AUTONOMIC IMBALANCE
– A PRECURSOR TO MYOPIA DEVELOPMENT?

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KEYWORDS

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ABSTRACT

While prolonged nearwork is considered to be an environmental risk factor associated with myopia development, an underlying genetic susceptibility to nearwork-induced accommodative adaptation may be one possible mechanism for human myopia development. As the control of accommodation by the autonomic system may be one such genetically predetermined system, this research sought to investigate whether an anomaly of the autonomic control of accommodation may be responsible for myopia development and progression.

The emphasis of this work was determining the effect of altering the sympathetic input to the ciliary muscle on accommodation responses such as tonic accommodation and nearwork-induced accommodative adaptation in myopes and non-myopes. The first study of the thesis was based on observations of Gilmartin and Winfield (1995) which suggested that a deficit in the sympathetic inputs to the ciliary muscle may be associated with a propensity for myopia development. The effect of β-antagonism with timolol application on accommodation characteristics was studied in different refractive error groups. Our results support the previous findings that a deficit of sympathetic facility during nearwork was not a feature of late-onset myopia. However it was found that classifying myopes according to stability of their myopia and their ethnic background was important and this allowed differentiation between accommodation responses and characteristics of the ciliary muscle autonomic inputs, with the greatest difference observed between Caucasian stable myopes and Asian progressing myopes.

Progressing myopes, particularly those with an Asian background, demonstrated enhanced susceptibility to nearwork-induced accommodative adaptation and this was suggested to result from a possible parasympathetic dominance and a relative sympathetic deficit to the ciliary muscle. In contrast, stable myopes, particularly
those with an Asian background, demonstrated minimal accommodation changes following nearwork (counter-adaptation in some cases), and increased accommodative adaptation with β-antagonism, suggesting sympathetic dominance as the possible autonomic accommodation control profile.

As ethnic background was found to be an important factor, a similar study was also conducted in a group of Hong Kong Chinese children to investigate if enhanced susceptibility to nearwork-induced changes in accommodation may explain in part the high prevalence of myopia in Hong Kong. Despite some minor differences in methodology between the two studies, the Hong Kong stable myopic children demonstrated counter-adaptive changes and greater accommodative adaptation with timolol, findings that were consistent with those of the adult Asian stable myopes. Both Asian progressing myopic children and adults also showed greater accommodative adaptation than the stable myopes and similar response profiles following β-adrenergic antagonism. Thus a combination of genetically predetermined accommodation profiles that confer high susceptibility and extreme environmental pressures is a likely explanation for the increase in myopia over the past decades in Asian countries.

The hypothesis that a sympathetic deficit is linked to myopia was also investigated by comparing the effect of β-stimulation with salbutamol, a β-agonist, on accommodation with that of β-antagonism using timolol. It was hypothesized that salbutamol would have the opposite effect of timolol, and that it would have a greater effect on subjects who demonstrated greater accommodative adaptation effects, i.e. the progressing myopes, compared to those who showed minimal changes in accommodation following nearwork. Consistent with the hypothesis, the effect of sympathetic stimulation with salbutamol application was only evident in the progressing myopes whom we hypothesized may have a parasympathetic dominance and a relative sympathetic deficit type of autonomic imbalance while it did not
Abstract

further enhance the rapid accommodative regression profile demonstrated by the stable myopes.

Characteristics of the convergence system and the interaction between accommodation and convergence were also investigated in the Hong Kong children. No significant differences in response AC/A ratios between the emmetropic, stable and progressing myopic children were found and it was concluded that elevated AC/A ratios were not associated with higher myopic progression rate in this sample of Hong Kong children. However, β-adrenergic antagonism with timolol application produced a greater effect on accommodative convergence (AC) in stable myopic children who presumably have a more adequate, robust sympathetic input to the ciliary muscle, but had little effect on AC of progressing myopic children. This finding again points to the possibility that the autonomic control of the accommodation and convergence systems may be different between stable and progressing myopia.

The primary contribution of this study to the understanding of myopia development is that differences in the autonomic control of the ciliary muscle may be responsible for producing anomalous accommodation responses. This could have significant impact on retinal image quality and thus results in myopia development. This knowledge may be incorporated into computer models of accommodation and myopia development and provides scope for further investigation of the therapeutic benefits of autonomic agents for myopia control.
# CONTENTS

## CHAPTER 1: INTRODUCTION

1. **Myopia: prevalence, classifications and socio-economic ramifications**
   1.1. Definition and prevalence
   1.1.2. Classification of myopia
   1.1.3. Socio-economic costs of myopia

2. **Aetiology of myopia**
   1.2.1. Genetic predisposition
   1.2.2. Environmental influences

3. **Role of accommodation in myopia development**
   1.3.1. Accommodation and refractive error
   1.3.1.1. Amplitude of accommodation
   1.3.1.2. Accommodation stimulus response
   1.3.1.3. Tonic accommodation
   1.3.1.4. Accommodative adaptation and regression (open-loop conditions)
   1.3.1.5. Nearwork-induced transient myopia (NITM) (closed-loop conditions)

4. **Autonomic correlates: ciliary muscle innervation and accommodation**
   1.4.1. Introduction
   1.4.2. Hypotheses of autonomic imbalance and myopia development
   1.4.3. Present understanding of ciliary smooth muscle dual innervation
   1.4.4. Autonomic control of accommodation

5. **Possible mechanisms linking autonomic input, accommodation and myopia development**
   1.5.1. Retinal defocus, accommodation and myopia
   1.5.2. Accommodation, ciliary muscle tonus, scleral stretching and myopia

6. **Myopia control treatments of relevance to accommodation and ANS**
   1.6.1. Myopia control using optical intervention
   1.6.1.1. Bifocal/progressive lenses
   1.6.1.2. Spectacle intervention
CHAPTER 2: EFFECT OF β-ADRENERGIC ANTAGONISM ON ACCOMMODATION IN DIFFERENT REFRACTIVE ERROR GROUPS

2.1. Introduction ................................................................. 49
2.2. Methods ................................................................. 53
   2.2.1. Subjects ................................................................. 53
   2.2.2. Measurements of accommodation ......................... 54
   2.2.3. Apparatus ............................................................. 56
   2.2.4. Target details ........................................................ 57
   2.2.5. Drug treatments .................................................... 57
   2.2.6. Data analysis ........................................................ 59
   2.2.7. Control treatments: saline vs betaxolol ................. 60
2.3. Results ................................................................. 60
   2.3.1. Subject characteristics ........................................... 60
   2.3.2. Tonic accommodation ........................................... 63
   2.3.3. Lag of accommodation and TA ............................ 67
   2.2.4. Changes in TA induced by timolol ......................... 68
   2.3.5. Effect of timolol on IOP, pupil size and amplitude of accommodation 72
   2.3.6. Accommodative adaptation effects and regression following nearwork 73
   2.3.7. Accommodative adaptation – standard analysis .......... 73
   2.3.8. Accommodative adaptation – standard analysis (timolol vs betaxolol) 74
   2.3.9. Accommodative adaptation - regression quotient (%) analysis .......... 82
   2.3.10. Accommodative adaptation - regression analysis (timolol vs betaxolol) ................................................................. 82
   2.3.11. Relationship between base-line TA and accommodative adaptation.... 88
2.4. Discussion ................................................................. 91
2.4.1. TA - refractive error, myopia progression and ethnic background........ 91
2.4.2. Accommodative adaptation - refractive error, myopia progression and ethnic background ................................................................. 92
2.4.3. Effect of β-antagonism on accommodation ........................................ 93
2.4.4. Possible autonomic imbalances in myopia .......................................... 94
2.4.5. Mechanism of autonomic imbalance in myopia ................................... 97
2.4.6. Comparison to findings of previous research ...................................... 101
2.5. Conclusion ............................................................................................. 103

