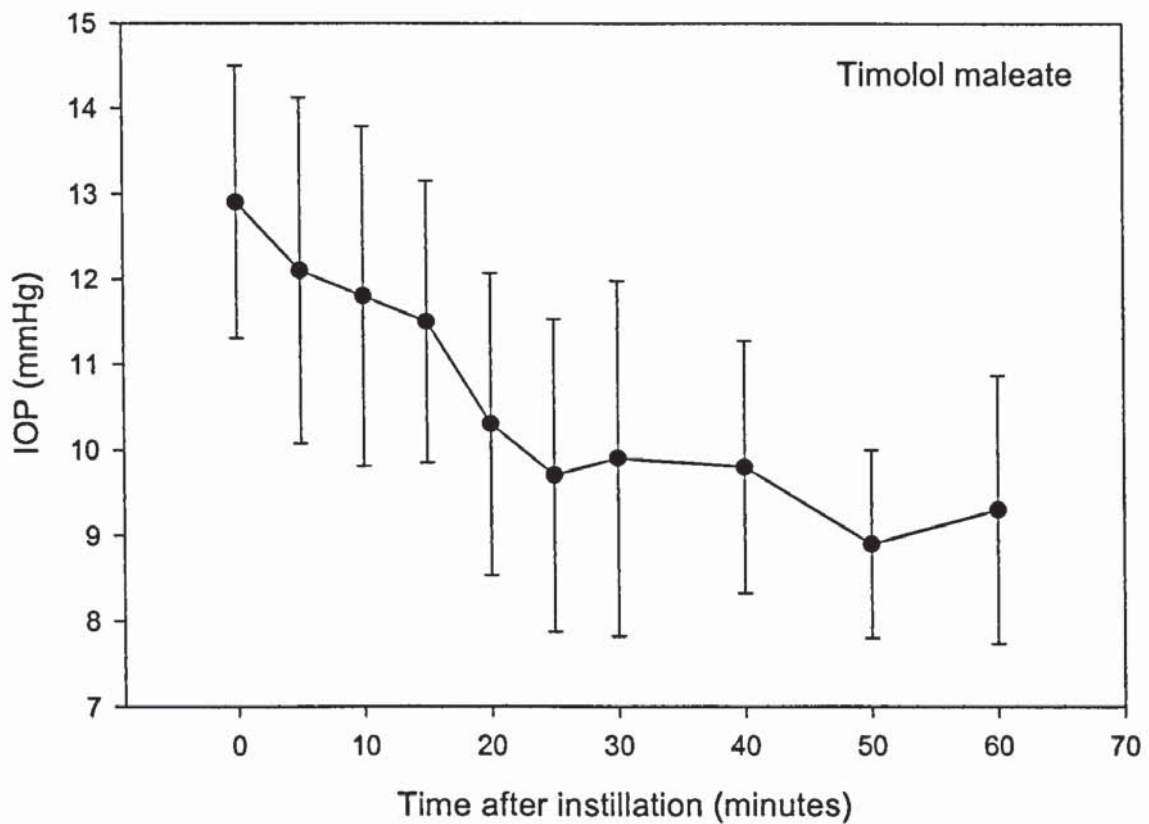

Figure A5.1 Mean IOP against time following instillation of timolol maleate 0.5%
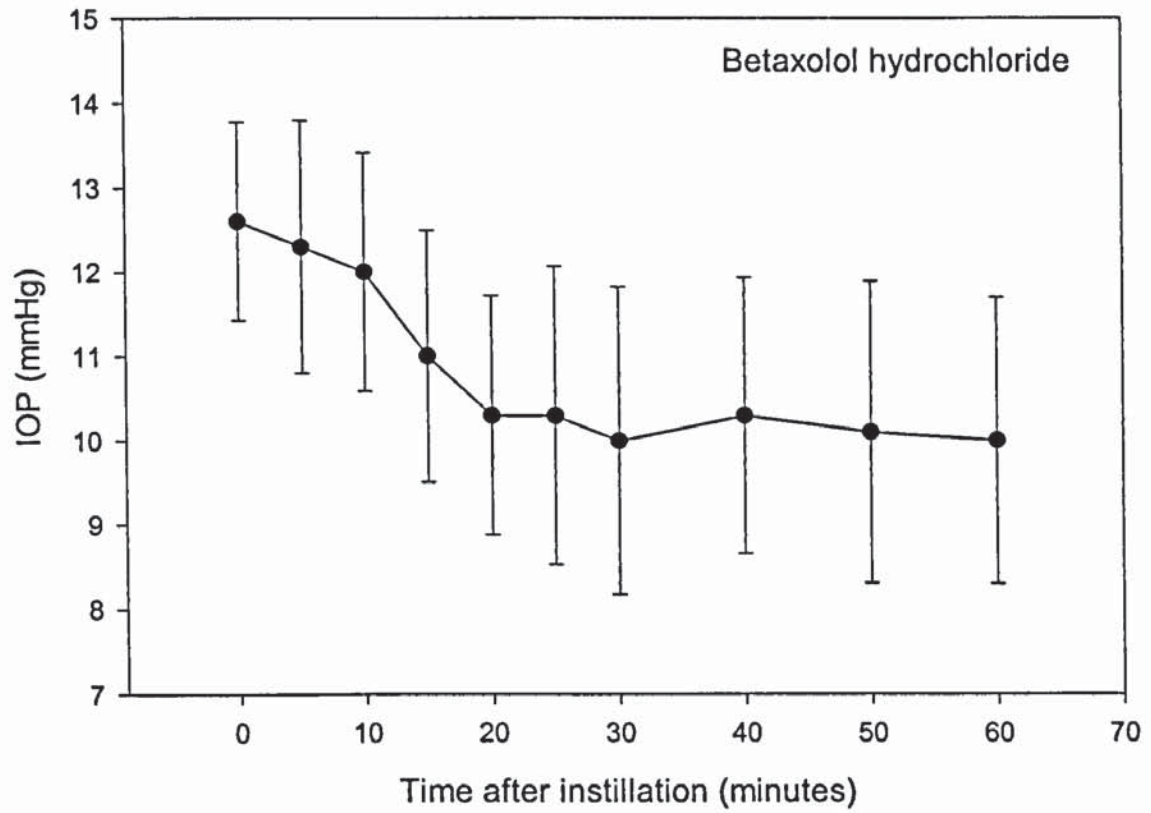
Figure A5.2 Mean IOP against time following instillation of betaxolol hydrochloride 0.5%
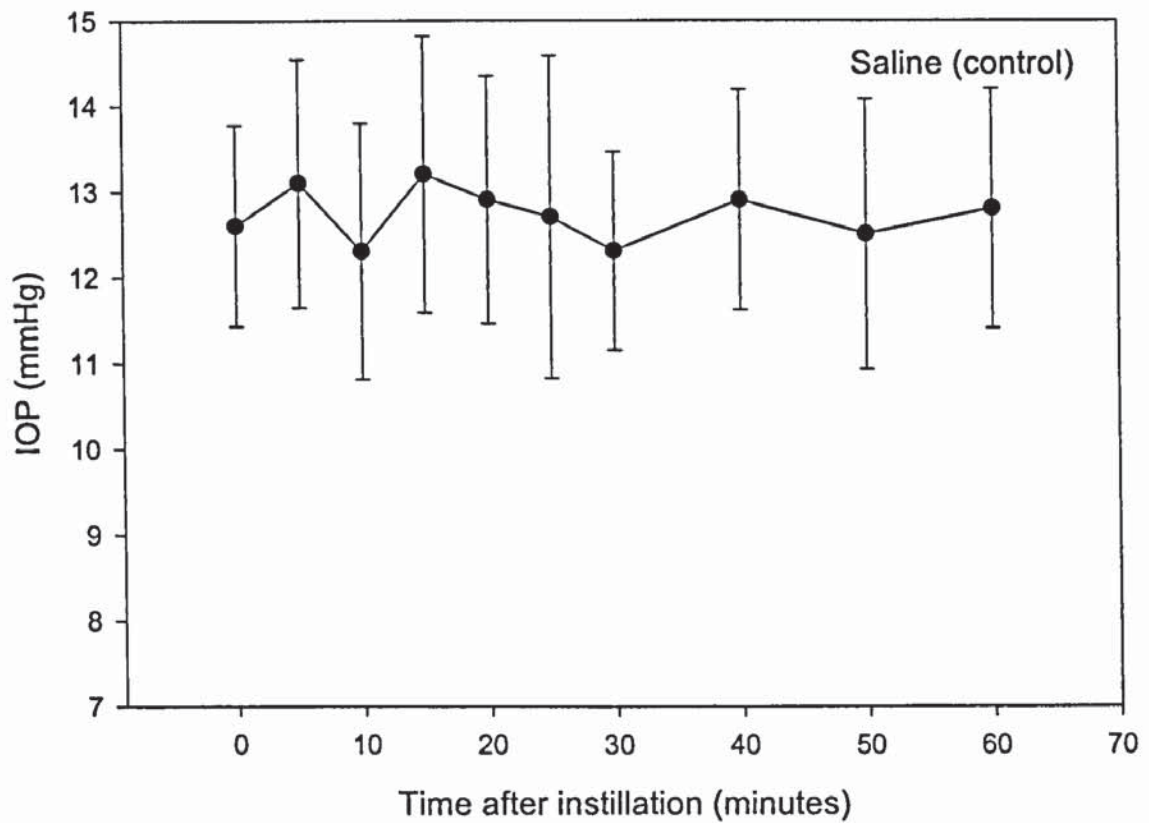

Figure A5.3 Mean IOP against time following instillation of a saline control (0.9%)

A5.4 Discussion.

Timolol and betaxolol produced consistent ocular hyoptensive effects of approximately 4 mmHg and 3 mmHg respectively. The hypotensive effect was seen to stabilise 20 minutes following instillation. From these findings it would seem reasonable to allow a 30 minute drug absorption period following instillation, prior to data collection.

APPENDIX 6

HUMAN SCIENCES ETHICAL COMMITTEE SUBMISSION

The following shows a duplicate of the forms submitted to the Human Sciences Ethical Committee, Aston University, for the approval of the use of topical pharmacological agents (including prescription only medicines) on human volunteers.

ASTON UNIVERSITY   PROJECT NO...........

THE SENATE   REG/   /

HUMAN SCIENCE ETHICAL COMMITTEE

Application for approval of a research project involving human volunteers

Please read the enclosed guidelines before completing this form - in typescript or black ink - and return the form to: The Secretary of the Human Science Ethical Committee, Registry. If you intend to administer or expose subjects to a physical procedure other than simple venepuncture **you must also submit an experimental protocol.**

Project title: Autonomic correlates of myopia onset and development in young adults.

Investigators:	Department /address:	Telephone:
Prof. B Gilmartin	**Optometry, Life and Health Sciences.**	X 5159
....	....	
Mr Edward Mallen	**Optometry, Life and Health Sciences.**	
....	....	
....	....	
....	....	
....	....	

A
Details of sponsoring/collaborating organisation (if any)

1.   Name: **The College of Optometrists**

2.   Does the sponsoring/collaborating organisation provide insurance?   **NO**

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3.   If drugs are used, do any require a clinical trials certificate or clinical trials
     exemption certificate?   **NO**

B
Summary of project

1.   Starting date: **March 2001**

2.   Duration: **2 years**

3.   Location: **Optometry, Life and Health Sciences, Aston University.**

4.   Physical procedures:
     Instillation of ophthalmic drugs.
     Fitting of single use soft contact lenses (1 hour maximum wear).
     Measurement of: Accommodation using standard auto-refractor,
     Intra-ocular pressure using a standard non-contact tonometer,
     Pulsatile ocular blood flow, using single-use disposable tip,
     Corneal topography using the *EyeSys* instrument.
     Measurement of axial length using *Zeiss IOLMaster*.

5.   Substances to be administered (a substance is anything other than normal food. Chemical
     constituents of food stuffs, ethanol and variation of the diet should be included here):
     The following substances are all eye drops.
     1. Proxymetacaine HCl 0.5%. Topical anaesthetic for short duration (15 mins) corneal
     anaesthesia. Topical anaesthetics are used routinely in general optometric practice.
     2. Timolol maleate 0.5%, 25 microlitres each eye. Non-selective beta-blocker.
     3. Betaxolol hydrochloride 0.5%, 50 microlitres each eye as 2 drops. Selective beta-
     blocker.
     4. Phenylephrine hydrochloride 2.5% and 10%. Sympathomimetic.
     5. Fluorescein sodium (sterile single use applicator) indicator dye for detection of
     corneal abrasion.

6.   Psychological assessment:

     N/A.

7.   Questionnaires: (only to be completed when project contains questionnaire(s) which fall
             within the types of questionnaire requiring HSEC approval [Guidelines D(3)])

     N/A.

C
Subjects

1.   Number of subjects to be used: **60. All second year undergraduate Optometry**
students.

2.   Over what time span? **2 years.**

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3.   Age of subjects: **18 to 21 years.**

4.   Sex of subjects: **Mixed.**

5.   Source: **Optometry undergraduate students.**

6.   Will payments be made to the subjects and if so, how much will each be paid? **No.**

7.   Are the subjects patients or healthy volunteers? (If patients, give diagnosis, clinic/responsible   practitioner). **All subjects are healthy volunteers.**

8.   Will any subjects be excluded and if so, on what grounds?
      Yes. The following grounds will be used for exclusion:
      i) asthma at any time in the past, however distant.
      ii) any history of obstructive airways disease.
      iii) any history of bradycardia, heart block or heart failure.
      iv) any abnormality reported following an ECG recording.
      v) diabetes which is poorly stabilized.
      vi) myasthenia gravis.
      Exclusion grounds i) to vi) pertain to the use of beta-blockers.
      vii) subjects with baseline intraocular pressure less than 12 mmHg.
      viii) subjects with mean spherical myopic refractive error greater than 3D

9.   Is the activity of the subject to be restricted in any way before of after the procedure? (eg diet, driving). **Driving is not restricted as the agents and procedures do not normally affect visual function.**

      The subject should avoid strenuous exercise before and after the instillation of beta-blockers (timolol and betaxolol).

10.   Consent: Please attach a copy of the consent form you intend to use, detailing how procedures and hazards will be explained. **Attached.**

D
Hazards

1.   Please give full details of any hazards which could affect the health, safety or welfare of any subject.
      1. Adverse reactions to drugs listed in section b, part 5. A rare adverse reaction to topical anaesthetics can occur. The reaction has a reported incidence of 1 in 1000 patients over the 55 years of age. Data is not available for young adults – there appear to have been 3 reactions reported in the last 10 years of undergraduate activities at Aston (approximately 3000 instillations). The reaction is essentially desquamation of the corneal epithelium which can cause a significant reduction in visual acuity for up to 2 hours, with no permanent effects.
      2. Adverse reaction to contact lenses.
      3. Possible risk of slight corneal abrasion following intra-ocular pressure or ocular blood flow measurements.
      4. Risk of fall in intra-ocular pressure during strenuous exercise in addition to the reduction in pressure due to the instillation of timolol or betaxolol. The drops will

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reduce intra-ocular pressure (IOP) by between 2 and 4mmHg and the effect will last for approximately 24 hours. Strenuous exercise (e.g. vigorous running, cycling, squash or weight training) can reduce IOP by a further 2 to 4 mmHg for a short period (approximately 15 minutes).

2. How do you propose to minimise these hazards?
1. Exclude certain subjects (see section c, part 8). If a reaction to the topical anaesthetic proxymetacaine occurs the subject's condition will be continuously monitored until visual acuity returns to normal levels.
2. Use single use disposable soft contact lenses to eliminate the risk of cross-infection.
3. Corneal integrity will be checked at the end of each experiment by slit lamp examination in conjunction with the use of fluorescein as an indicator dye. Visual acuity will be checked by using a Snellen chart. All investigators are UK GOC registered Optometrists.
4. Subjects should cease strenuous exercise a minimum of 30 minutes prior to the instillation of timolol or betaxolol. Strenuous exercise should be then be avoided for 24 hours following the instillation of timolol or betaxolol (note that each subject will have only one instillation of timolol and one instillation of betaxolol during the project). In addition, subjects with baseline intraocular pressure lower than 12 mmHg will be excluded (population mean 15.5 +/- 2.5) mmHg).

Medical advisor: Mr.J. Ainsworth.
Consultant Pediatric Ophthalmologist,
Birmingham Children's Hospital.
Honorary Senior Lecturer,
Birmingham University.

3. Is there any precedent for these experiments? If so, please give details with references if possible. Yes.

The references for similar projects given approval by Aston University HSEC in the past are: 85E; 85I and 86G.

Similar projects have also recently been undertaken, without adverse incident, by research workers at The University of Bradford and Glasgow Caledonian University.

Research reports using similar drug protocols:
Culhane H, Winn B and Gilmartin B. (1999) Human dynamic closed-loop accommodation augmented by sympathetic inhibition. *Invest. Ophthalmol. Vis. Sci.* 40, 1137-1143.

Gilmartin B and Winfield NR. (1995) The effect of topical ß-adrenoceptor antagonists on accommodation in emmetropia and myopia. *Vision Res.* 35, 1305-1312.

Gilmartin B. Autonomic correlates of the near vision response in emmetropia and myopia. In *Myopia and Nearwork*. Rosenfield M and Gilmartin B. (Eds) Butterworth Heinemann, Oxford, pp 117-146.

4. Has this project been considered/is it being considered by any other Ethical Committee? If so, please give details and decision made. No.

E

STATEMENT BY NAMED INVESTIGATORS, HEAD OF DEPARTMENT AND (if necessary) RESEARCH SUPERVISOR

I consider that the details given constitute a true summary of the projects and that the hazards and potential risks to any subject are accurately described.

Investigator...
        date.......................................

Investigator...
        date.......................................

Investigator...
        date.......................................

Investigator...
        date.......................................

Investigator...
        date.......................................

Head of Department...
        date.......................................

Supervisor...
        date.......................................

The following are attached:

      *subject consent form
      *experimental protocol

APPENDIX 7

INFORMATION AND CONSENT FORMS FOR EXPERIMENTAL PARTICIPANTS.

Following are information and consent forms for subjects participating in experiments where ophthalmic drugs or invasive procedures were employed.

EXPLANATION AND CONSENT FORM FOR VOLUNTEER SUBJECTS

DESCRIPTION OF PROJECT

TITLE:
The effect of timolol maleate (0.5%) and betaxolol HCl (0.5%) on accommodative adaptation induced by sustained near-vision tasks.

RESEARCH WORKERS AND SCHOOL RESPONSIBLE:
Supervisor: Professor. B. Gilmartin, B.Sc., Ph.D., FCOptom, FAAO;
PhD scholar: Mr. E. Mallen, B.Sc., MCOptom;
Neurosciences Research Institute, School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham. B4 7ET.

EXPLANATION OF PROCEDURES TO BE USED INCLUDING ASSESSMENT

OF ANY HAZARDS:

Tonic resting positions of accommodation (i.e. the position of focus of the eyes in an 'empty' visual field) will be measured objectively using consulting room equipment i.e. the Shin-Nippon infra-red autorefractor. These tonic positions have implications with respect to the autonomic control of accommodation and may be related to the facility that the accommodation system has to adapt to sustained visual tasks. The accommodation measurements will be taken before and after a 3 minute near-vision task requiring approximately 3 dioptres of accommodation. You will be required to attend three trials on different days, each trial being of approximately 40 minutes duration. Eye drops will be used in all trials.

Drugs will be randomly allocated to each trial. Intraocular pressure will be measured using a standard non-contact tonometer following the instillation of one drop of the topical anaesthetic proxymetacaine. Each subject's refractive error will be corrected by fitting single use ultra-thin disposable soft contact lenses and subjects will be required to wear them during the experiment for a period not exceeding 20 minutes.

The axial length of the eyes will be measured using a Zeiss *IOLMaster* device. Additional measurements of pulsatile ocular bloodflow, and corneal topography using the *Eyesys* may be taken.

Prior to the near-vision task, one of each of the following combinations of ophthalmic drugs will be instilled into both eyes:
- a) proxymetacaine 0.5% (topical anaesthetic) and one drop of timolol (0.5%)
- b) proxymetacaine 0.5% and two drops of betaxolol (0.5%) separated by 5 min.
- c) proxymetacaine 0.5% and two drops of normal saline separated by 5 min.

DETAILS OF DRUGS USED:

i)   proxymetacaine 0.5%: this drug is used to anaesthetize the cornea in order to inhibit reflex tear formation when other ophthalmic drugs are instilled.

ii)   timolol maleate (0.5%): this drug is used in medicine to lower intraocular pressure and this dosage is usually used daily over long periods of time. You will have just one drop per eye.

iii) betaxolol (0.5%): this drug is similar to timolol and is used in medicine to lower intraocular pressure; this dosage is usually used daily over long periods of time. You will have just two drops per eye.

iv) normal saline: this will be a 'placebo' drug.

All the above drugs are routinely employed in Optometric (proxymetacaine and saline) and Ophthalmological (timolol and betaxolol) practice. The risk of adverse reactions to these drugs is very small but **subjects suffering from any important medical condition and/or taking any systemic medication are not eligible as volunteers.**

In particular, subjects having the following conditions must **NOT** take part in the study:

i) **ASTHMA** at any time in the past, however distant.
ii) Any abnormality reported following an **ECG recording.**
iii) **Cardiac failure or diabetes** which is poorly stabilized.
iv) **Myasthenia gravis.**

Please note

The drops will reduce intra-ocular pressure (IOP) by between 2 and 4mmHg and the effect will last for approximately 24 hours. Because strenuous exercise (e.g. vigorous running, cycling, squash or weight training) can reduce IOP by a further 2 to 4 mmHg for a short period (approximately 15 minutes), you are advised not to undertake this type of activity for a minimum of 30 minutes prior to the instillation of timolol or betaxolol or for 24 hours following the instillation of timolol or betaxolol. You will not be accepted as a subject if your normal base line IOP is less than 12mmHg. Also, subjects with mean spherical refractive error greater than −3D will not be eligible to take part in the study.

Details pertaining to the experiment, the identity of subjects and data collected will be confidential with respect to any resulting publications.

STATEMENT OF VOLUNTEER

I have read and understood the above explanation. I have had the opportunity to discuss it with the investigators and to ask any questions and I understand that I am free to withdraw at any time. I understand that partaking in this experiment is not a requirement of my undergraduate or postgraduate course and that no sanctions will be taken against me if I refuse to participate or withdraw from the project. Consent to participate does not compromise my rights in law. I agree to take part in the above project.

Name of volunteer:..

Signed:..

Date:..

DESCRIPTION OF PROJECT

TITLE:
The effect of timolol maleate (0.5%) and betaxolol HCl (0.5%) on intra-ocular pressure.

RESEARCH WORKERS AND SCHOOL RESPONSIBLE:
Supervisor: Professor. B. Gilmartin, B.Sc., Ph.D., FCOptom, FAAO;
PhD scholar: Mr. E. Mallen, B.Sc., MCOptom;
Neurosciences Research Institute, School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham. B4 7ET.

EXPLANATION OF PROCEDURES TO BE USED INCLUDING ASSESSMENT

OF ANY HAZARDS:

Drugs will be randomly allocated to each trial. Intraocular pressure will be measured using a standard non-contact tonometer following the instillation of one drop of the topical anaesthetic proxymetacaine.

Prior to the intra-ocular pressure measurements, one of each of the following combinations of ophthalmic drugs will be instilled into both eyes:
   d) proxymetacaine 0.5% (topical anaesthetic) and one drop of timolol (0.5%)
   e) proxymetacaine 0.5% and two drops of betaxolol (0.5%) separated by 3 min.
   f) proxymetacaine 0.5% and two drops of normal saline separated by 3 min.

Intra-ocular pressure will be measured using a standard non-contact tonometer at 10 minute intervals for a period of 1 hour.

DETAILS OF DRUGS USED:

   v)   proxymetacaine 0.5%: this drug is used to anaesthetize the cornea in order to inhibit reflex tear formation when other ophthalmic drugs are instilled.
   vi)   timolol maleate (0.5%): this drug is used in medicine to lower intraocular pressure and this dosage is usually used daily over long periods of time. You will have just one drop per eye.
   vii) betaxolol (0.5%): this drug is similar to timolol and is used in medicine to lower intraocular pressure; this dosage is usually used daily over long periods of time. You will have just two drops per eye.
   viii) normal saline: this will be a 'placebo' drug.

All the above drugs are routinely employed in Optometric (proxymetacaine and saline) and Ophthalmological (timolol and betaxolol) practice. The risk of adverse reactions to these drugs is very small but **subjects suffering from any important medical condition and/or taking any systemic medication are not eligible as volunteers.**

It is important to avoid strenuous exercise following this experiment.

In particular, subjects having the following conditions must **NOT** take part in the study:

i) **ASTHMA** at any time in the past, however distant.

ii) Any abnormality reported following an **ECG recording.**

iii) **Cardiac failure or diabetes** which is poorly stabilized.

iv) **Myasthenia gravis.**

Details pertaining to the experiment, the identity of subjects and data collected will be confidential with respect to any resulting publications.

STATEMENT OF VOLUNTEER

I have read and understood the above explanation. I have had the opportunity to discuss it with the investigators and to ask any questions and I understand that I am free to withdraw at any time. I understand that partaking in this experiment is not a requirement of my undergraduate or postgraduate course and that no sanctions will be taken against me if I refuse to participate or withdraw from the project. Consent to participate does not compromise my rights in law. I agree to take part in the above project.

Name of volunteer:...

Signed:...

Date:..

APPENDIX 8

LONGITUDINAL REFRACTIVE ERROR, BIOMETRY AND PERIPHERAL REFRACTION DATA

A8.1 Longitudinal refractive error data relating to Chapter 3.

Subject	Initial MRE R (D)	Initial MRE L (D)	Initial Rx group	MRE shift R (D)	MRE shift L (D)	LOM onset
1	+0.00	+0.12	EMM	+0.13	-0.13	
2	+0.50	+0.25	EMM	-0.44	-0.50	#
3	+0.50	+0.75	EMM	-0.01	-0.56	#
4	-1.25	-1.25	EOM	-0.25	+0.06	
5	-0.38	-0.44	EMM	-0.56	-0.57	#
6	+0.13	+0.63	EMM	+0.06	-0.06	
7	+0.63	+0.75	EMM	-0.01	-0.06	
8	-1.50	-1.25	EOM	-1.00	-0.94	
9	-0.38	+0.13	EMM	-0.44	-0.94	#
10	+0.25	+0.50	EMM	+0.06	-0.25	
11	+0.38	-0.13	EMM	+0.13	+0.19	
12	-4.88	-5.00	EOM	+0.00	-0.25	
13	+0.13	0.00	EMM	-0.19	0.00	
14	-0.44	-0.25	EMM	-0.06	-0.31	
15	+0.50	+0.25	EMM	-0.31	-0.13	
16	+0.50	+0.25	EMM	-0.26	+0.19	
17	+0.00	0.00	EMM	+0.13	+0.37	
18	-0.38	0.00	EMM	+0.19	+0.19	
19	+0.00	-0.13	EMM	-0.31	-0.06	
20	+0.75	-0.25	EMM	-0.19	+0.31	
21	+0.75	+0.75	EMM	-0.69	-0.25	#
22	+0.25	0.00	EMM	-0.19	-0.25	
23	+0.50	+0.38	EMM	+0.13	+0.06	
24	-0.63	-0.63	LOM	-0.68	-0.69	
25	-0.38	-0.38	EMM	-0.63	-0.81	#
26	-3.63	-3.25	EOM	-0.19	-0.56	
27	-0.43	-0.38	EMM	-0.25	-1.25	#
28	+0.38	0.00	EMM	-0.01	+0.50	
29	0.00	+0.38	EMM	+0.19	+0.13	
30	+0.25	-0.13	EMM	-0.38	-0.37	
31	+0.38	+0.50	EMM	+0.12	+0.25	
32	+0.25	-0.50	EMM	-0.13	-0.31	
33	-4.13	-3.25	EOM	-0.12	+0.13	
34	-1.13	-1.38	EOM	-0.06	-0.37	
35	0.00	-2.38	EOM	+0.31	+0.20	
36	-3.75	-3.63	EOM	-0.31	-0.43	
37	+0.25	+0.75	EMM	+0.06	-0.50	#
38	+0.19	+0.75	EMM	-0.75	-0.06	#
39	0.00	+0.38	EMM	-0.32	+0.19	
40	-0.07	+0.25	EMM	-0.12	-0.88	#

Table A8.1. Longitudinal refractive error data.

A8.2 General biometric data relating to Chapter 5.

Subject	R MRE	R AL	R ACD	R CC	R AL:CC	L MRE	L AL	L ACD	L CC	L AL:CC
1	-6.00	24.87	3.95	7.22	3.45	-4.94	24.46	3.90	7.13	3.43
2	+0.06	24.07	3.59	8.06	2.99	+0.12	24.08	3.57	8.07	2.99
3	+0.75	22.12	3.28	7.49	2.95	+0.94	22.23	3.14	7.58	2.93
4	-0.01	24.08	3.88	8.12	2.97	+0.25	24.11	3.88	8.14	2.96
5	+0.94	22.11	3.64	7.42	2.98	+0.25	22.19	3.68	7.46	2.97
6	-1.23	22.79	4.15	7.06	3.23	-1.38	22.78	4.13	7.09	3.21
7	-1.19	23.17	3.58	7.24	3.20	-1.06	22.90	3.68	7.14	3.21
8	-8.06	26.24	4.15	7.52	3.49	-7.50	26.22	4.16	7.53	3.48
9	+0.13	22.71	3.15	7.46	3.04	+0.75	22.53	3.08	7.45	3.02
10	+0.38	23.80	3.78	7.83	3.04	+0.56	23.68	3.68	7.85	3.02
11	-1.69	23.91	3.77	7.65	3.13	-1.75	23.71	3.72	7.67	3.09
12	-0.56	23.97	3.40	7.76	3.09	-0.44	24.19	3.37	7.81	3.10
13	+0.19	24.45	3.71	8.29	2.95	+0.25	24.51	3.72	8.31	2.95
14	-2.00	25.09	3.92	7.81	3.21	-1.93	25.22	3.92	7.79	3.24
15	-2.38	23.77	3.66	7.36	3.23	-2.38	23.60	3.51	7.43	3.18
16	+0.31	23.75	3.44	7.93	3.00	-0.06	23.75	3.48	7.92	3.00
17	-4.63	25.66	3.76	7.73	3.32	-4.68	25.74	3.68	7.77	3.32
18	-5.37	25.73	3.60	7.74	3.33	-4.62	25.42	3.52	7.76	3.28
19	-1.68	24.15	4.23	7.37	3.28	-1.25	24.11	4.21	7.42	3.25
20	-0.19	24.22	3.57	8.08	3.00	0.00	24.13	3.54	8.04	3.00
21	-0.44	22.82	3.92	7.36	3.10	-0.75	22.77	4.08	7.35	3.10
22	+0.19	24.80	3.92	8.12	3.05	+0.31	24.53	3.86	8.03	3.05
23	+0.25	23.99	3.89	7.83	3.06	+0.12	23.89	3.82	7.83	3.05
24	-13.62	28.26	3.98	7.49	3.78	-12.68	28.12	4.03	7.50	3.75
25	+0.12	23.31	3.56	7.67	3.04	-0.01	23.42	3.61	7.70	3.04
26	-0.88	23.55	3.25	7.63	3.09	-1.00	23.61	3.60	7.64	3.09
27	-5.81	25.24	3.83	7.49	3.37	-6.75	25.54	3.82	7.45	3.43
28	+4.19	23.25	3.60	8.32	2.79	+7.31	22.35	3.48	8.38	2.67
29	-0.44	23.00	3.65	7.60	3.03	-0.01	23.16	3.72	7.64	3.03
30	+0.50	23.62	3.62	8.01	2.95	+0.69	23.47	3.65	7.96	2.95
31	-2.56	24.23	3.70	7.41	3.27	-1.06	23.62	3.45	7.45	3.17
32	-0.37	23.87	3.35	8.17	2.92	-0.44	23.87	3.36	8.13	2.94
33	-3.94	25.69	3.32	8.04	3.20	-4.06	25.44	3.34	7.93	3.21
34	+0.62	22.43	3.38	7.55	2.97	+0.19	22.68	3.41	7.53	3.01
35	+0.50	23.75	3.27	8.02	2.96	+0.50	23.65	3.25	7.95	2.98
36	+0.12	24.18	3.39	8.24	2.94	+0.06	24.26	3.35	8.26	2.94
37	+0.50	23.48	3.35	7.85	2.99	-0.01	23.72	3.31	7.86	3.02
38	-1.44	25.83	3.88	8.08	3.20	-1.31	25.67	3.83	8.00	3.21
39	-0.81	23.34	3.66	7.50	3.11	-0.44	23.31	3.62	7.51	3.11
40	-3.75	26.19	3.94	7.82	3.35	-3.69	26.12	4.22	7.81	3.34
41	-3.00	25.40	3.56	7.87	3.23	-2.19	24.92	3.54	7.83	3.18
42	-1.19	25.31	3.78	8.13	3.11	-1.62	25.37	3.79	8.03	3.16
43	+0.12	22.67	3.41	7.68	2.95	+0.25	22.60	3.40	7.64	2.96
44	-3.93	24.89	3.39	7.63	3.26	-3.62	24.62	3.53	7.65	3.22
45	+0.19	23.90	3.69	7.94	3.01	+0.31	23.88	3.64	7.96	3.00
46	-0.01	23.56	3.58	7.88	2.99	-0.38	23.66	3.37	7.89	3.00
47	+0.50	23.35	3.49	7.78	3.00	+0.81	23.35	3.38	7.81	2.99
48	-0.13	23.88	3.74	8.01	2.98	-0.81	24.01	3.64	7.97	3.01
49	-1.00	25.68	3.75	7.99	3.21	-2.00	25.79	3.74	7.94	3.25
50	-1.56	23.39	3.84	7.33	3.19	-1.68	23.45	3.88	7.30	3.21
51	+0.19	23.85	3.41	7.86	3.03	+0.13	23.75	3.44	7.83	3.03
52	+4.38	20.60	2.97	7.29	2.83	+1.25	21.53	3.16	7.31	2.95