CHAPTER 3: EFFECT OF β-ADRENERGIC STIMULATION ON ACCOMMODATION – A FOLLOW-UP STUDY......................... 104

3.0. Summary ............................................................................................... 104
3.1. Introduction ........................................................................................... 105
3.2. Methods ................................................................................................ 109
  3.2.1. Subject details .................................................................................... 109
  3.2.2. Accommodation measurements ....................................................... 110
  3.2.3. Target details ..................................................................................... 111
  3.2.4. Drug treatments ................................................................................ 111
  3.2.5. Apparatus ........................................................................................ 112
3.3. Results ................................................................................................. 114
  3.3.1. Refraction change over 16 months .................................................... 114
  3.3.2. TA change over 16 months ............................................................... 115
  3.3.3. Nearwork-induced accommodative adaptation change over 16 months ....................................................................................... 116
  3.3.4. Effect of salbutamol ......................................................................... 117
  3.3.5. Standard analysis: comparison of accommodative adaptation of salbutamol vs control trials ......................................................... 119
  3.3.6. Regression quotient (%) analysis: comparison of accommodative adaptation of salbutamol vs control trials ......................................... 122
  3.3.7. Scenarios of possible autonomic imbalance ...................................... 125
3.4. Discussion ............................................................................................ 130
  3.4.1. Changes in accommodation over time ................................................ 130
  3.4.2. Sympathetic input ............................................................................ 130

vii
CHAPTER 4: THE EFFECT OF β-ADRENERGIC ANTAGONISM ON ACCOMMODATIVE ADAPTATION IN HONG KONG CHINESE CHILDREN

4.0. Summary
4.1. Introduction
4.2. Methods
4.2.1. Subjects
4.2.2. Accommodation measurements
4.2.3. Apparatus
4.2.4. Drug treatments
4.2.5. Data analysis
4.3. Results
4.3.1. Subject characteristics
4.3.2. Tonic accommodation
4.3.3. Accommodative adaptation
4.3.4. β-antagonism
4.4. Discussion
4.4.1. TA – refractive error and myopia progression
4.4.2. Accommodative adaptation – refractive error and myopia progression
4.4.3. Effect of β-antagonism on accommodation
4.4.4. Comparison to Asian myopic adults
4.5. Conclusion

CHAPTER 5: EFFECT OF β-ADRENERGIC ANTAGONISM ON AC/A RATIOS IN MYOPIC AND EMMETROPIC HONG KONG CHINESE CHILDREN

5.0. Summary
5.1. Introduction
5.2. Methods
5.2.1. Subjects
5.2.2. Accommodation and vergence measurements
Table of Contents

5.2.3. Apparatus .............................................................................................. 173
5.2.4. Drug treatments ..................................................................................... 173
5.2.5. Data analysis ......................................................................................... 174
5.3. Results ........................................................................................................ 175
   5.3.1. Subject details ....................................................................................... 175
   5.3.2. Accommodation .................................................................................... 175
   5.3.3. Heterophoria measures ........................................................................ 178
   5.3.4. Accommodation and heterophoria ...................................................... 181
   5.3.5. AC/A ratios .......................................................................................... 183
   5.3.6. Beta-antagonism .................................................................................. 185
5.4. Discussion ................................................................................................... 188
   5.4.1. Esophoria, lags of accommodation and myopic progression .............. 188
   5.4.2. Elevated AC/A ratios and myopic progression ..................................... 190
   5.4.3. Sympathetic input ............................................................................... 192
5.5. Conclusion .................................................................................................. 193

CHAPTER 6: CONCLUSIONS ................................................................. 194
   6.1. Summary and implications of results ...................................................... 194
   6.2. A relative sympathetic deficit – neurotransmitters and receptors revisited.. 198
   6.3. Hypotheses of autonomic imbalance ...................................................... 203
   6.4. Computer modelling of accommodation .............................................. 205
   6.5. Future experiments ............................................................................... 208

APPENDIX 1: QUESTIONNAIRES ..................................................... 209
   Questionnaire used in Chapter 2 .................................................................. 209
   Questionnaire used in Chapters 4 and 5 ...................................................... 210

APPENDIX 2: EFFECT OF MONOCULAR VS BINOCULAR
INSTILLATION ON TONIC ACCOMMODATION ............................. 212
   Drug volume ................................................................................................. 213
   Monocular vs binocular application ............................................................ 213
APPENDIX 3: BEHAVIOURAL MANIPULATION OF THE AUTONOMIC INNERVATION IN ACCOMMODATION........215

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3.0. Summary</td>
<td>215</td>
</tr>
<tr>
<td>A3.1. Introduction</td>
<td>216</td>
</tr>
<tr>
<td>A3.2. Methods</td>
<td>218</td>
</tr>
<tr>
<td>A3.2.1. Subjects</td>
<td>218</td>
</tr>
<tr>
<td>A3.2.2. Tonic accommodation measurements</td>
<td>219</td>
</tr>
<tr>
<td>A3.2.3. Apparatus</td>
<td>219</td>
</tr>
<tr>
<td>A3.2.4. Intraocular and blood pressures measurements</td>
<td>220</td>
</tr>
<tr>
<td>A3.2.5. Procedure</td>
<td>220</td>
</tr>
<tr>
<td>A3.2.6. Data analysis</td>
<td>220</td>
</tr>
<tr>
<td>A3.3. Results</td>
<td>221</td>
</tr>
<tr>
<td>A3.3.1. Subject characteristics</td>
<td>221</td>
</tr>
<tr>
<td>A3.3.2. Effect of FUNB on TA</td>
<td>222</td>
</tr>
<tr>
<td>A3.3.3. Effect of FUNB on IOP</td>
<td>226</td>
</tr>
<tr>
<td>A3.3.4. IOP and refractive error</td>
<td>228</td>
</tr>
<tr>
<td>A3.4. Discussion</td>
<td>230</td>
</tr>
<tr>
<td>A3.5. Conclusion</td>
<td>231</td>
</tr>
</tbody>
</table>

APPENDIX 4: PILOT STUDIES OF DRUG DOSAGE AND CONCENTRATION: TROPICAMIDE AND PILOCARPINE ..232

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4.0. Summary</td>
<td>232</td>
</tr>
<tr>
<td>A4.1. Method</td>
<td>233</td>
</tr>
<tr>
<td>A4.1.1. Subjects</td>
<td>233</td>
</tr>
<tr>
<td>A4.1.2. Measurements of accommodation and pupil size</td>
<td>233</td>
</tr>
<tr>
<td>A4.1.3. Apparatus</td>
<td>233</td>
</tr>
<tr>
<td>A4.1.4. Drug treatments</td>
<td>234</td>
</tr>
<tr>
<td>A4.1.5. Iris colour grading scale</td>
<td>234</td>
</tr>
<tr>
<td>A4.2. Results</td>
<td>235</td>
</tr>
<tr>
<td>Dose-response curve of tropicamide</td>
<td>235</td>
</tr>
<tr>
<td>Time-response curves</td>
<td>236</td>
</tr>
<tr>
<td>Effect of 0.125% tropicamide and pilocarpine on TA</td>
<td>238</td>
</tr>
</tbody>
</table>
APPENDIX 5: NEARWORK-INDUCED TRANSIENT MYOPIA:
COMPARISON OF OPEN- AND CLOSED-LOOP MEASURES

.............................................................. 239
A5.0. Summary ............................................................... 239
A5.1. Results ............................................................... 240
  A5.1.1. Refractive error and NITM (closed-loop) ....................... 240
  A5.1.2. Effect of timolol on NITM (closed-loop) ....................... 241
A5.2. Discussion ....................................................... 245
  A5.2.1. Closed-loop vs open-loop accommodative adaptation .......... 245
  A5.2.2. Significance of sympathetic control of accommodation .......... 245

APPENDIX 6: AUTOREFRACTOR MEASUREMENTS OF
ACCOMMODATION ........................................ 247
  Correction factor to Canon autorefractor data ....................... 247
  Canon vs Shin-Nippon autorefractor ................................. 247

APPENDIX 7: STATISTICS .......................................... 249
  Repeated measures analysis of variance ............................... 249
  Sample size ............................................................. 249

LITERATURE CITED ............................................. 251
LIST OF FIGURES

Figure 1.1. Ray diagram of myopia ................................................................. 2
Figure 1.2. The experimental sequence for assessment of accommodation adaptation under open-loop conditions ............................................. 16
Figure 1.3. A schematic representation of possible post-task accommodative regression patterns .............................................................. 17
Figure 1.4. The sequence and experimental paradigms for assessment of accommodative adaptation assessment under closed-loop conditions 20
Figure 1.5. A diagram of the central and peripheral pathways for autonomic innervation of accommodation, the neurotransmitters and the post-synaptic receptors ................................................................. 24
Figure 1.6. Overall distribution of muscarinic, α- and β-receptors in the ocular structures and autonomic agents that act on them ..................... 31
Figure 1.7. Schematic illustration of the predicted and actual effects of autonomic agents on tonic accommodation ........................................... 34
Figure 2.1. A schematic representation of the experimental measurement of accommodative adaptation under open-loop conditions .......... 55
Figure 2.2. Frequency distribution of tonic accommodation .............................................. 63
Figure 2.3. A scattergram of the relationship between tonic accommodation and ocular refraction ............................................................... 64
Figure 2.4. A scattergram of the relationship between tonic accommodation and myopia progression rate .................................................... 64
Figure 2.5. Differences in mean base-line TA levels when separating subjects based on A: refractive error, B: myopic progression rate, and C: myopic progression rate/ethnic background .............................................. 66
Figure 2.6. A scattergram of the relationship between TA and lag of accommodation ......................................................................................... 67
Figure 2.7. Differences in timolol-induced TA shift when subjects were separated based on A: refractive error, B: myopic progression rate, and C: myopic progression rate/ethnic background .............................................. 69
Figure 2.8. A scattergram of the relationship between base-line TA and the change in TA induced by the instillation of timolol ................................ 71
Figure 2.9. Regression patterns of non-normalised and normalised accommodation measures following nearwork of non-myopes, stable myopes and progressing myopes ................................................................. 75

Figure 2.10. Regression of non-normalised and normalised accommodation measures following nearwork in groups with different myopic progression rate and ethnic background ........................................................................... 76

Figure 2.11. Accommodation regression patterns for timolol and betaxolol trials of non-myopes, EOMs and LOMs .......................................................... 78

Figure 2.12. Accommodation regression patterns for timolol and betaxolol trials of non-myopes, stable myopes and progressing myopes ........................................ 78

Figure 2.13. Accommodation regression patterns for timolol and betaxolol trials of myopes when separated based on myopia progression rate and ethnic background..................................................................................... 81

Figure 2.14. Accommodative regression patterns (% regression quotient) in timolol and betaxolol trials of non-myopes, EOMs and LOMs ..................... 84

Figure 2.15. Accommodative regression patterns (% regression quotient) in timolol and betaxolol trials of non-myopes, stable myopes and progressing myopes .......................................................... 85

Figure 2.16. Percentage regression quotients for timolol and betaxolol trials of myopes when separated based on myopia progression rate and ethnic background..................................................................................... 87

Figure 2.17. Comparison of nearwork-induced accommodative adaptations of standard analysis and regression quotient analysis when subjects were separated based on base-line TA ......................................................... 89

Figure 2.18. Accommodative regression patterns in timolol and betaxolol trials of subjects separated based on pre-task TA ............................................. 90

Figure 2.19. A conceptual block diagram of the possible factors involved in myopia progression for Asian myopes ......................................................... 99

Figure 2.20. A conceptual block diagram of the possible factors involved in myopia progression for Caucasian myopes ............................................. 100

Figure 3.1. The effect of the passage of time on the distribution of tonic accommodation .............................................................................................. 115

Figure 3.2. The base-line TA levels in subjects with refraction change and no refraction change .......................................................................................... 116
Figure 3.3. Nearwork-induced accommodative adaptation in subjects with refraction change and no refraction change ...........................................................117
Figure 3.4. The scattergram between base-line IOP and the reduction in IOP induced by salbutamol application ..............................................................118
Figure 3.5. Accommodation regression patterns for salbutamol and control trials of non-myopes, EOMs and LOMs .........................................................120
Figure 3.6. Accommodation regression patterns for salbutamol and control trials of No Rx change group and Rx change group ............................................121
Figure 3.7. Accommodative regression patterns (% regression quotient) in salbutamol and control trials of non-myopes, EOMs and LOMs ..........123
Figure 3.8. Accommodative regression patterns (% regression quotient) in salbutamol and control trials of No Rx change group and Rx change group .......................................................................................................124
Figure 3.9. Regression patterns of the timolol trial (year 2000) and salbutamol trial (year 2002) of progressing myopes ........................................127
Figure 3.10. Regression patterns of the timolol trial (year 2000) and salbutamol trial (year 2002) of progressing myopes-turned-stable myopes ..........128
Figure 3.11. Regression patterns of the timolol trial (year 2000) and salbutamol trial (year 2002) of stable myopes .............................................................129
Figure 4.1. A schematic representation of the experimental measurement of accommodative adaptation following video game playing ...............142
Figure 4.2. Frequency distribution of tonic accommodation in children ..........148
Figure 4.3. Differences in mean base-line TA levels when separating subjects based on refractive error and myopic progression rate .........................149
Figure 4.4. A scattergram of the relationship between TA and the age of myopia onset ......................................................................................................150
Figure 4.5. A scattergram of the relationship between TA and myopia duration ....150
Figure 4.6. Regression of accommodative adaptation effects of A: emmetropes and myopes, B: emmetropes, stable myopes and progressing myopes ......152
Figure 4.7. Mean timolol-induced change in accommodative adaptation effects of emmetropes, stable myopes and progressing myopes .........................153
Figure 4.8. Mean accommodative adaptation for saline and timolol trials of emmetropes and myopes ........................................................................ 155
Figure 4.9. Mean accommodative adaptation for saline and timolol trials of emmetropes, stable myopes and progressing myopes ..................................... 156
Figure 4.10. Regression patterns for timolol and control trials of Asian myopes (children vs adults) ..................................................................................... 163
Figure 5.1. Mean accommodation responses for A: emmetropes and myopes, B: emmetropes, stable myopes and progressing myopes ..................... 177
Figure 5.2. Frequency distribution of distance phorias and near phorias ............ 179
Figure 5.3. Mean heterophorias for A: emmetropes and myopes, B: emmetropes, stable myopes and progressing myopes for the four testing conditions 180
Figure 5.4. The relationship between distance and near heterophoria ................. 182
Figure 5.5. The relationship between accommodation response and heterophoria for myopic children ................................................................ 182
Figure 5.6. Distance- and lens-induced AC/A ratios of A: emmetropes and myopes, B: emmetropes, stable myopes and progressing myopes .......... 184
Figure 5.7. Mean AC/A ratios for the distance and lens-induced conditions of both saline control and timolol trials .......................................................... 185
Figure 5.8. Timolol-induced changes in accommodation convergence, accommodation and AC/A ratios in the negative lens-induced condition .............................................................................................................. 187
Figure 6.1. Schematic diagrams of pharmacological events at the neuro-effector junction......................................................................................... 200
Figure 6.2. A schematic representation of the proposed effects of pharmacological agents ................................................................................................. 202
Figure 6.3. The adaptive accommodation model.............................................. 207
Figure A3.1. A scattergram of the relationship between base-line TA and change in TA produced by left FUNB ................................................................. 224
Figure A3.2. Tonic accommodation before and after left FUNB and the change in TA (ranked by pre-LFUNB TA level) ......................................................... 224
Figure A3.3. TA before and after right and left FUNB of A: non-myopes, EOMs and LOMs, B: non-myopes, stable myopes and progressing myopes ...... 225
Figure A3.4. IOP before and after right and left FUNB of A: non-myopes, EOMs and LOMs, B: non-myopes, stable myopes and progressing myopes 229
Figure A4.1. Time course of the effect of three different volumes and concentration combinations of two subjects......................................................... 235
Figure A4.2. Time-response curves of 0.125% tropicamide for A: the effect on amplitude of accommodation, and B: the effect on pupil size ............ 236
Figure A4.3. Time-response curves of 0.125% pilocarpine for A: the effect on amplitude of accommodation, and B: the effect on pupil size .......... 237
Figure A4.4. Effect on tonic accommodation of A: 0.125% tropicamide, and B: 0.125% pilocarpine ................................................................. 238
Figure A5.1. A schematic representation of the experimental protocol in NITM .. 240
Figure A5.2. Regression patterns of NITM when subjects were separated based on A: refractive error, B: myopia progression rate, C: myopia progression/ethnic background .......................................................... 242
Figure A5.3 Post-task decay of NITM in non-myopes, EOMs, and LOMs ............ 243
Figure A5.4. Post-task decay of NITM in non-myopes, stable myopes and progressing myopes............................................................................. 244
LIST OF TABLES