53	-4.25	25.12	3.99	7.52	3.34	-3.31	24.53	3.91	7.47	3.29
54	+0.50	23.05	3.47	7.80	2.96	+0.38	22.89	3.51	7.71	2.97
55	-0.56	23.68	3.63	7.78	3.05	-0.62	23.71	3.66	7.78	3.05
56	-6.75	25.93	4.14	7.57	3.42	-6.25	25.86	4.08	7.58	3.41
57	-5.62	27.29	3.58	8.33	3.28	-5.81	27.15	3.56	8.29	3.28
58	-3.00	24.94	3.55	7.59	3.29	-3.44	25.13	3.48	7.60	3.31
59	-1.00	24.36	3.79	7.94	3.07	-1.87	24.77	3.36	7.93	3.12
60	-3.00	25.07	3.68	7.72	3.25	-2.56	25.05	3.69	7.70	3.25
61	-5.75	25.22	3.72	7.37	3.42	-7.43	25.56	3.71	7.35	3.48
62	-0.13	24.42	3.87	8.22	2.97	-2.13	24.00	4.05	7.66	3.13
63	-3.63	25.14	3.84	7.76	3.24	-4.06	25.15	3.82	7.71	3.26
64	+0.62	22.27	3.60	7.27	3.06	+0.50	22.23	3.56	7.31	3.04
65	-4.00	25.62	3.80	7.93	3.23	-3.13	25.47	3.78	7.99	3.19
66	-0.25	23.18	3.59	7.74	3.00	+0.50	22.55	3.49	7.62	2.96
67	+3.94	22.69	3.42	8.05	2.82	+0.44	24.05	3.30	8.14	2.96
68	+0.62	22.48	2.81	7.78	2.89	+0.75	22.44	3.02	7.72	2.91
69	-0.44	25.06	3.60	8.16	3.07	-0.93	25.12	3.71	8.09	3.10
70	-6.13	26.36	3.92	7.81	3.38	-6.5	26.4	3.94	7.82	3.38

Table A8.2. General biometric data relating to Chapter 5.

A8.3 Peripheral refraction data (Shin-Nippon SRW-5000), D.

Subject	R MRE	R 30° Temp	R 30° Nasal	L MRE	L 30° Temp	L 30° Nasal
1	-6.00	-4.43	-1.50	-4.94	-4.50	-1.31
2	+0.06	+0.19	-0.06	+0.12	+0.57	+0.19
3	+0.75	+0.32	+1.81	+0.94	-0.12	+1.57
4	-0.01	+0.25	+0.44	+0.25	+0.50	0.00
5	+0.94	+1.00	+2.06	+0.25	+0.32	+1.44
6	-1.19	+0.12	-0.50	-1.06	-0.38	-0.07
7	-8.06	-5.69	-6.81	-7.50	-6.31	-5.25
8	+0.13	+0.19	+1.25	+0.75	-0.25	+1.19
9	+0.38	+0.69	+1.88	+0.56	+0.06	+0.56
10	-1.69	-0.76	-1.50	-1.75	-0.50	-0.93
11	-0.56	-0.19	+0.57	-0.44	-0.81	+0.32
12	+0.19	+0.25	+0.31	+0.25	+0.25	+0.50
13	-2.00	-0.13	-0.88	-1.93	-0.56	-0.50
14	-2.38	-1.56	-1.25	-2.38	-0.56	-1.31
15	+0.31	-0.63	0.00	-0.06	-0.38	0.00
16	-4.63	-3.25	-4.00	-4.68	-4.06	-4.38
17	-5.37	-5.13	-3.75	-4.62	-5.37	-4.62
18	-1.68	+1.00	+0.06	-1.25	+1.44	+0.12
19	-0.19	-0.50	-0.26	0.00	-1.13	-0.32
20	-0.44	-1.06	+0.06	-0.75	+0.13	-0.06
21	+0.19	-1.07	-0.31	+0.31	-0.81	+0.38
22	+0.25	+1.07	+1.75	+0.12	+0.82	+0.82
23	-13.62	-8.56	-16.68	-12.68	-9.18	-14.19
24	+0.12	+0.81	+0.50	-0.01	+1.06	+0.32
25	-0.88	+0.31	-0.07	-1.00	+0.38	-0.44
26	-5.81	-5.31	-5.37	-6.75	-6.06	-5.94
27	+4.19	+0.82	+4.07	+7.31	+2.94	+4.19
28	-0.44	-2.93	+1.44	-0.01	-1.56	+1.19
29	+0.50	+0.56	+0.44	+0.69	+1.75	+0.57
30	-0.69	-1.12	+0.81	-1.75	+1.19	+1.57
31	-2.56	-0.38	-0.31	-1.06	+1.19	-1.00
32	-0.37	-1.38	-0.76	-0.44	-1.19	-0.75
33	-3.94	-4.75	-5.31	-4.06	-4.06	-4.87
34	+0.62	+1.69	+1.57	+0.19	+1.57	+1.19
35	+0.50	+0.25	+0.19	+0.50	+0.50	+0.32
36	+0.50	-1.31	-0.88	-0.01	-2.18	-0.44
37	-1.44	-1.87	-0.81	-1.31	-1.81	-0.75
38	-0.81	+0.25	0.00	-0.44	-0.19	+0.12
39	-3.75	-1.81	-2.75	-3.69	-1.19	-2.87
40	-3.00	-2.62	-1.56	-2.19	-1.62	-1.38
41	-1.19	-0.93	-0.75	-1.62	-1.19	-1.12
42	+0.12	+1.06	+0.94	+0.25	+1.50	+0.57
43	-3.93	-3.00	-2.12	-3.62	-3.19	-1.44
44	+0.19	-0.69	-0.25	+0.31	-0.06	-0.50
45	-0.01	-0.06	+0.38	-0.38	+0.25	+0.32
46	+0.50	-0.06	-0.38	+0.81	0.00	-0.01
47	-0.13	-0.56	+1.12	-0.81	-0.63	+0.25
48	-1.00	-0.75	-0.19	-2.00	-2.38	-1.06
49	-1.56	+0.19	0.00	-1.68	+0.19	+0.25
50	+0.19	+1.06	+1.75	+0.13	+1.44	+1.12
51	+4.38	+1.56	+5.50	+1.25	+2.44	+1.32
52	-4.25	-2.06	-2.25	-3.31	-1.12	-1.75
53	+0.50	+1.19	-0.01	+0.38	+0.06	+0.06
54	-0.56	+0.57	+0.44	-0.62	+0.56	+0.44

55	-6.75	-4.00	-6.00	-6.25	-3.43	-6.38
56	-5.62	-5.68	-6.18	-5.81	-5.68	-6.43
57	-3.00	-2.37	-2.38	-3.44	-3.31	-3.19
58	-1.00	-0.69	-0.75	-1.87	-1.25	-1.06
59	-3.00	-2.25	-2.25	-2.56	-3.31	-1.56
60	-5.75	-4.06	-4.13	-7.43	-5.56	-6.62
61	-0.13	-2.87	-2.25	-2.13	-1.06	-0.87
62	-3.63	-1.31	-0.07	-4.06	-1.43	-0.37
63	+0.62	-0.01	+1.38	+0.50	+0.06	+1.19
64	-4.00	-2.63	-3.75	-3.13	-2.56	-2.31
65	-0.25	-0.88	+0.94	+0.50	-1.13	+0.94
66	+3.94	+1.07	-0.88	+0.44	+0.31	+1.13
67	+0.62	-0.26	+0.25	+0.75	-1.50	+0.44
68	-0.44	+0.69	+1.57	-0.93	+1.25	+1.12

Table A8.3. Peripheral refraction data.

A8.4 Peripheral length measurements (*IOLMaster*) mm.

Subject	R AL	R 30° Temp	R 30° Nasal	L AL	L 30° Temp	L 30° Nasal
1	24.87	23.68	23.77	24.46	23.50	23.18
2	24.07	23.28	23.84	24.08	23.41	23.83
3	22.12	22.23	21.63	22.23	22.44	21.76
4	24.08	23.73	24.02	24.11	23.76	24.02
5	22.11	21.83	22.02	22.19	21.86	22.15
6	23.17	22.26	22.88	22.90	22.38	22.72
7	26.24	25.20	26.07	26.22	25.60	26.05
8	23.80	23.67	23.63	23.68	23.65	23.65
9	23.91	22.77	23.38	23.71	23.08	23.15
10	23.97	23.65	23.65	24.19	23.87	23.55
11	24.45	23.81	24.03	24.51	23.88	24.32
12	25.09	23.74	24.72	25.22	24.25	24.45
13	27.22	25.68	26.34	27.40	26.38	25.68
14	25.66	25.13	24.72	25.74	25.08	25.28
15	25.73	24.68	25.01	25.42	24.62	25.16
16	24.15	23.02	23.56	24.11	23.38	23.09
17	24.22	24.02	24.00	24.13	23.95	23.84
18	22.82	22.31	22.69	22.77	22.35	22.53
19	24.80	24.40	24.69	24.53	24.04	24.40
20	23.99	23.24	23.58	23.89	23.21	23.41
21	28.26	25.32	30.32	28.12	26.86	28.17
22	23.31	22.62	22.91	23.42	22.98	22.88
23	23.55	22.86	23.16	23.61	23.29	23.23
24	25.24	24.22	24.42	25.54	24.41	24.67
25	23.00	22.92	22.73	23.16	22.55	22.72
26	23.62	23.24	23.41	23.47	23.08	23.27
27	24.23	22.93	23.23	23.62	22.54	22.69
28	23.48	23.09	23.59	23.72	23.65	23.55
29	25.83	25.31	25.41	25.67	25.18	25.27
30	23.34	22.92	23.19	23.31	22.67	22.75
31	26.19	24.81	25.78	26.12	25.28	25.51
32	25.40	24.60	25.07	24.92	24.49	24.56
33	25.31	24.34	24.68	25.37	24.46	24.59
34	22.67	22.40	22.52	22.60	22.32	22.40
35	23.90	23.64	23.77	23.88	23.39	23.68
36	23.35	22.75	23.14	23.35	22.93	23.01
37	25.68	25.88	25.63	25.79	25.69	25.55
38	23.39	22.32	22.63	23.45	22.70	22.60
39	23.85	23.33	23.31	23.75	23.17	23.19
40	20.60	20.83	20.09	21.53	21.29	21.19
41	25.12	24.00	24.86	24.53	23.81	24.19
42	23.05	22.41	22.68	22.89	22.29	22.43
43	23.68	22.98	23.15	23.71	23.16	23.11
44	25.93	24.60	25.51	25.86	25.36	25.22
45	27.29	26.06	27.20	27.15	26.21	26.87
46	24.94	24.31	24.68	25.13	24.82	24.56
47	24.36	24.11	24.14	24.77	24.32	24.49
48	25.07	24.42	24.69	25.05	24.58	24.49
49	25.22	24.29	24.79	25.56	24.95	25.19
50	24.42	23.86	23.75	24.00	23.46	23.31
51	25.14	23.25	23.77	25.15	23.50	23.04
52	22.27	21.80	22.23	22.23	21.71	22.14
53	25.62	24.95	25.22	25.47	24.98	24.92
54	23.18	22.63	23.05	22.55	22.37	22.91

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55	22.69	22.91	22.82	24.05	23.57	23.27
56	25.08	24.70	24.92	24.81	24.40	24.61
57	25.06	24.33	24.52	25.12	24.16	24.36

Table A8.4. Peripheral length measurements.