Table 1.1. Prevalence of myopia by occupation .......................................................... 6
Table 1.2. Findings of studies measuring the amplitude of accommodation as a function of refractive error .......................................................... 10
Table 1.3. Findings of studies measuring the accommodation stimulus response curve (ASRC) as a function of refractive error ................................. 11
Table 1.4. Findings of studies investigating tonic accommodation as a function of refractive error .......................................................... 14
Table 1.5. Findings of studies investigating accommodative adaptation as a function of refractive error (open-loop conditions) ...................................... 18
Table 1.6. Findings of studies investigating regression of accommodative adaptation as a function of refractive error (open-loop conditions) .......... 19
Table 1.7. Findings of studies investigating NITM .................................................. 22
Table 1.8. A summary of the receptor types in the human iris/ciliary body structures. ........................................................................................................ 29
Table 2.1. Subject characteristics based on separating myopes according to the age of myopia onset ............................................................. 61
Table 2.2. Subject characteristics based on separating myopes according to the myopia progression rate ............................................................. 62
Table 2.3. Number of subjects who demonstrated myopic vs hyperopic changes in TA following timolol instillation ........................................................ 70
Table 2.4. Mean change in IOP, pupil diameter, and amplitude of accommodation following betaxolol and timolol instillation ........................................... 72
Table 2.5. Main findings and indicated autonomic imbalance model of stable and progressing myopia .............................................................. 95
Table 2.6. Main findings and indicated autonomic imbalance model of stable and progressing myopia for individuals with Asian or Caucasian backgrounds .............................................................. 97
Table 3.1. A summary of the effects of sympathetic stimulation using sympathomimetics on TA .................................................................................. 108
Table 3.2. Characteristics of the subjects separated into groups of different refractive error and age of onset of myopia ...................................................... 114
Table 3.3. Accommodation responses, IOP, pupil diameter pre- and post-salbutamol instillation
............................................................................................................................. 118

Table 4.1. Summary results of studies investigating tonic accommodation in children
........................................................................................................................................ 138

Table 4.2. Summary results of studies investigating accommodative adaptation in children
....................................................................................................................................... 139

Table 4.3. Characteristics of the Hong Kong children ............................................. 146

Table 4.4. Subject characteristics when myopic children were separated based on myopia progression rate 
................................................................................................................................. 147

Table 4.5. Main findings and the indicated autonomic imbalance model of stable and progressing myopia in Asian myopes (children and adults) .......... 161

Table 5.1. Summary of near heterophorias associated with the onset of myopia. ... 167

Table 5.2. Summary results of AC/A ratios as a function of refractive error .......... 170

Table 6.1. The proposed effect of pharmacological agents on an anomalous innervation system cf. a normal innervation system .............................. 201

Table A2.1. Summary on dosage information of previous studies ...................... 212

Table A2.2. Effect of monocular vs binocular instillation of timolol on tonic accommodation ..................................................................................... 214

Table A3.1. Predicted ocular and systemic effect of right and left FUNB based on brain lateralization of autonomic activity ............................................. 218

Table A3.2. Base-line refractive error, IOP and TA levels of different subject groups ........................................................................................................ 221

Table A3.3. Base-line refractive error, IOP and TA levels of subjects when separated based on myopia progression rate............................................. 222

Table A3.4. Effect of 20 minutes of FUNB on TA.................................................. 223

Table A3.5. Mean changes in IOP following right and left FUNB ....................... 227

Table A3.6. Effect of 20 minutes of FUNB on heart rate ...................................... 227

Table A3.7. Effect of 20 minutes of FUNB on blood pressure ............................. 228

Table A5.1. Magnitude of nearwork-induced transient myopia (D) as a function of refractive group (myopia onset, progression rate and ethnic background) averaged over the 90 s post-task period ................................................... 241

Table A6.1. Comparison of the Canon and Shin-Nippon autorefractors .............. 248
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA</td>
<td>Tonic accommodation</td>
</tr>
<tr>
<td>NITM</td>
<td>Nearwork-induced transient myopia</td>
</tr>
<tr>
<td>EOM</td>
<td>Early-onset myope</td>
</tr>
<tr>
<td>LOM</td>
<td>Late-onset myope</td>
</tr>
<tr>
<td>Emm</td>
<td>Emmetropes</td>
</tr>
<tr>
<td>Hyp</td>
<td>Hyperopes</td>
</tr>
<tr>
<td>SM</td>
<td>Stable myopes</td>
</tr>
<tr>
<td>PM</td>
<td>Progressing myopes</td>
</tr>
<tr>
<td>AC</td>
<td>Accommodative convergence</td>
</tr>
<tr>
<td>SERE</td>
<td>Spherical equivalent refractive error</td>
</tr>
<tr>
<td>ASRC</td>
<td>Accommodation stimulus response curve</td>
</tr>
<tr>
<td>IOP</td>
<td>Intraocular pressure</td>
</tr>
<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>FUNB</td>
<td>Forced unilateral nostril breathing</td>
</tr>
</tbody>
</table>
STATEMENT OF ORIGINAL AUTHORSHIP

The work contained in this thesis has not been previously submitted for a degree or diploma at any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Jennifer C. Chen
19 June 2003
I would like to thank my supervisor Dr Katrina Schmid for her guidance and support throughout my studies. Due to her help, I was able to have a vast variety of experiences in terms of presenting my work and collaborating with other researchers. My associate supervisor, Professor Brian Brown, has also instilled in me good research skills and allowed me to be an independent researcher.

I would also like to acknowledge the support and encouragement given to me by Professors Leo Carney and Peter Swann over the past years while I was both an undergraduate and postgraduate student at the Optometry School.

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Finally, I would like to give the biggest thanks to my family, especially my mother, for their love, patience, and support throughout the entire process.
CHAPTER 1
INTRODUCTION

An apparent increase in the prevalence of myopia over recent decades has been observed. It is speculated that the greater nearwork demands of modern society may have interacted with an underlying genetic susceptibility to result in the increased prevalence. A key question is, what is this genetic susceptibility that interacts with environmental factors such as increased nearwork? An imbalance of the autonomic nervous system may be the genetic precursor to myopia development, which is triggered by the increased amount of nearwork and gives rise to anomalous accommodation responses during or following sustained nearwork to result in or exacerbate myopia. As background to this hypothesis, research investigating the role of accommodation in myopia development is reviewed and discussed in relation to an autonomic imbalance model. Anatomical, physiological and pharmacological aspects of the autonomic inputs to the ciliary muscle in relation to accommodation and the possible mechanisms of autonomic imbalance in myopia development are also discussed.

1.1. Myopia: prevalence, classifications and socio-economic ramifications

1.1.1. Definition and prevalence

Myopia is the type of refractive error that results from the eye being too long for its optical power. In myopic eyes, parallel rays of light are brought to a focus (F’e) anterior to the retina and result in blurred retinal images (Figure 1.1). An increase in the prevalence of myopia has been observed over recent decades (Rose et al., 2001), such that approximately 25% of individuals in Caucasian populations today are myopic (Sperduto et al., 1983, McCarty et al., 1997, Wensor et al., 1999). Near
epidemic levels of myopia (up to 80%) have been reported in countries such as Hong Kong (Lam and Goh, 1991, Yap et al., 1993b, Edwards, 1999, Lam et al., 1999), Taiwan (Lin et al., 1998, Lin et al., 1999), Singapore (Tan et al., 2000, Wong et al., 2000, Wu et al., 2001) and Japan (Matsumura and Hirai, 1999).

![Diagram](image_url)

**Figure 1.1.** Myopia: parallel light rays entering the eye are focussed anteriorly to the retina. The eye is too long for its optical power.

1.1.2. Classification of myopia

There are undoubtedly several types of myopia of varying severity and aetiology (Edwards and Lam, 1999). A plethora of classifications systems exist in the literature with most based on the age of onset or the aetiology of the condition. A classification system proposed by Grosvenor (1987) divided myopia into four categories based on age-related prevalence and age of onset: i) congenital, ii) youth-onset, iii) early adult-onset, and iv) late adult-onset myopia. In Grosvenor’s system, congenital myopia refers to a condition that is present at birth and remains through infancy and childhood. Myopia with an onset from about six years of age to teenage years is classified as youth-onset, onset between the age of 20 to 40 classified as early adult-onset, and onset after 40 years classified as late adult-onset.
Myopia has also been divided into two broad clinical types: i) pathological myopia, and ii) physiological myopia (Curtin, 1979). Pathological myopia typically presents at an early age and advances rapidly. Axial length is always abnormally large, due to the formation of a posterior staphyloma (Curtin, 1985). It is generally believed that the aetiology of this type of myopia is different from other types, in that environmental factors such as nearwork have not been implicated in its development (Edwards, 1998). In contrast, physiological myopia is an optical condition of the eye in which the components of refraction all lie within the ranges found in emmetropia, yet the combination of these normal components renders the eye myopic. Curtin (1979) has also defined physiological myopia as eyes which do not have any of the fundus characteristics of pathological myopia.

There is increasing evidence to suggest that the accommodation system in persons who develop myopia between the ages of about 18 to 25 years is different from that found in emmetropes and those with youth-onset myopia (McBrien and Millodot, 1986b, Bullimore and Gilmartin, 1987a, Gilmartin and Bullimore, 1991, Strang et al., 1994). These findings suggest that the causes of this type of myopia may be different and lead to yet another classification system: i) early-onset myopia (EOM) for when myopia occurs before 15 years of age, and ii) late-onset myopia (LOM) for when myopia occurs after 15 years of age (Goldschmidt, 1968). As most myopia research tends to be conducted in two major groups: children aged from eight to 12 years (youth-onset) and young adults aged from 18 to 25 years (early adult-onset), the age of onset of 15 years easily divides the subjects into EOMs and LOMs. While studies conducted using children will clearly only contain EOMs, young adult subject populations may comprise of both EOMs and LOMs. Studies reported in this thesis use this classification system.
1.1.3. Socio-economic costs of myopia

The cost of myopia to society is enormous and it includes the expense of regular eye examinations, the cost of spectacles and contact lenses and, in recent years, the cost of refractive surgery. In the United States, the cost was estimated to be $12.8 billion in 1990 (Javitt and Chiang, 1994). Of a greater importance are the sight-threatening ocular complications associated with myopia. There is an increased incidence of open-angle glaucoma (Mitchell et al., 1999), cataracts (Lim et al., 1999), chorioretinal degeneration and retinal detachment (The eye disease case-control study group, 1993) in myopic eyes compared to emmetropic eyes. Refractive surgical procedures for the correction of myopia also increase the risk of retinal detachment (Vinger, 1997, Ruiz-Moreno et al., 2000).

1.2. Aetiology of myopia

1.2.1. Genetic predisposition

The contrasting lines of evidence of genetic and environmental contributions to myopia development continue to stimulate the long-running “nature versus nurture” argument. Even in the presence of abundant evidence of an environmental contribution, one cannot doubt the importance of a genetic predisposition to myopia. Studies have shown that there is a greater prevalence of myopia among children of myopic parents than among those of non-myopic parents (Gwiazda et al., 1993a, Yap et al., 1993a, Goss and Jackson, 1996b, Wu and Edwards, 1999). Pacella and co-workers (1999) found that children with two myopic parents were six times more likely to become myopic than children with one or no myopic parents. It is also reported that children of myopic parents are less hyperopic and have longer eyes,
even before the onset of juvenile myopia (Zadnik et al., 1994). The high degree of concordance of myopia onset and development for uniovular twins is also compelling evidence for a genetic predisposition in the aetiology of myopia (Sorsby and Fraser, 1964, Chen et al., 1985, Hammond et al., 2001).

1.2.2. Environmental influences

Evidence of an environmental influence on myopia development has largely come from epidemiological studies. The prevalence of myopia is exceptionally high in occupations requiring intensive nearwork, reaching approximately 70% in clinical microscopists (Adams and McBrien, 1992, McBrien and Adams, 1997), 80% in Orthodox Jewish school boys (Zylbermann et al., 1993), and 90% in medical students (Chow et al., 1990, Midelfart et al., 1992, Lin et al., 1996)(Table 1.1).

Association between myopia and nearwork has also been reported across races and it has been suggested that the recently observed increased prevalence in Taiwanese, Singaporean, and Inuit Eskimo populations has been caused by increased formal education and nearwork (Au Eong et al., 1993, Norn, 1997, Lin et al., 1999). However, studies of myopia and nearwork have not demonstrated a cause-effect relationship but merely associations. Limitations are inherent in studies of myopia and nearwork as they are mostly non-standardized surveys without proper control groups. Furthermore, the performance of nearwork cannot be considered in isolation. Factors such as demographics, occupation, age, socio-economic status, education and intelligence also influence the association between myopia and nearwork, making the issue of causation difficult to assess (Zadnik and Mutti, 1998, Lam and Edwards, 1999).
Table 1.1. Prevalence of myopia by occupation

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Source/occupational group</th>
<th>Age (yr)</th>
<th>No. of subjects</th>
<th>Prevalence of myopia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Adams and McBrien, 1992)</td>
<td>British clinical microscopists</td>
<td>21-63</td>
<td>251</td>
<td>71 %</td>
</tr>
<tr>
<td>(Zylbermann et al., 1993)</td>
<td>Jewish Orthodox school boys</td>
<td>14-18</td>
<td>193</td>
<td>81.3 %</td>
</tr>
<tr>
<td>(Lin et al., 1996)</td>
<td>Taiwanese medical students</td>
<td>18-21</td>
<td>345</td>
<td>95.8 %</td>
</tr>
<tr>
<td>(Midelfart et al., 1992)</td>
<td>Norwegian medical students</td>
<td>22-26</td>
<td>133</td>
<td>50.3 %</td>
</tr>
<tr>
<td>(Chow et al., 1990)</td>
<td>Singaporean medical students</td>
<td>20-22</td>
<td>128</td>
<td>82%</td>
</tr>
<tr>
<td>(Septon, 1984)</td>
<td>American optometry students</td>
<td>21-37.5</td>
<td>447</td>
<td>74.3%</td>
</tr>
<tr>
<td>(Kinge et al., 2000)</td>
<td>Norwegian engineering students</td>
<td>19.5-21.7</td>
<td>192</td>
<td>65%</td>
</tr>
<tr>
<td>(Loman et al., 2002)</td>
<td>American law students</td>
<td>~27</td>
<td>177</td>
<td>66%</td>
</tr>
</tbody>
</table>

1.3. Role of accommodation in myopia development

1.3.1. Accommodation and refractive error

If the need for sustained accommodation effort during nearwork is in some way a precursor to myopia, then fundamental differences in the characteristics of accommodation responses between myopes and non-myopes are expected. An important question then is, are these differences in accommodation due to differences in the underlying autonomic innervation to the ciliary muscle? The following sections discuss accommodation responses, with emphasis on the effect of
pharmacological modification of accommodation, particularly that involving the sympathetic system. The accommodation responses described here include: i) amplitude of accommodation, ii) accommodation stimulus response, iii) tonic accommodation, iv) accommodative adaptation and regression, and v) nearwork-induced transient myopia.

i) Amplitude of accommodation

The amplitude of accommodation is a measure of the maximum accommodation response. Patients with lower amplitudes of accommodation will use more of their accommodation reserve for nearwork. Under this circumstance, myopia could potentially develop to reduce the accommodation demand.

A number of studies have investigated the relationship between amplitude of accommodation and refractive error (Table 1.2). Maddock et al. (1981), McBrien and Millodot (1986a) and Fledelius (1981) reported higher amplitudes of accommodation in myopes than emmetropes, while Fong (1997) reported lower amplitudes in myopes, and Fisher et al. (1987a) and Gawron (1981) did not observe any association. Whether the reported amplitudes relate to ocular or spectacle plane is important. Failure to consider the effectivity of the spectacle lens power yields artificially inflated amplitudes of accommodation in myopes and relatively lower values in hyperopes. Only two of the above-mentioned studies, that of McBrien and Millodot (1986a) and that of Fisher et al. (1987a), compensated for lens effectivity, and the outcomes of these two studies differ, i.e. McBrien and Millodot (1986a) found higher measured amplitude of accommodation in myopes while Fisher et al. (1987a) found no effect of refractive error.
ii) Accommodation stimulus response

The accommodation response to different accommodation demands can be measured and is termed the accommodation stimulus response. Typically young observers show a lead of accommodation at low accommodation demands and a lag of accommodation at higher accommodation demands (Fisher et al., 1987a, Gilmartin and Bullimore, 1987). If the accommodation accuracy is not maintained during prolonged nearwork, the lag of accommodation may increase, and the resulting hyperopic retinal defocus may then lead to myopia (Gwiazda et al., 1993b, Abbott et al., 1998). The axial elongation that occurs with myopia may be an attempt to reduce the degree of hyperopic retinal defocus.