Abbreviations:

ACD	Anterior chamber depth (mm)
AL	Axial length (mm)
AL:CC	Axial length:corneal curvature ratio
CC	Mean corneal curvature (mm)
EMM	Emmetrope
EOM	Early-onset myope
L	Left eye
LOM	Late-onset myopia
MRE	Mean refractive error (D)
R	Right eye

DYNAMIC ACCOMMODATION GAIN AND PHASE LAG PLOTS

A9.1 Accommodative gain plots: Individual subjects, effect of adaptive task on accommodative gain. Error bars indicate 1 standard deviation throughout.
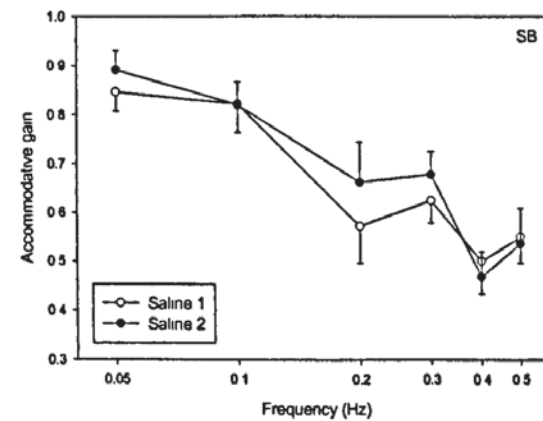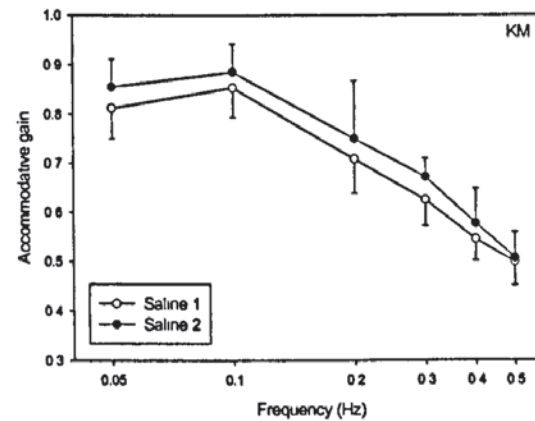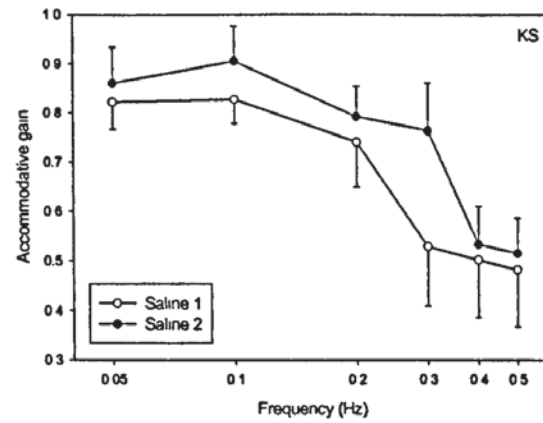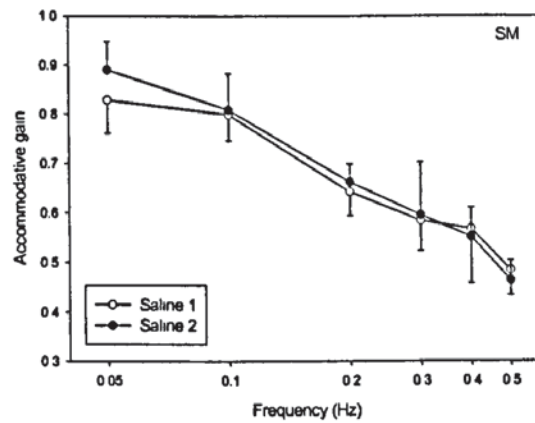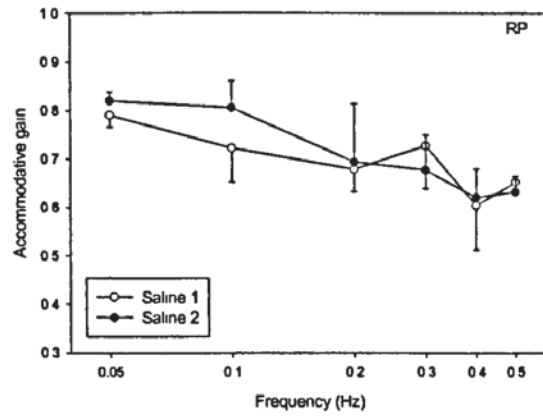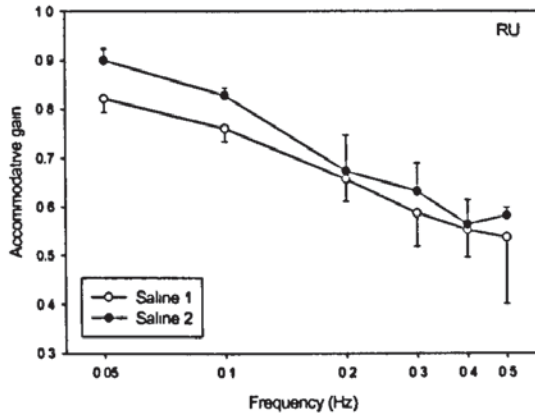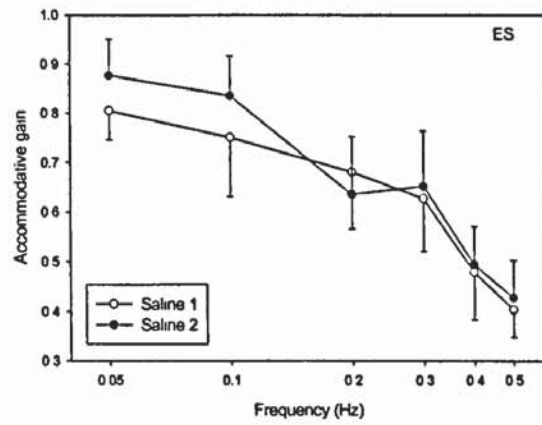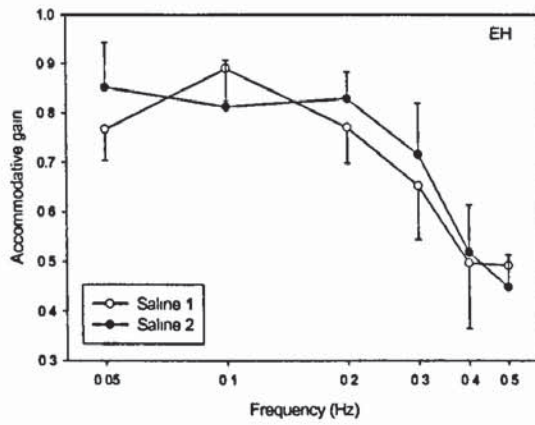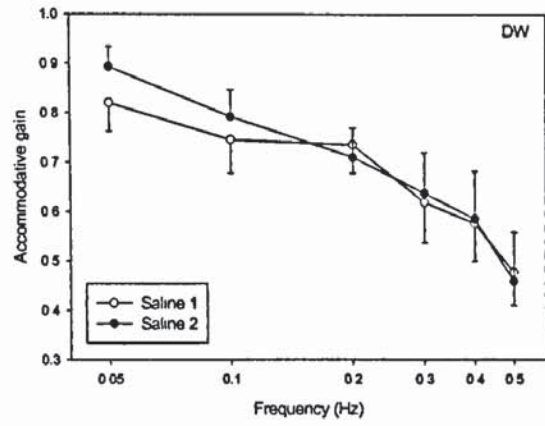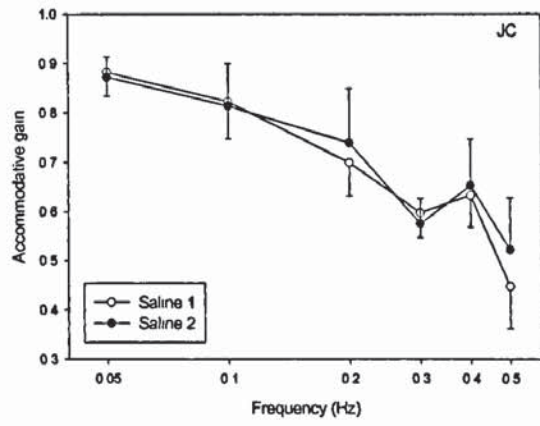
A9.2 Accommodative response phase lag plots: Individual subjects, effect of adaptive task under saline conditions.