Despite considerable methodological differences, reduced accommodation stimulus responses in myopes have been reported in many studies, i.e. lags of accommodation tend to be higher in myopes (Table 1.3). As the identification of factors that predict myopia progression is required for optimal myopia management, it is important to know whether the increased lag of accommodation is observed before or after the onset of myopia. Findings on this are equivocal: greater lags of accommodation have been observed in emmetropic children prior to them becoming myopic (Goss, 1991, Portello et al., 1997), while other studies report that the greater lag of accommodation accompanies the development of myopia rather than precedes it (Gwiazda et al., 1998, Mutti et al., 2002).

Related to this, greater lags of accommodation have been observed in adult progressing myopes compared to those with stable myopia (Abbott et al., 1998, Vera-Diaz et al., 2000). This difference between progressing and stable myopes was greatest when accommodation was stimulated using negative lenses; in fact, no difference between refractive error groups was observed when changing target
distance was used to stimulate accommodation (Abbott et al., 1998). The reduced accommodation response of myopic subjects to minus lenses has been observed in several studies (Gwiazda et al., 1993b, Chen and O'Leary, 2000, Hazel and Strang, 2002), as has the lack of difference when close targets are used to induce accommodation (Hazel and Strang, 2002, Rosenfield et al., 2002).

Lens effectivity must also be considered here. For example, an accommodative stimulus of 3 D in front of a myopic subject who is fully corrected with a –5 D spectacle lens with a back vertex distance of 14 mm is reduced to 2.63 D at the ocular plane (Rosenfield, 1997), whereas it remains as a 3 D stimulus for an emmetrope. The accommodation response may be lower in a spectacle-corrected myope when compared with an emmetrope, due to the reduced ocular accommodation demand and this may be misinterpreted as being a greater lag of accommodation. All studies in Table 1.3 except that of Rosenfield et al. (1987b) have either corrected the myopes with contact lenses or used formulae to take lens effectivity into account (though the formulae used vary).
Table 1.2. Findings of studies measuring the amplitude of accommodation as a function of refractive error

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Age (yr)</th>
<th>N</th>
<th>Refractive error criteria</th>
<th>Testing conditions</th>
<th>Amplitude of accommodation (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(McBrien and Millodot, 1986a)</td>
<td>18-22</td>
<td>80</td>
<td>Hyp (≥+0.75 to +4.75 sph) Emm (−0.25 to +0.75 sph) EOM (≥−0.625 to −9.875 sph) LOM (≥−0.375 to −2.875 sph)</td>
<td>Monocular push-up</td>
<td>LOMs have higher amplitudes of accommodation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contact lens correction</td>
<td></td>
</tr>
<tr>
<td>(Fledelius, 1981)</td>
<td>18</td>
<td>137</td>
<td>Hyp (≥+1.00 sph) Emm (plano to −0.90 sph) Myope (≥−0.90 sph)</td>
<td>Monocular push-up</td>
<td>Myopes have higher amplitudes of accommodation</td>
</tr>
<tr>
<td>(Maddock et al., 1981)</td>
<td>~25</td>
<td>40</td>
<td>Emm (plano) Low myope (≤−3.00 sph) High myope (≥−3.00 sph)</td>
<td>Measured with laser optometer</td>
<td>Myopes have higher amplitudes of accommodation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spectacle lens correction</td>
<td></td>
</tr>
<tr>
<td>(Fong, 1997)</td>
<td>26.3-</td>
<td>696</td>
<td>Emm (≥−0.20 sph) Myope (≥−2.60 sph)</td>
<td>N.A.</td>
<td>Myopes have lower amplitudes of accommodation</td>
</tr>
<tr>
<td></td>
<td>27.2</td>
<td></td>
<td></td>
<td></td>
<td>Emm (4.33) &gt; Myope (4.03)</td>
</tr>
<tr>
<td>(Fisher et al., 1987a)</td>
<td>21-35</td>
<td>48</td>
<td>Hyp (≥+0.75 sph) Emm (≥±0.75 sph) Low myope (≥−0.75 &amp; ≤−4.00 sph) High myope (≥−4.00 sph)</td>
<td>Monocular push-up</td>
<td>No significant differences</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contact lens correction</td>
<td></td>
</tr>
<tr>
<td>(Gawron, 1981)</td>
<td>17-28</td>
<td>152</td>
<td>Hyp (≥+0.25 sph) Emm (plano to −1.00 sph) Myope (≥−1.00 sph)</td>
<td>Push-up technique</td>
<td>No significant differences</td>
</tr>
</tbody>
</table>

Abbreviations: Hyp = hyperopes, Emm = emmetropes, EOM = early-onset myopes, LOM = late-onset myopes, N.A = not available
<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Age (yr)</th>
<th>N</th>
<th>Refractive error criteria</th>
<th>Testing conditions</th>
<th>Results (slope of ASRC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(McBrien and Millodot, 1986b)</td>
<td>18-23</td>
<td>40</td>
<td>Hyp (+0.75 sph) Emm (0.25 to +0.75 sph) EOM (0.25 sph) LOM (0.25 sph) &amp; ≤1.00 cyl</td>
<td>Binocular Contact lens correction 1.5' @ 0.2, 0.25, 0.33, 0.5, 1, 2, 6 m</td>
<td>Shallower slopes of ASRC in myopia Hyp (0.97) &gt; Emm (0.92) &gt; EOM (0.88) &gt; LOM (0.87)</td>
</tr>
<tr>
<td>(Gwiazda et al., 1995a)</td>
<td>6-18</td>
<td>63</td>
<td>Emm (0.25 to +0.75 sph) Myope (–0.38 to −5.25 sph) &amp; ≤1.00 cyl</td>
<td>Monocular Spectacle lens correction 20/100 letters @ 4 m with plano to −10 D lens in 0.5 or 1.00 D steps</td>
<td>Shallower slopes of ASRC in myopia Emm (0.7) &gt; Myope (0.5)</td>
</tr>
<tr>
<td>(Gwiazda et al., 1993b)</td>
<td>5-17</td>
<td>64</td>
<td>Emm (0.25 to +0.50 sph) Myope (0.50 to −6.25 sph) &amp; ≤1.00 cyl</td>
<td>Monocular Spectacle lens correction DDS: 20/30 &amp; 20/100 letters @ 0.25 to 4 m PLS: target @ 0.25 m with plano to +4.00 D lens NLS: target @ 4 m with plano to −4.00 D lens</td>
<td>Shallower slopes of ASRC in myopia DDS: Emm (0.88) &gt; Myope (0.78) NLS: Emm (0.61) &gt; Myope (0.20) PLS: Emm (0.69) &gt; Myope (0.64)</td>
</tr>
<tr>
<td>(Abbott et al., 1998)</td>
<td>18-31</td>
<td>32</td>
<td>Emm (0.25 to +0.75 sph) EOM (0.25 sph) LOM (0.25 sph) &amp; ≤0.50 cyl</td>
<td>Monocular Contact lens correction DDS: 6/9 letters @ 0.25 to 4 m in 7 steps PLS: target @ 0.25 m with plano to +4.00 D lens NLS: target @ 4 m with plano to −4.00 D lens</td>
<td>Shallower slopes of ASRC in progressing myopia Emm (0.84±0.13) &gt; Stable myopes (0.85±0.05) &gt; Progressing myopes (0.70±0.14) for NLS No differences were found for DDS and PLS</td>
</tr>
<tr>
<td>(Rosenfield and Gilmartin, 1988)</td>
<td>~21</td>
<td>20</td>
<td>Emm (±0.50 sph) LOM (−0.75 to −4.00 sph)</td>
<td>Binocular Contact lens correction N6 numbers @ 33 cm</td>
<td>LOMs showed lower accommodation response than Emm</td>
</tr>
<tr>
<td>(Rosenfield and Gilmartin, 1987b)</td>
<td>~21</td>
<td>51</td>
<td>Emm (±0.50 sph) EOM (±0.50 sph) LOM (−0.50 sph) &amp; ≤0.50 cyl</td>
<td>Binocular Spectacle lens correction N6 targets @ 3, 3.9, 4.6 D</td>
<td>No differences in ASRC between EOMs and LOMs</td>
</tr>
<tr>
<td>(Rosenfield et al., 2002)</td>
<td>21-27</td>
<td>16</td>
<td>Hyp (+0.50 sph) Emm (0.25 to +0.50 sph) Myope (−0.25 sph) &amp; ≤0.75 cyl</td>
<td>Binocular Contact lens correction Snellen acuity chart @ 0.2, 0.25, 0.33, 0.4 m</td>
<td>No differences in the slopes of ASRC between stable and progressing myopes Became myopic (1.02) &gt; Emm (0.99) &gt; Remained myopic (0.87)</td>
</tr>
</tbody>
</table>

Abbreviations: ASRC = accommodation stimulus response curve, Hyp = hyperopes, Emm = emmetropes, EOM = early-onset myopes, LOM = late-onset myopes, PLS = positive lens series, NLS = negative lens series, DDS = decreasing distance series.
iii) Tonic accommodation

Tonic accommodation (TA) has been suggested to represent the resting position of the accommodation system or a state of equilibrium between the parasympathetic and sympathetic inputs to the ciliary muscle (Gilmartin and Hogan, 1985b, Gilmartin, 1986). It manifests when target quality is sufficiently degraded, either by reduced illumination, reduced contrast and spatial frequency content, or in the absence of any visual stimuli (e.g. in darkness)(Fisher et al., 1987a).

Whether the level of TA varies as a function of refractive error has been examined, however no consistent pattern has emerged. Variations may be attributed to one, or a combination, of the following factors: refractive error criteria, instrumentation (Bullimore et al., 1986, Rosenfield et al., 1993), methods to open the accommodation loop (Schor et al., 1985, Gray et al., 1998, Strang et al., 2000), mental effort (Post et al., 1985, Bullimore and Gilmartin, 1987b, Bullimore and Gilmartin, 1987a, Bullimore and Gilmartin, 1988), surround propinquity (Rosenfield and Ciuffreda, 1991, Chiu and Rosenfield, 1994), and inter-subject variability (Schaeffel et al., 1993). The most consistent finding is that TA is lower in myopia (particularly in LOM) than in emmetropia, by approximately 0.4 D (Table 1.4).

Whether reduced TA causes myopia or occurs secondary to myopia development remains unclear, as longitudinal studies report conflicting findings. Either no difference in base-line TA (Adams and McBrien, 1993, Yap et al., 1998, Zadnik et al., 1999) or higher base-line TA (Jiang, 1995, Jiang, 1998) has been reported in emmetropes who later became myopic compared to those who remained emmetropic. However in Jiang’s study (1995), only six out of 33 emmetropic subjects became myopic during the study period. Two additional longitudinal studies (Owens et al., 1989, Adams and McBrien, 1993) reported a correlation between reduced TA levels
and higher myopia progression rate in myopic subjects and suggested that reduced TA levels may be a possible risk factor for future myopia progression.

iv) Accommodative adaptation and regression (open-loop conditions)

Following a period of sustained near viewing, shifts in accommodation could occur, usually towards the myopic direction (Ebenholtz, 1983). The term accommodative adaptation or accommodative hysteresis has been used to describe this nearwork-induced shift in accommodation and TA is the reference point against which accommodative adaptation is measured. (Rosenfield et al., 1993, Rosenfield et al., 1994b, Gilmartin, 1998). Figure 1.2 outlines the experimental sequence used in the assessment of accommodative adaptation under open-loop conditions. The pattern of regression back to the pre-task TA level is often also used to assess the degree of adaptation generated by the near task. The time course of regression from adapted levels to pre-task values, ranges from several seconds, (Baker et al., 1983, Gilmartin and Bullimore, 1987), to a few minutes (Fisher et al., 1987a, McBrien and Millodot, 1988, Gwiazda et al., 1995b), to even a few hours (Ebenholtz, 1983). The extended time course of accommodative decay led investigators to first postulate a relationship between accommodative adaptation and myopia development
<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Age (yr)</th>
<th>N</th>
<th>Refractive error criteria</th>
<th>Instrument</th>
<th>Testing conditions</th>
<th>TA results (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Gawron, 1981)</td>
<td>17-28</td>
<td>152</td>
<td>Hyp (≥+0.25 sph) Emm (plano to −1.00 sph) Myope (−1.00 sph)</td>
<td>Polarised vernier optometer</td>
<td>Darkness No refractive correction</td>
<td>Myopes have higher TA levels Myope (3.37±1.48) &gt; Emm (0.90±0.57) &gt; Hyp (0.28±0.62)</td>
</tr>
<tr>
<td>(Tokoro, 1988)</td>
<td>20-35</td>
<td>32</td>
<td>≤−3.50 &amp; &lt;1.00 cyl</td>
<td>Infrared optometer</td>
<td>Darkness Spectacle lens correction</td>
<td>Myopes have higher TA levels Myope (0.18±0.30) &gt; Emm (0.06±0.34)</td>
</tr>
<tr>
<td>(Maddock et al., 1981)</td>
<td>&lt; 25</td>
<td>40</td>
<td>Emm (plano) Low myope (≤−3.00 sph) High myope (&gt;−3.00 sph)</td>
<td>Laser optometer</td>
<td>Darkness Spectacle lens correction</td>
<td>Myopes have lower TA levels Emm (1.62±1.15) &gt; Low myope (1.54±1.12) &gt; High myope (0.94±0.46)</td>
</tr>
<tr>
<td>(McBrien and Millodot, 1987)</td>
<td>19-25</td>
<td>62</td>
<td>Hyp (&gt;+0.75 sph) Emm (−0.25 to +0.75 sph) EOM (&gt;−0.25 sph) LOM (≤−0.25 sph) &amp; ≤1.00 cyl</td>
<td>Infrared optometer</td>
<td>Darkness Contact lens correction</td>
<td>LOMs have lower TA levels Hyp (1.35) &gt; Emm (0.85) ≈ EOM (0.8) &gt; LOM (0.5)</td>
</tr>
<tr>
<td>(Gilmartin and Bullimore, 1991)</td>
<td>19-25</td>
<td>30</td>
<td>Emm (plano to +0.50 sph) LOM (−0.50 to −2.25 sph) &amp; ≤0.50 cyl</td>
<td>Infrared optometer</td>
<td>Darkness Contact lens correction</td>
<td>LOMs have lower TA levels Emm (1.08±0.36) &gt; LOM (0.75±0.19)</td>
</tr>
<tr>
<td>(Bullimore and Gilmartin, 1987a)</td>
<td>19-26</td>
<td>30</td>
<td>Emm (plano to +0.50 sph) LOM (−0.50 to −3.50 sph) &amp; ≤0.50 cyl</td>
<td>Infrared optometer</td>
<td>Darkness No refractive correction</td>
<td>LOMs have lower TA levels Emm (1.14±0.46) &gt; LOM (0.81±0.46)</td>
</tr>
<tr>
<td>(Jiang, 1995)</td>
<td>18-27</td>
<td>44</td>
<td>Emm (−0.25 to +0.37 sph) LOM (≥−0.37 sph)</td>
<td>Infrared optometer</td>
<td>Darkness Spectacle lens correction</td>
<td>LOMs have lower TA levels Emm (~1.34) &gt; LOM (~0.45)</td>
</tr>
<tr>
<td>(Rosner and Rosner, 1989)</td>
<td>6-14</td>
<td>113</td>
<td>Hyp (&gt;+0.75 sph) Emm (−0.25 to +0.75 sph) EOM (&gt;−0.25 sph)</td>
<td>Dynamic retinoscopy</td>
<td>Gaussian target @ 40 cm Spectacle lens correction</td>
<td>EOMs have lower TA levels Hyp (1.73±0.40) &gt; Emm (1.54±0.49) &gt; EOM (1.36±0.46)</td>
</tr>
<tr>
<td>Study</td>
<td>Age Range</td>
<td>Sample Size</td>
<td>Diagnostics</td>
<td>Condition</td>
<td>Refractive Correction</td>
<td>Findings of TA Levels</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
<td>-----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>(Gwiazda et al., 1995b)</td>
<td>6.5-16.5 87</td>
<td>Hyp (+1.00 to +4.12 sph) Emm (–0.25 to +0.75 sph) EOM (–0.25 to –7.00 sph)</td>
<td>Infrared optometer</td>
<td>Darkness Spectacle lens correction</td>
<td>EOMs have lower TA levels Hyp (0.94) &gt; Emm (0.75) &gt; EOM (0.30)</td>
<td></td>
</tr>
<tr>
<td>(Woung et al., 1998)</td>
<td>7-12 34</td>
<td>Emm (–0.25 to +0.75 sph) EOM (–1.25 to –5.25 sph)</td>
<td>Infrared optometer</td>
<td>Internal asterisk @ 8 D No refractive correction</td>
<td>EOMs have lower TA levels Emm (1.37±0.33) &gt; EOM (1.03±0.36)</td>
<td></td>
</tr>
<tr>
<td>(Yap et al., 1998)</td>
<td>7-16 210</td>
<td>Hyp (≥+0.75 sph) Emm (–0.50 to +0.75 sph) EOM (&gt;–0.50 sph)</td>
<td>Infrared optometer</td>
<td>Darkness No refractive correction</td>
<td>EOMs have lower TA levels Hyp (0.67±0.36) &gt; Emm (0.69±0.31) &gt; EOM (0.44±0.31)</td>
<td></td>
</tr>
<tr>
<td>(Zadnik et al., 1999)</td>
<td>6-11 790</td>
<td>Hyp (≥+1.00 sph) Emm (–0.50 to +0.75 sph) EOM (≥–0.75 sph)</td>
<td>Infrared optometer</td>
<td>Empty-field condition</td>
<td>EOMs have lower TA levels Hyp (2.25±1.78) &gt; Emm (1.92±1.59) &gt; EOM (1.02±1.18)</td>
<td></td>
</tr>
<tr>
<td>(Strang et al., 1994)</td>
<td>~23 20</td>
<td>Emm (–0.25 to +0.50 sph) LOM (–1.00 to –3.25 sph) &amp; ≤–0.50cyl</td>
<td>Infrared optometer</td>
<td>Darkness Contact lens correction</td>
<td>No significant differences Emm (0.86±0.62) ≥ LOM (0.90±0.63)</td>
<td></td>
</tr>
<tr>
<td>(Woung et al., 1993)</td>
<td>19-38 51</td>
<td>Emm (–0.25 to +0.75 sph) EOM (&gt;–0.50 sph &amp; &lt;1.00 cyl) LOM (&gt;–0.50 sph &amp; &lt;1.00 cyl)</td>
<td>Infrared optometer</td>
<td>Internal asterisk @ 8 D No refractive correction</td>
<td>No significant differences Emm (0.79±0.56) &gt; EOM (0.65±0.46) &gt; LOM (0.59±0.55)</td>
<td></td>
</tr>
<tr>
<td>(Fisher et al., 1987a)</td>
<td>21-35 48</td>
<td>Hyp (&gt;–0.75 sph) Emm (±0.75 sph) Low myope (&gt;–0.75 &amp; ≤–4.00 sph) High myope (&gt;–4.00 sph)</td>
<td>Hartinger optometer</td>
<td>Darkness Spectacle lens correction</td>
<td>No significant differences Emm (~2.00) &gt; High myope (~1.8) &gt; Hyp (~1.6) &gt; Low myope (~1.2)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Hyp = hyperopes, Emm = emmetropes, EOM = early-onset myopes, LOM = late-onset myopes
Open-loop conditions (i.e. in total darkness)