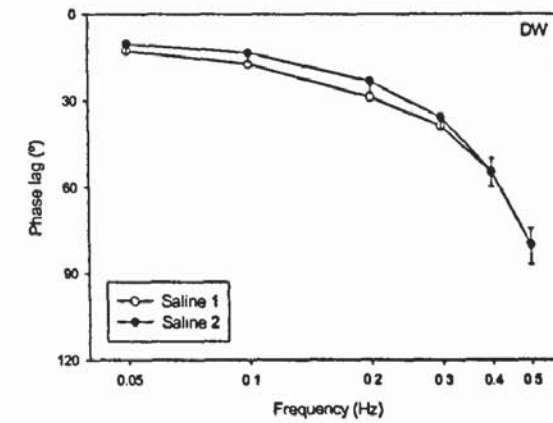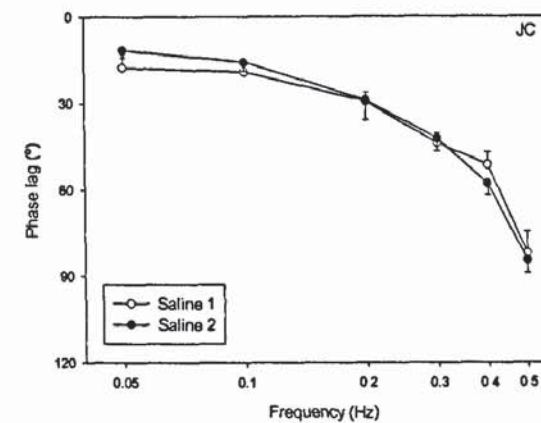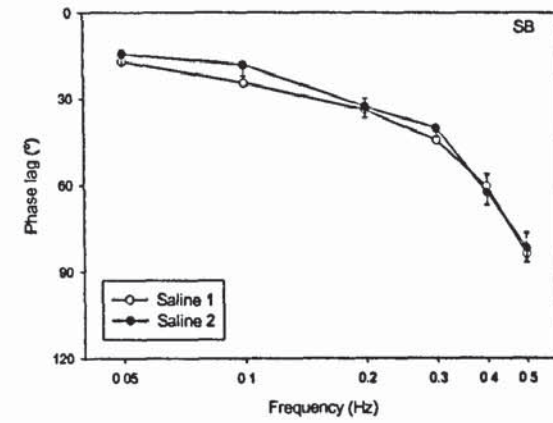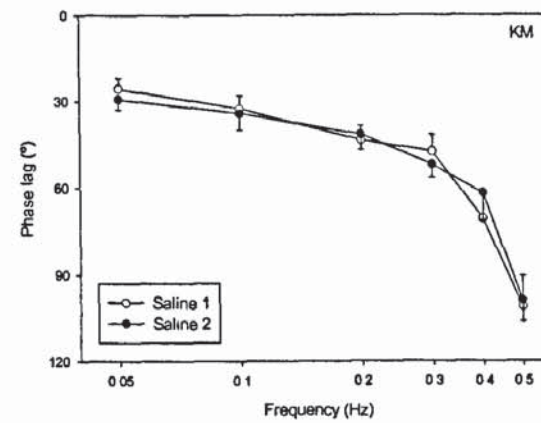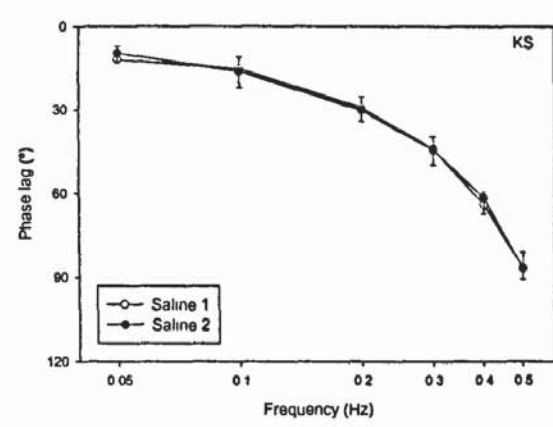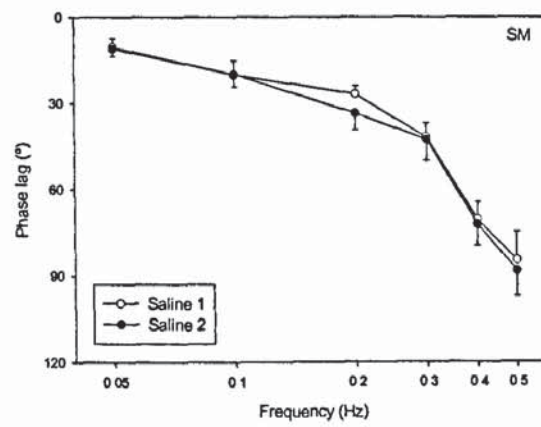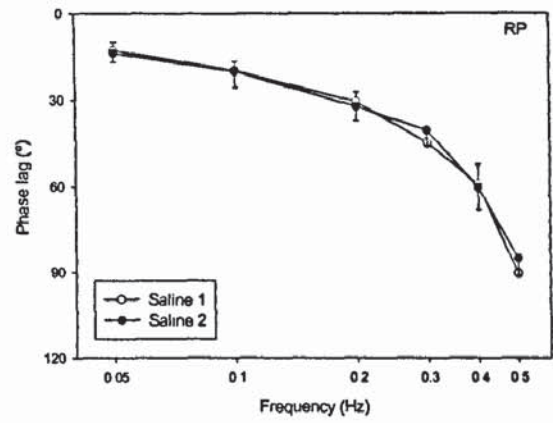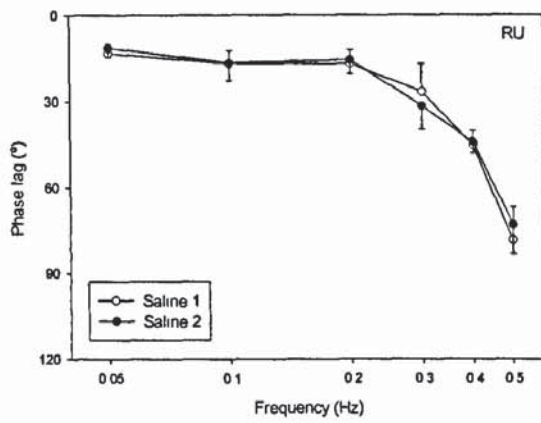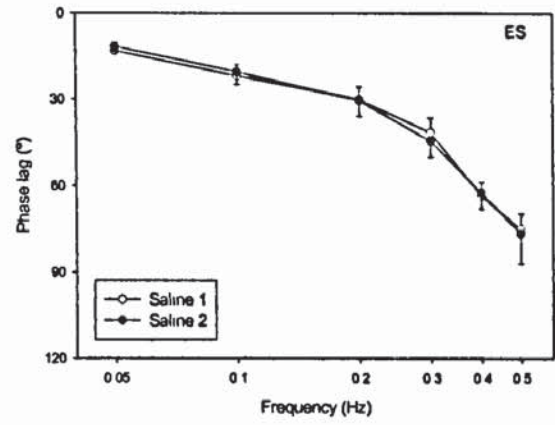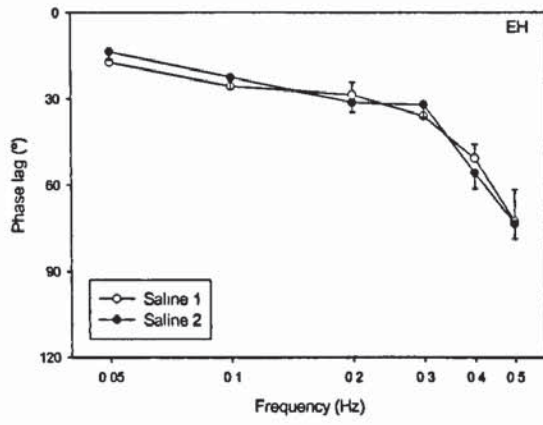
A9.3 Accommodative gain plots: Individual subjects, effect of timolol and betaxolol.
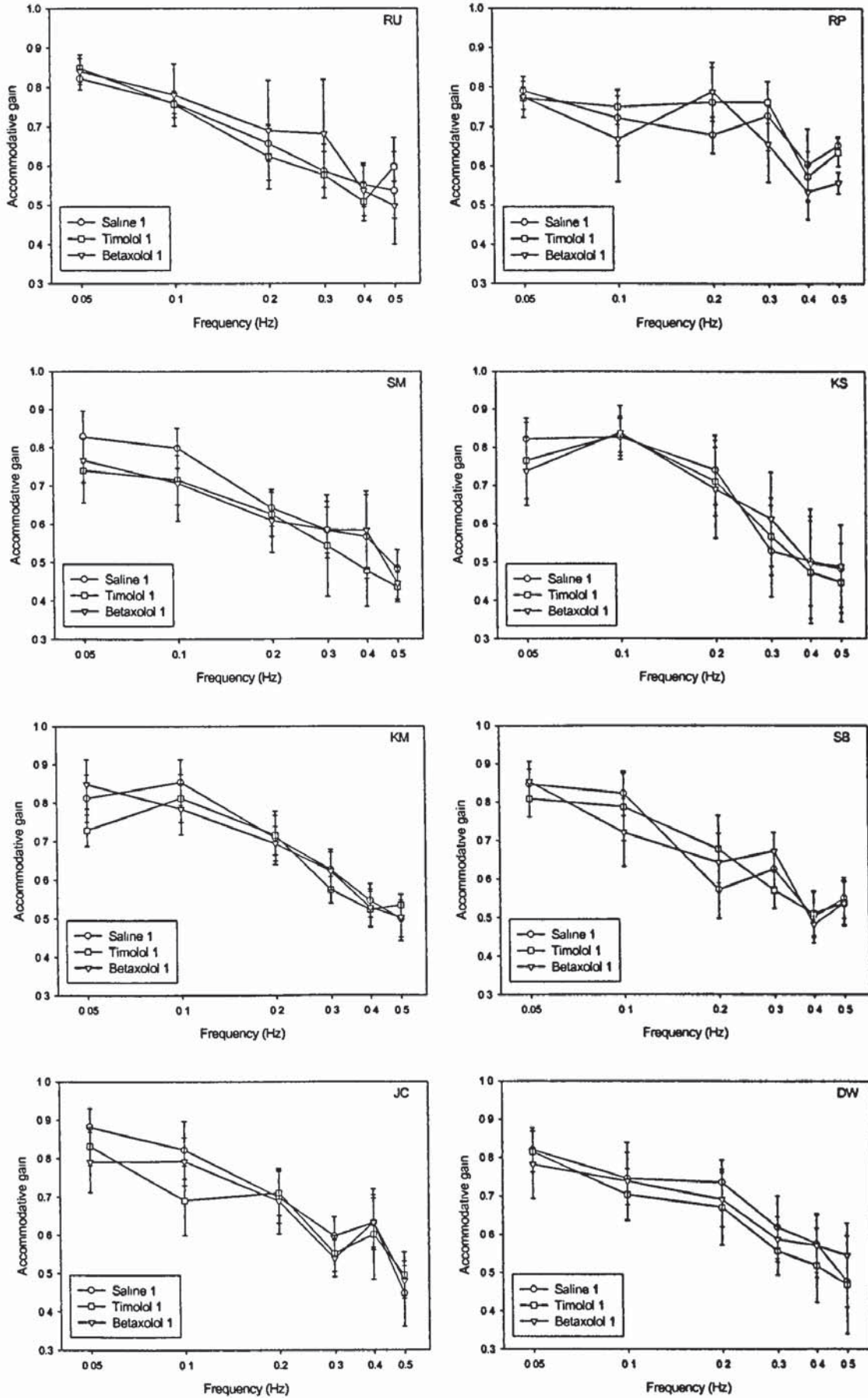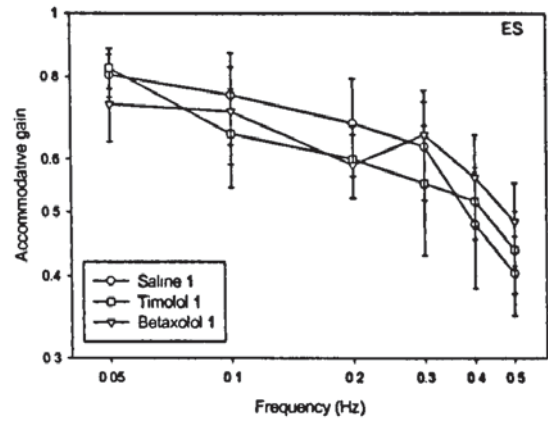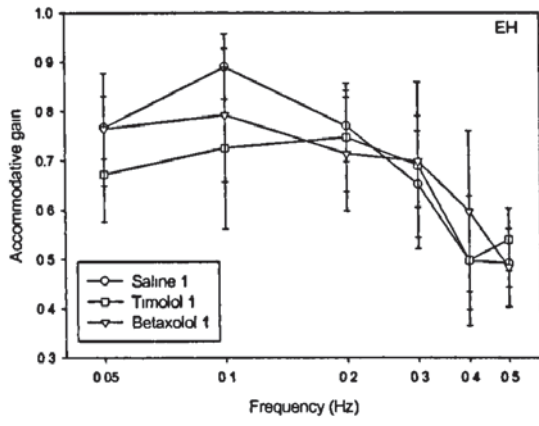
A9.4 Accommodative response phase lag plots: Individual subjects, effect of timolol and betaxolol.
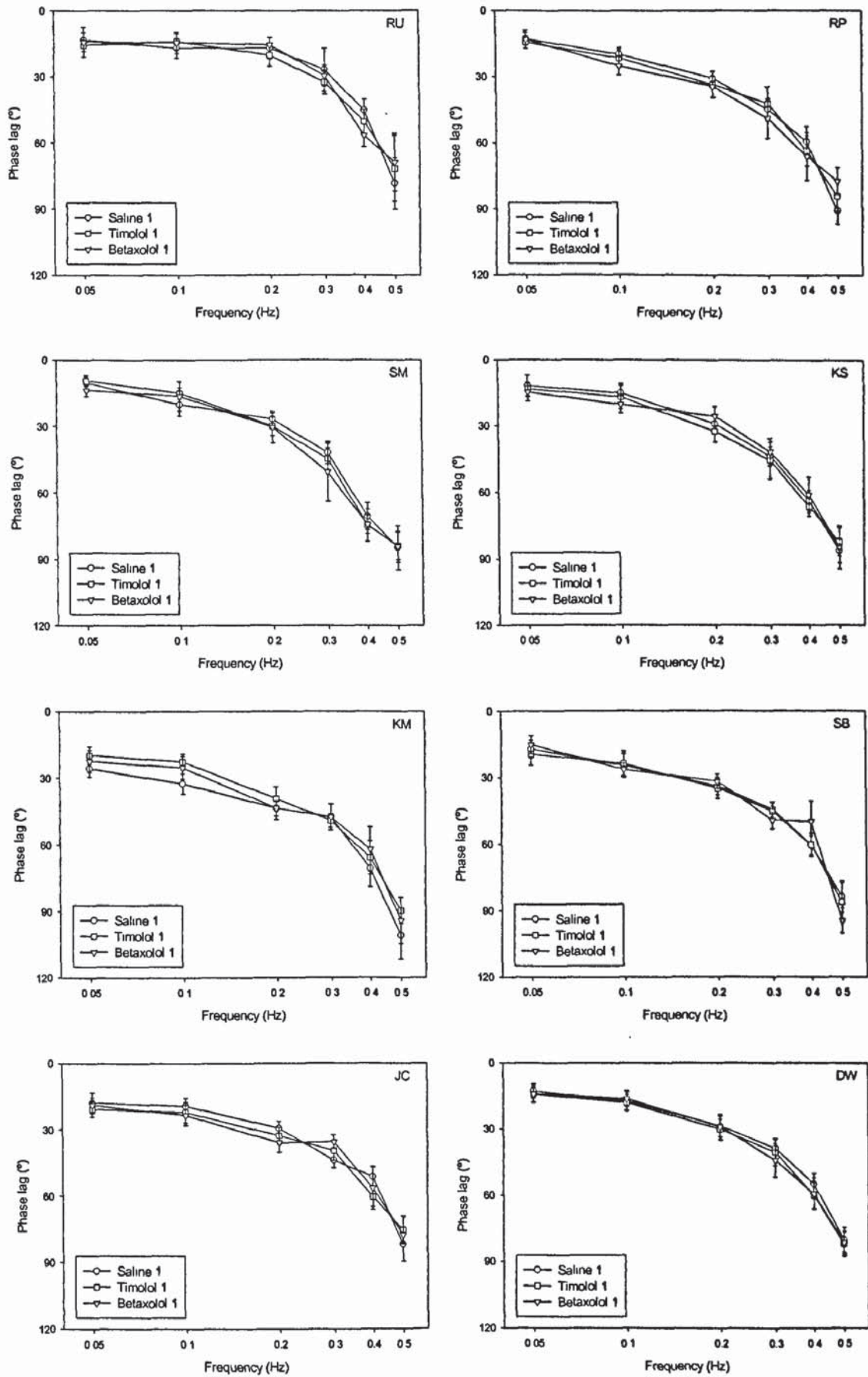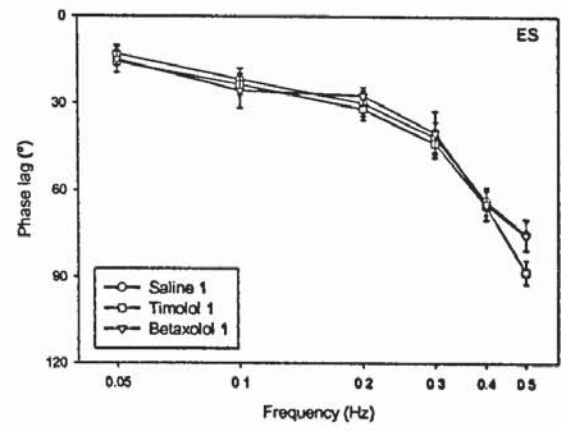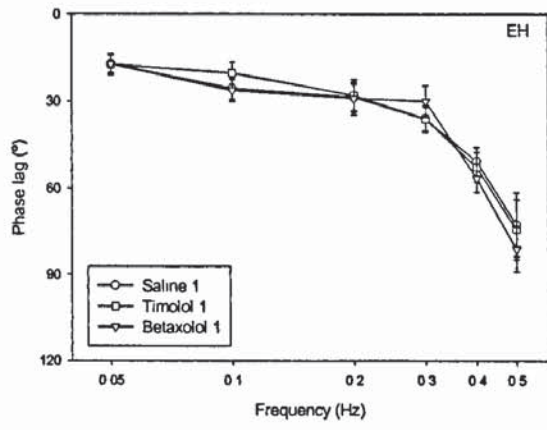
A9.5 Accommodative gain plots: Individual subjects, saline against phenylephrine.
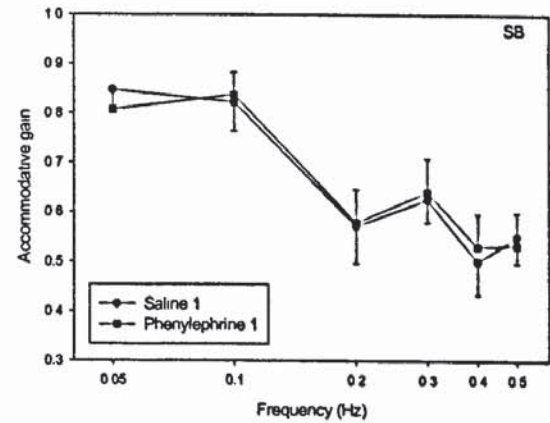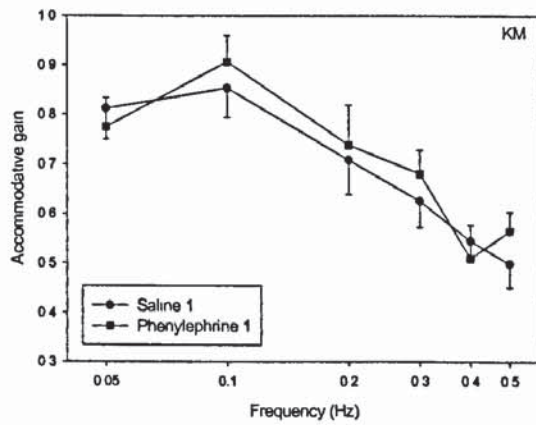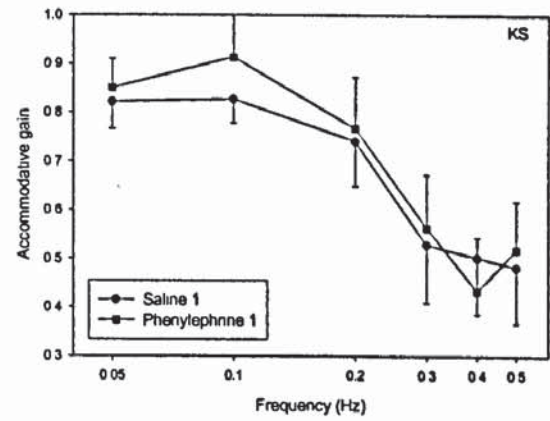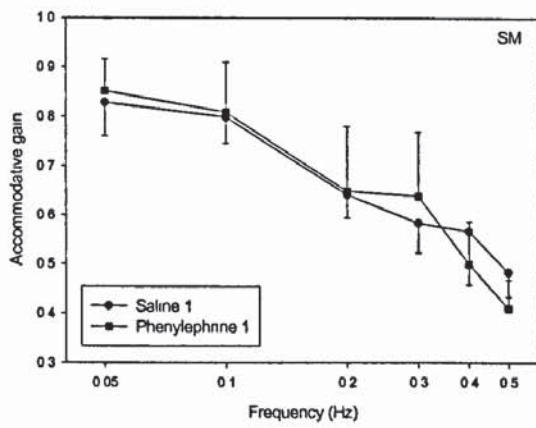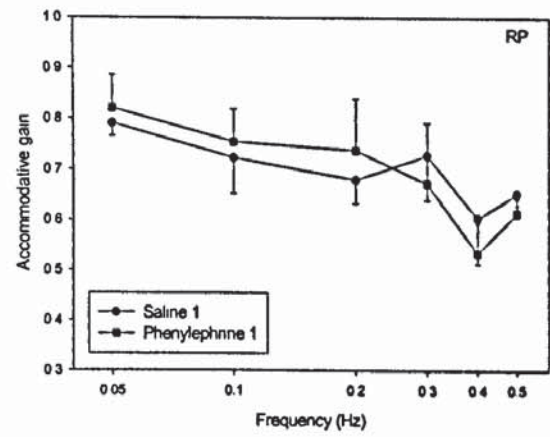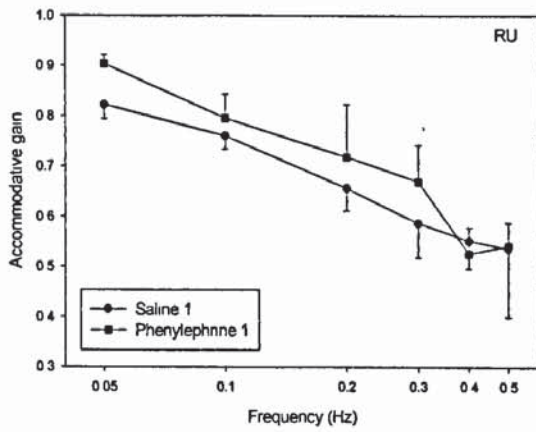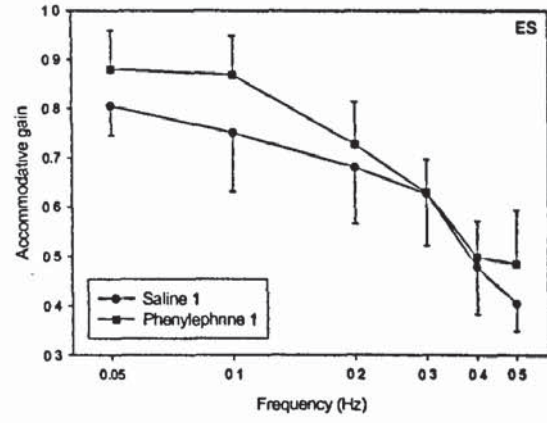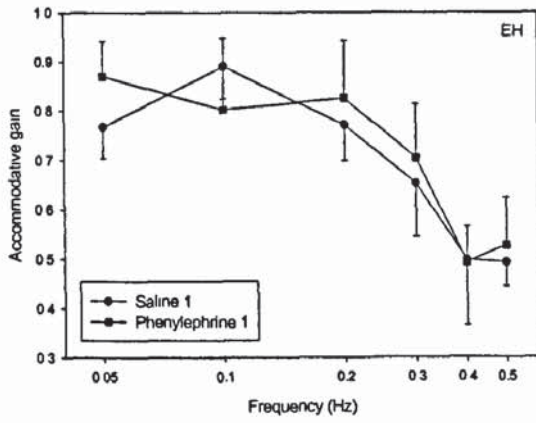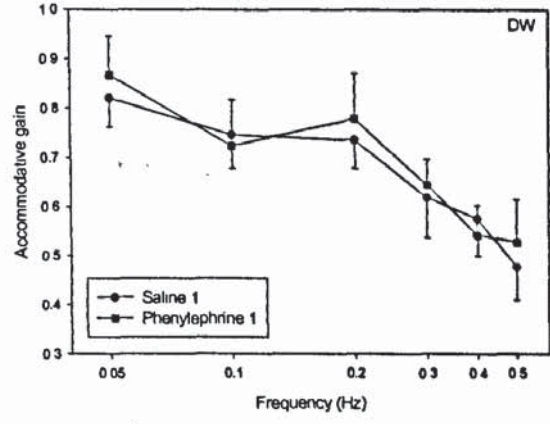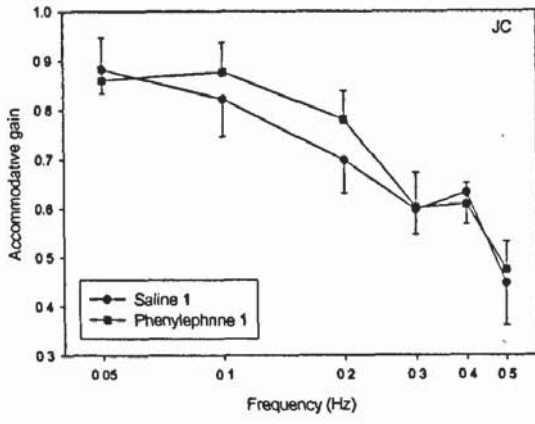
A9.6 Accommodative response phase lag plots: Individual subjects, saline against phenylephrine.
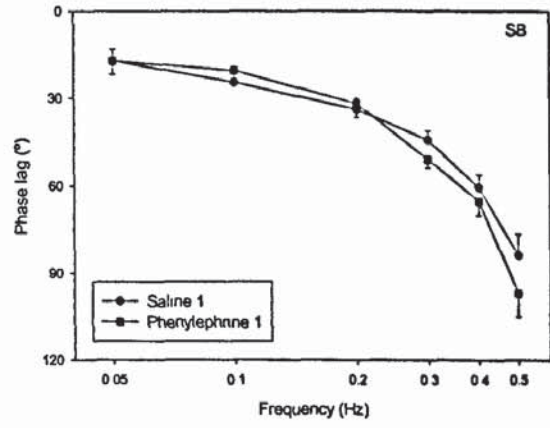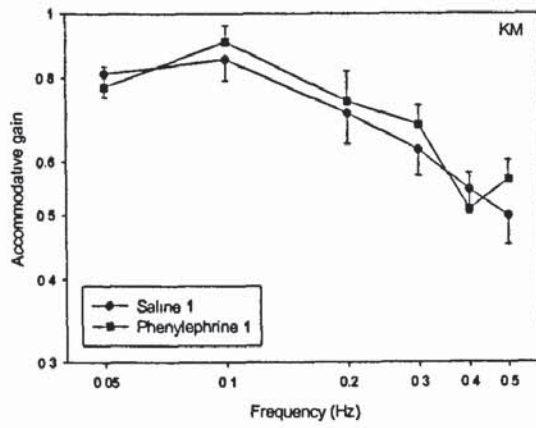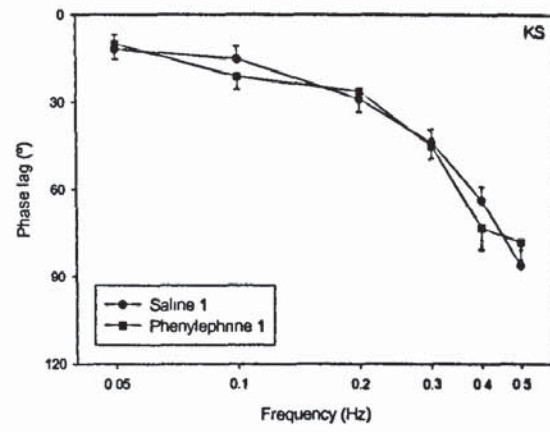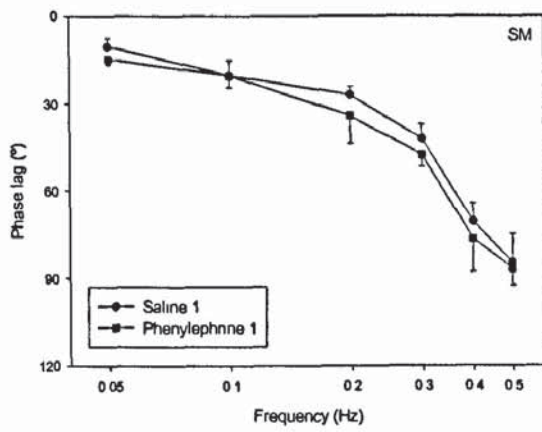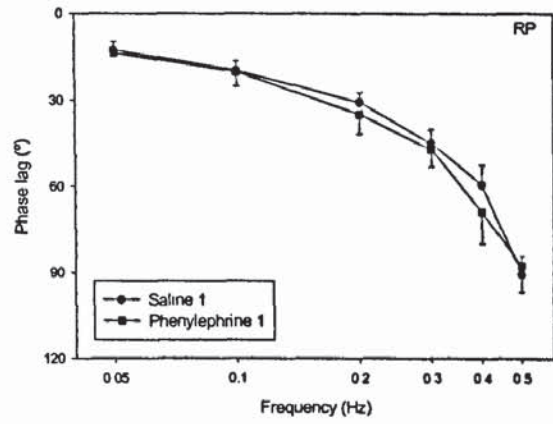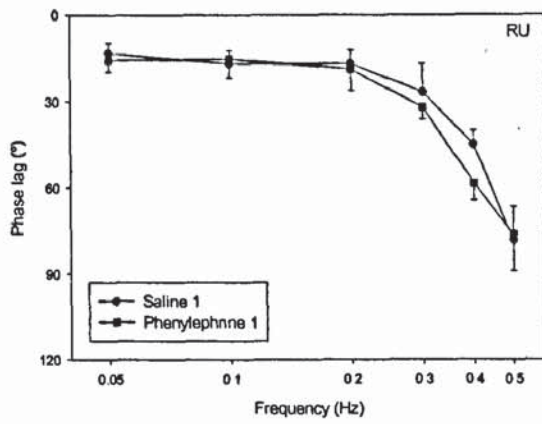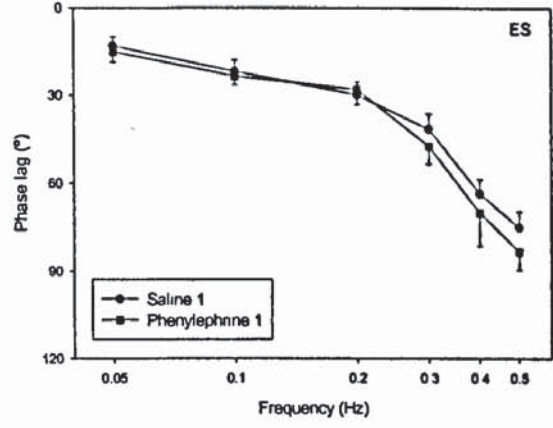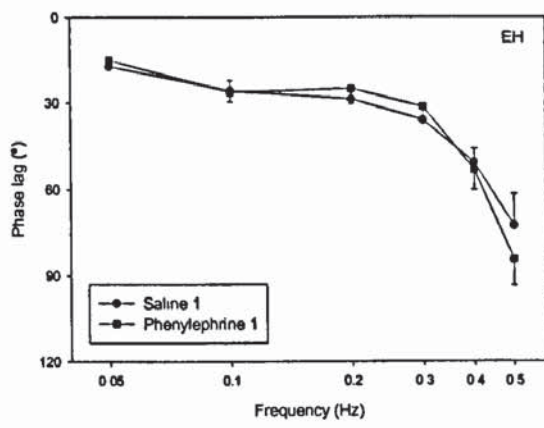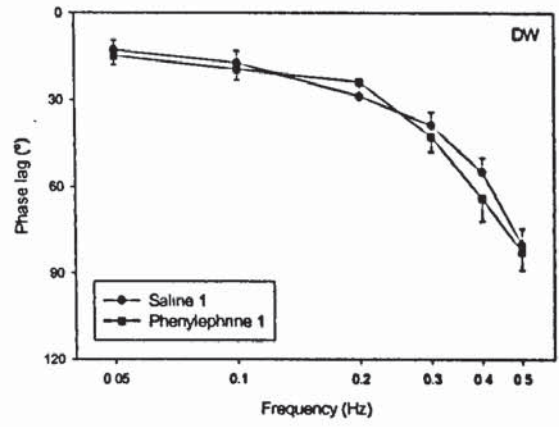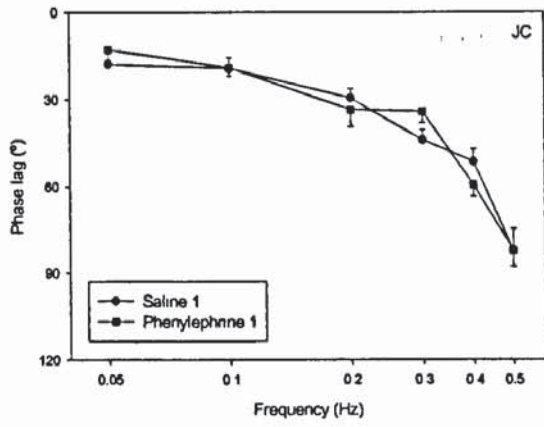
ACCOMMODATIVE REGRESSION PLOTS
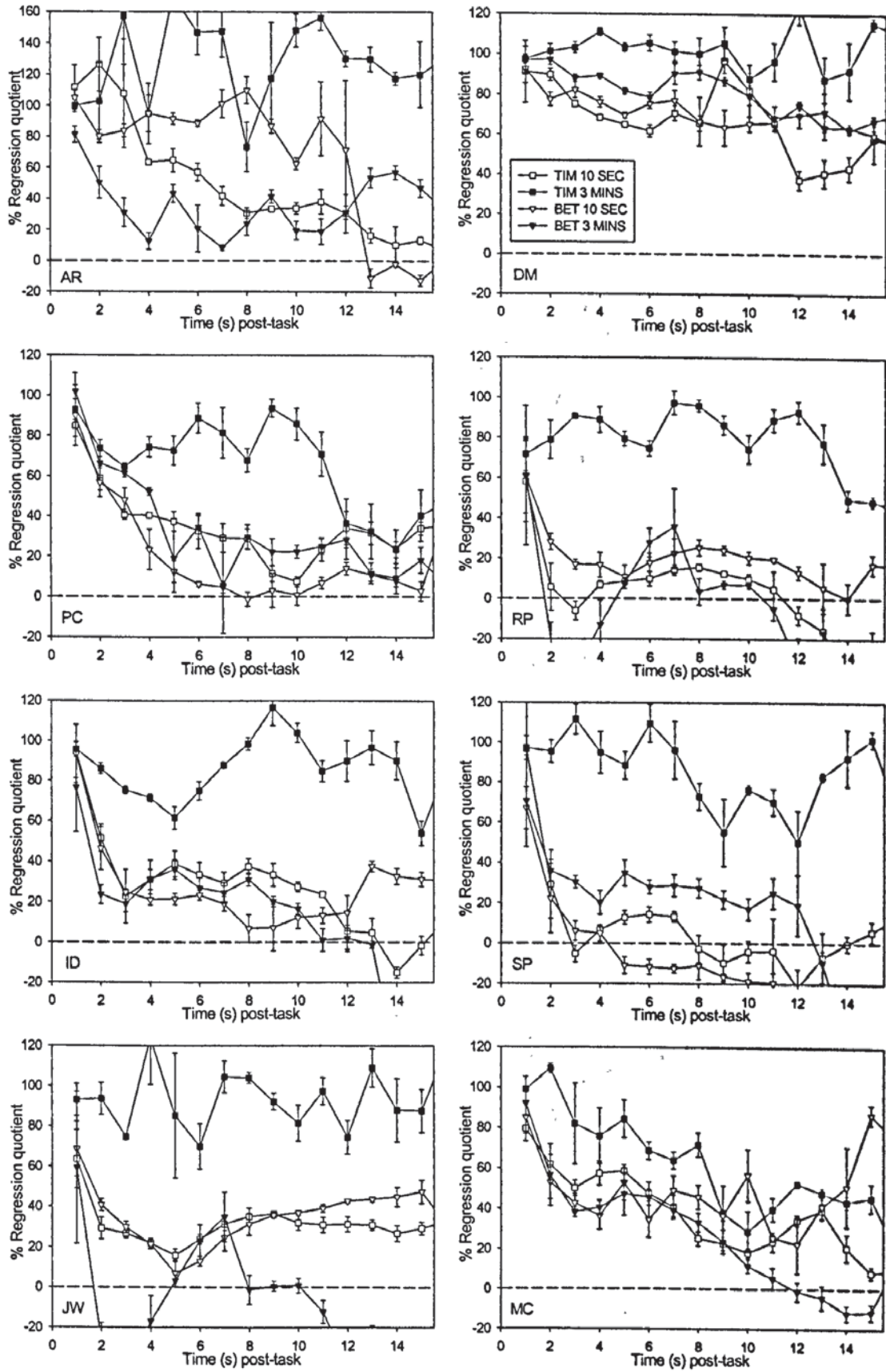
Figure A10.1a. Post-task regression plots – Subjects responding to timolol.
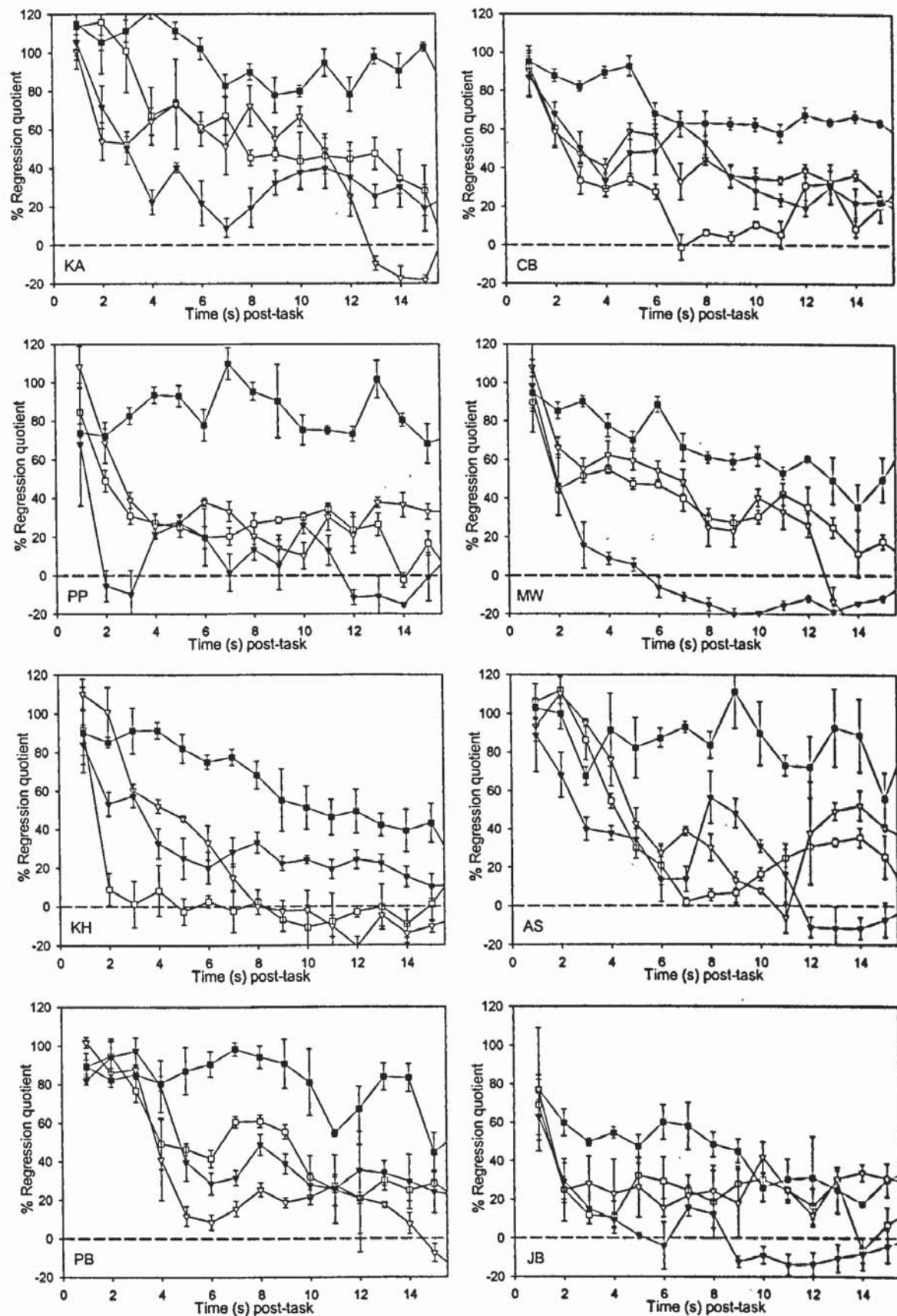
Figure A10.1b. Post-task regression plots – Subjects responding to timolol.
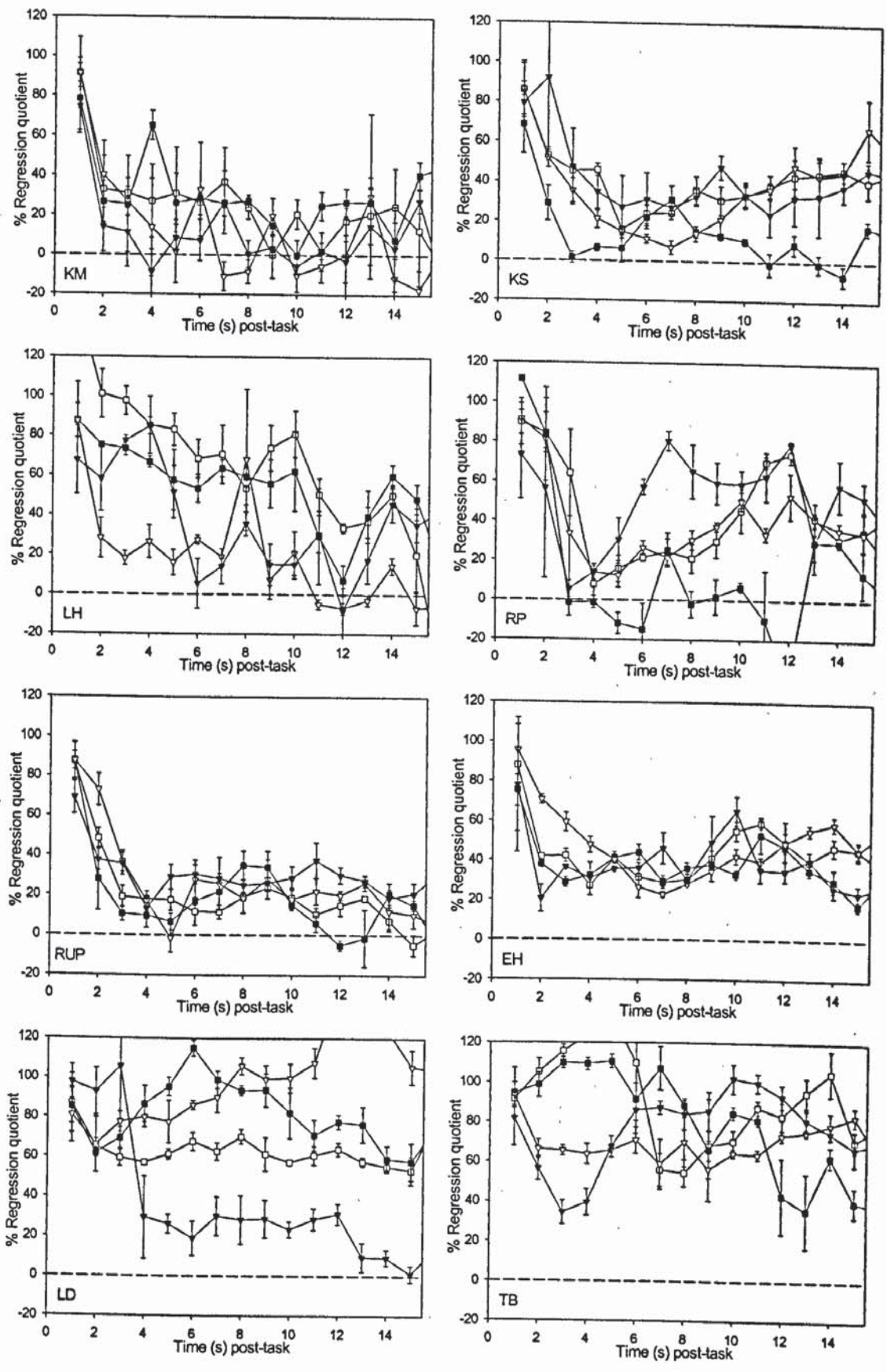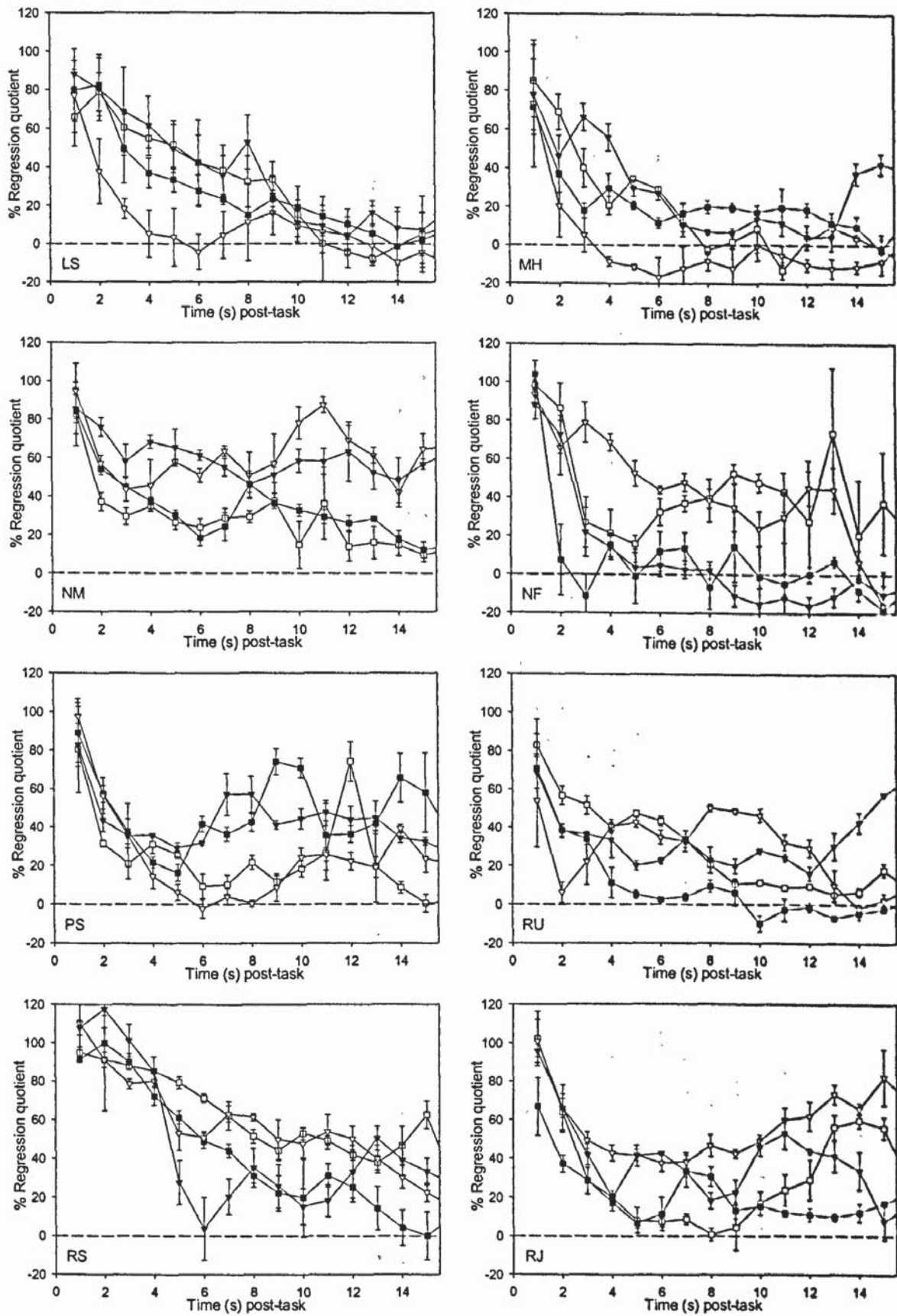
276
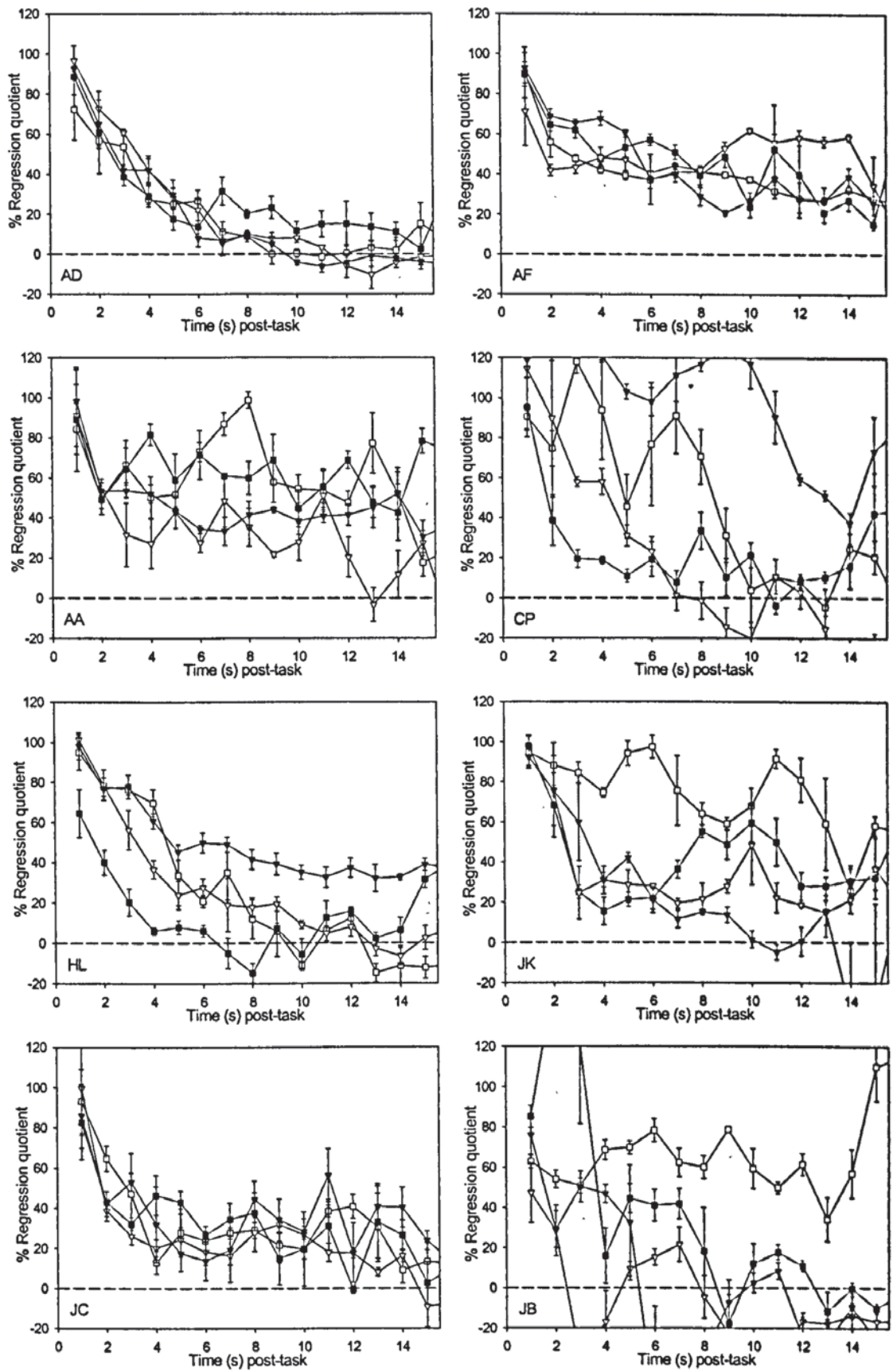
Figure A10.2a. Subjects not responding to timolol.

Figure A10.2b. Subjects not responding to timolol.

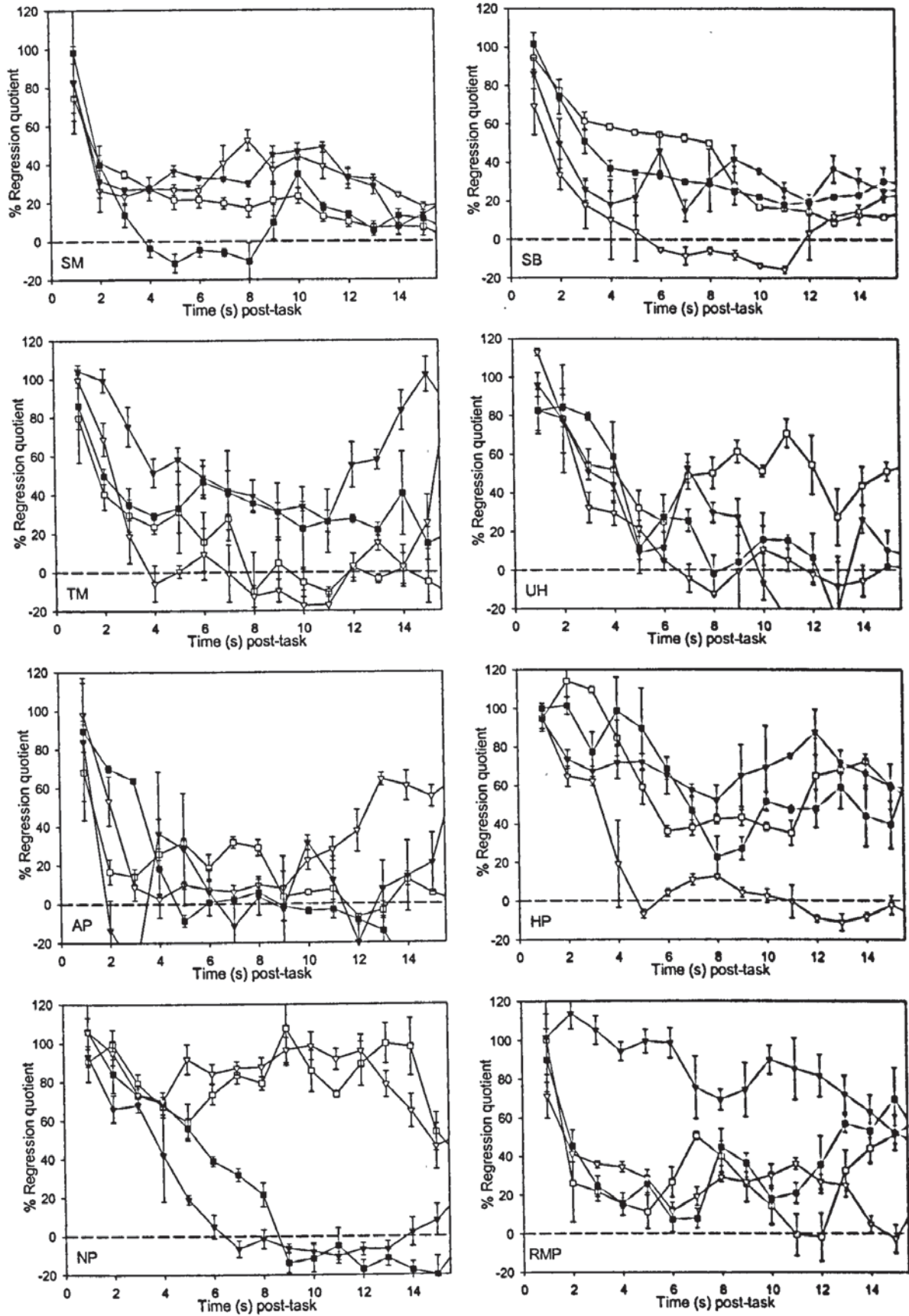Figure A10.2c. Subjects not responding to timolol.

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Figure A10.2d. Subjects not responding to timolol.

Figure A10.2e. Subjects not responding to timolol.

Figure A10.2f. Subjects not responding to timolol.
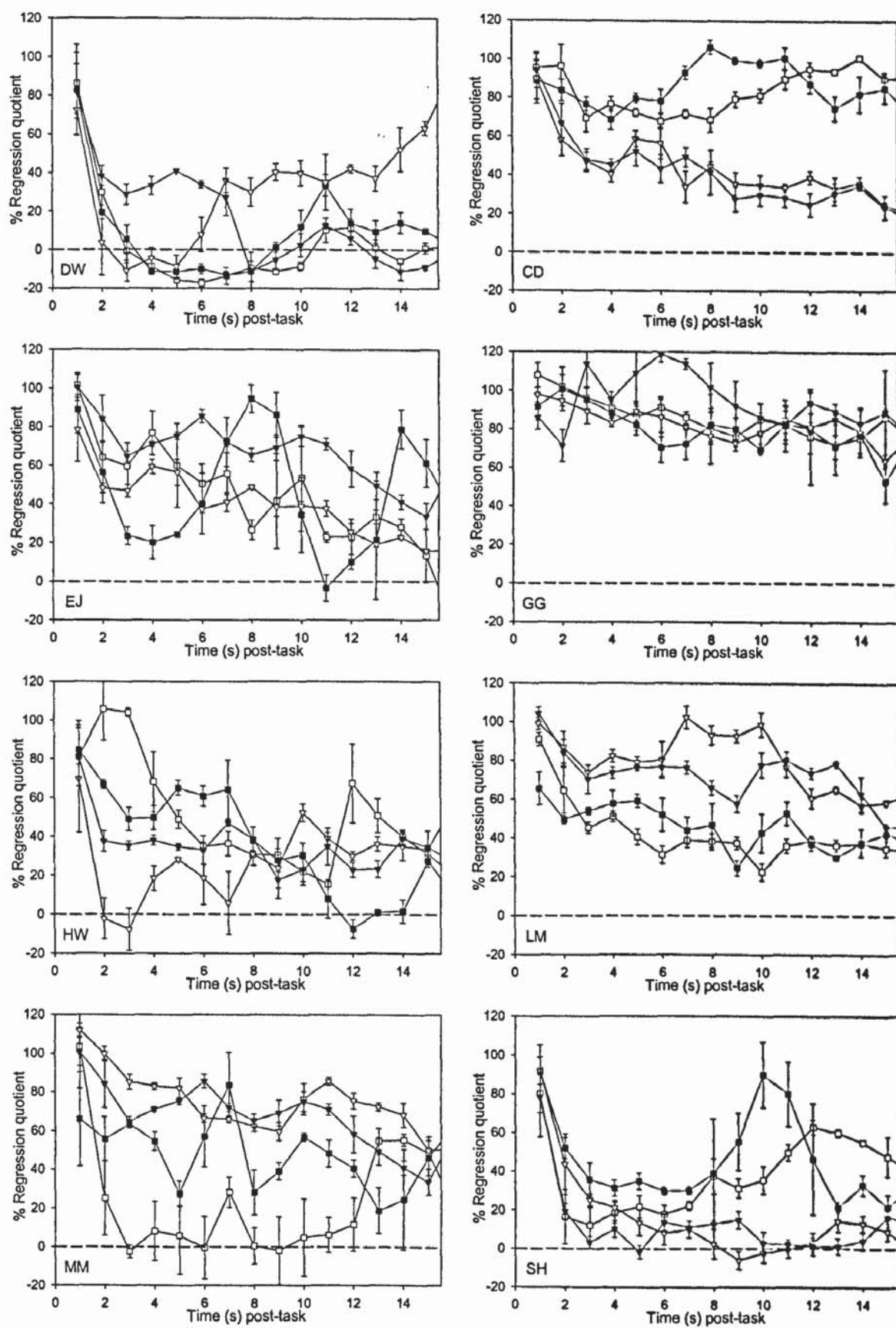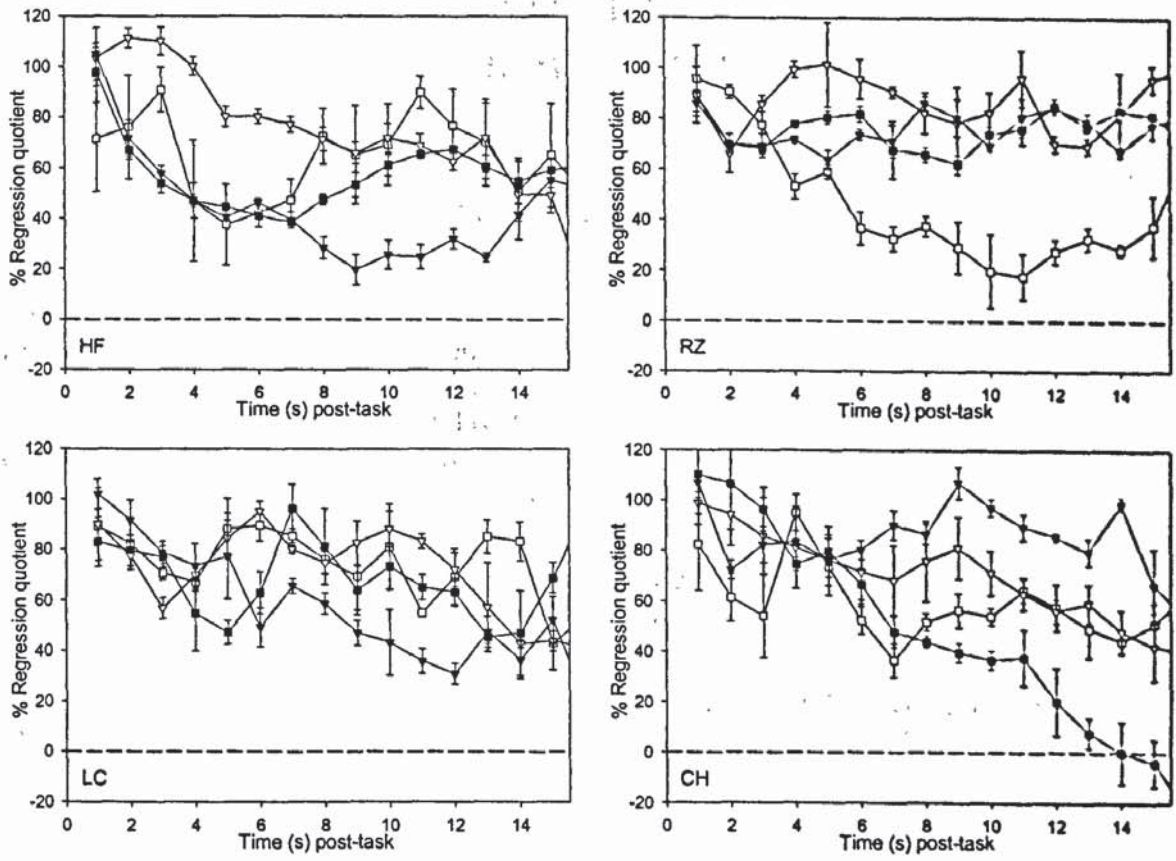
EYE VOLUME CALCULATION

Calculation for eye volume

The eye is divided into 5 parts
Total volume is the sum of:
V1 = volume of corneal section of eye
V2 = volume of the anterior nasal part
V3 = volume of the anterior temporal part
V4 = volume of the posterior nasal part
V5 = volume of the posterior temporal part

Horizontal visible iris diameter $= I$
r_0 = apical radius
The cornea is defined by the equation
$y^2 = 2r_0x - px^2$

For posterior nasal part of eye
$y = gx^2 + hx + i$

For posterior temporal part of eye
$y = jx^2 + kx + l$

INPUT PARAMETERS

$I := 12.2$ $r_0 := 7.81$

$p := 0.70$

$g := -0.0771$ $j := -0.0899$

$h := -0.1895$ $k := 0.1917$

$i := 26.31$ $l := 26.201$

$x_1 := \dfrac{I}{2}$ $r := \dfrac{r_0}{p}$

$x_1 = 6.1$ $r = 11.157$

$a := 0.269$ $d := 0.398$

$b := 3.609$ $e := -5.409$

$c := 16.395 - 15$ $f := 23.134 - 15$

$c = 1.395$ $f = 8.134$

To calculate the volume of the corneal section of the eye

$$V1 := \pi \cdot \sqrt{p} \cdot \left[\left[r \cdot (r + x_1) \cdot \sqrt{2 \cdot x_1 \cdot r - (x_1)^2} \right] - \frac{\left[2 \cdot x_1 \cdot r - (x_1)^2 \right]^{\frac{3}{2}}}{3} - \left(r^3 \cdot \mathrm{asin}\left(\frac{x_1 - r}{r} \right) \right) - \frac{\pi \cdot r^3}{2} \right]$$

$V1 = 154.307$

To calculate the volume of the front nasal part of the eye

$$y := 0.269 \cdot x^2 + 3.609 \cdot x + 16.395 - 15 \quad \blacksquare$$

$$x_3 := \frac{-b + \sqrt{b^2 - 4 \cdot a \cdot c}}{2 \cdot a}$$

$$x_4 := \frac{-b - \sqrt{b^2 - 4 \cdot a \cdot c}}{2 \cdot a}$$

$$x_3 = -0.398$$

$$x_4 = -13.018$$

$$x_2 := x_4$$

$$x_2 = -13.018$$

$$V2 := \frac{\pi}{12} \cdot \left[3 \cdot a \cdot \left[(x_2)^4 - (x_1)^4 \right] + \left[(x_2)^3 - (x_1)^3 \right] \cdot 2 \cdot b \right]$$

$$V2 = 1.177 \times 10^3$$

To calculate volume of the front temporal part of the eye

$$y := 0.398 \cdot x^2 - 5.409 \cdot x + 23.134 - 15 \quad \blacksquare$$

$$x_5 := \frac{-e + \sqrt{e^2 - 4 \cdot d \cdot f}}{2 \cdot d}$$

$$x_6 := \frac{-e - \sqrt{e^2 - 4 \cdot d \cdot f}}{2 \cdot d}$$

$$x_6 = 1.722$$

$$x_5 = 11.868$$

$$x_{23} := x_5$$

$$x_{23} = 11.868$$

$$V3 := \frac{\pi}{12} \cdot \left[3 \cdot d \cdot \left[(x_{23})^4 - (x_1)^4 \right] + \left[(x_{23})^3 - (x_1)^3 \right] \cdot 2 \cdot e \right]$$

$$V3 = 1.668 \times 10^3$$

To calculate volume of the back nasal part of the eye

$$x_{24} := 0 \qquad m := i - 15 \qquad m = 11.31$$

$$x_7 := \frac{-h + \sqrt{h^2 - 4 \cdot g \cdot m}}{2 \cdot g} \qquad\qquad x_8 := \frac{-h - \sqrt{h^2 - 4 \cdot g \cdot m}}{2 \cdot g}$$

$$x_8 = 10.945$$

$$x_7 = -13.403$$

$$x_{14} := x_7$$

$$x_{14} = -13.403$$

$$V4 := \frac{\pi}{12} \left[3 \cdot g \cdot \left[(x_{24})^4 - (x_{14})^4 \right] + \left[(x_{24})^3 - (x_{14})^3 \right] \cdot 2 \cdot h \right]$$

$$V4 = 1.715 \times 10^3$$

To calculate volume of the back temporal part of the eye

$$x_{25} := 0 \qquad n := 1 - 15 \qquad n = 11.201$$

$$x_9 := \frac{-k + \sqrt{k^2 - 4 \cdot j \cdot n}}{2 \cdot j} \qquad\qquad x_{10} := \frac{-k - \sqrt{k^2 - 4 \cdot j \cdot n}}{2 \cdot j}$$

$$x_9 = -10.147 \qquad\qquad x_{10} = 12.279$$

$$x_{15} := x_{10}$$

$$x_{15} = 12.279$$

$$V5 := \frac{\pi}{12} \left[3 \cdot j \cdot \left[(x_{25})^4 - (x_{15})^4 \right] + \left[(x_{25})^3 - (x_{15})^3 \right] \cdot 2 \cdot k \right]$$

$$V5 = 1.419 \times 10^3$$

Total volume of eye = V

$$V := V1 + V2 + V3 + V4 + V5$$

$$V = 6.134 \times 10^3$$

SUPPORTING PUBLICATIONS

REFEREED PUBLICATIONS:

Gilmartin, B., Mallen, E. A. H. and Wolffsohn, J. S. (2002). Sympathetic control of accommodation: evidence for inter-subject variation. *Ophthalmic and Physiological Optics* **22**, 366-371.

Mallen, E. A. H., Wolffsohn, J. S., Gilmartin, B. and Tsujimura, S. (2001). Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in adults. *Ophthalmic and Physiological Optics.* **21**, 101-107. *

Santodomingo-Rubido, J., Mallen, E. A. H., Gilmartin, B. and Wolffsohn, J. S. (2002). A new non-contact optical device for ocular biometry. *British Journal of Ophthalmology.* **86**, 458-462.

Wolffsohn, J. S., Gilmartin, B., Mallen, E. A. H. and Tsujimura, S. (2001). Continuous recording of accommodation and pupil size using the Shin-Nippon SRW-5000 autorefractor. *Ophthalmic and Physiological Optics.* **21**, 108-113.

Davies, L. N., Mallen, E. A. H., Wolffsohn, J. S. and Gilmartin, B. Clinical evaluation of the Shin-Nippon Nvision-K 5001/Grand Seiko WR-5100K autorefractor. *Optometry and Vision Science.* (In press).

REFEREED PUBLISHED ABSTRACTS FROM CONFERENCE PROCEEDINGS:

J. S. Wolffsohn, R. Thomas, B. Gilmartin and E. A. H. Mallen. (2002). Myopia, cognitive demand and accommodative hysteresis. *9th International Conference on Myopia.*

E. Mallen, B. Gilmartin and J. S. Wolffsohn. (2003). Sympathetic control of accommodation in young adults. *Investigative Ophthalmology and Visual Science (Supplement).* (Accepted).

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