A period of adaptation in the dark  
Pre-task accommodation measured in the dark (pre-task TA)  
A period of near work in the light  
Post-task accommodation measured in the dark (accommodative adaptation + pre-task TA)

**Figure 1.2.** The experimental sequence for assessment of accommodation adaptation under open-loop conditions.

Refractive error groups show differences in susceptibility to accommodative adaptation (Table 1.5), with the time course of accommodative decay to pre-task TA levels varying significantly (Figure 1.3). LOMs exhibit significantly greater TA adaptation following near viewing, followed by a slower rate of decay to pre-task TA levels, compared with other refractive error groups (Table 1.6). A greater difference in the rate of decay occurs as the accommodation stimulus level is increased (Gilmartin and Bullimore, 1987, Gilmartin and Bullimore, 1991). Accommodative adaptation effects are not evident in the data of emmetropes and EOMs, while hyperopes show rapid dissipation and, in some cases, a counter-adaptive decrease, i.e. TA goes below the base-line pre-task level (McBrien and Millodot, 1988). Nevertheless, a number of investigations have failed to observe any relationship between accommodative adaptation and refractive error (Fisher et al., 1987a, Morse and Smith, 1993, Jiang and White, 1999).
Figure 1.3. A schematic representation of possible post-task accommodative regression patterns, based on the results of studies presented in Tables 1.5 and 1.6. **A**: a rapid decay and counter adaptive decrease may be observed in hyperopic subjects; **B**: monotonic regression typifies emmetropes and EOMs; and **C**: retarded regression with values remaining well above the pre-task TA levels (i.e. accommodative adaptation) are commonly observed in LOMs.

Accommodative adaptation has also been reported in children although available data are more limited (Owens et al., 1991, Rosenfield et al., 1994a, Gwiazda et al., 1995b, Woung et al., 1998). Gwiazda et al. (1995b) found that young myopes showed greater adaptation than emmetropes or hyperopes, and myopes of recent onset showed the largest effects. This implies that greater accommodative adaptation may occur during the early stages of myopia development, and that assessing accommodative adaptation in a clinical setting may be useful in identifying children who are at risk of developing myopia.
### Introduction

Table 1.5. Findings of studies investigating accommodative adaptation as a function of refractive error (open-loop conditions)

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Age (yr)</th>
<th>N</th>
<th>Refractive error criteria</th>
<th>Instrument</th>
<th>Testing conditions</th>
<th>Adaptation results (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(McBrien and Millodot, 1988)</td>
<td>18-27</td>
<td>47</td>
<td>Hyp (≥+0.75 sph) Emm (–0.25 to +0.75 sph) EOM (≥0.25 sph &amp; &lt;1.00 cyl) LOM (≥0.25 sph &amp; &lt;1.00 cyl)</td>
<td>Infrared optometer</td>
<td>Counting exercise at 0.2 m, 0.37 m for 15 min Contact lens correction</td>
<td><strong>LOM</strong> have greater accommodative adaptation LOM (~0.38) &gt; Emm (~0.10) &gt; EOM (~0.25) ≈ Hyp (~0.25)</td>
</tr>
<tr>
<td>(Woung et al., 1993)</td>
<td>19-38</td>
<td>51</td>
<td>Emm (–0.25 to +0.75 sph) EOM (≥0.25 sph &amp; &lt;1.00 cyl) LOM (≥0.25 sph &amp; &lt;1.00 cyl)</td>
<td>Infrared optometer</td>
<td>Internal asterisk-shaped target at 4 D above far point for 2 min No refractive correction</td>
<td><strong>LOM</strong> have greater accommodative adaptation LOM (1.19±0.92) &gt; Emm (0.66±0.59) &gt; EOM (0.27±0.40)</td>
</tr>
<tr>
<td>(Gwiazda et al., 1995b)</td>
<td>6.5-16.5</td>
<td>87</td>
<td>Hyp (+1.00 to +4.12 sph) Emm (–0.25 to +0.75 sph) EOM (–0.25 to –7.00 sph)</td>
<td>Infrared optometer</td>
<td>Video game at 4 D for 15 min Spectacle correction</td>
<td><strong>EOM</strong> have greater accommodative adaptation EOM (1.15) &gt; Emm (0.68) &gt; Hyp (0.24)</td>
</tr>
<tr>
<td>(Fisher et al., 1986)</td>
<td>21-35</td>
<td>48</td>
<td>Hyp (≥+0.75 sph) Emm (±0.75 sph) Low myope (–0.75 &amp; ≤–4.00 sph) High myope (&gt;–4.00 sph)</td>
<td>Hartinger optometer</td>
<td>Near task at accommodative amplitude for 10 min Spectacle lens correction</td>
<td>No significant differences in adaptation Hyp ≈ Emm ≈ Low myope ≈ High myope</td>
</tr>
<tr>
<td>(Morse and Smith, 1993)</td>
<td>N.A.</td>
<td>28</td>
<td>N.A.</td>
<td>Infrared optometer</td>
<td>4, 1, 0.33, 0.22 D for 5 min</td>
<td>No significant differences in adaptation Emm ≈ EOM ≈ LOM</td>
</tr>
<tr>
<td>(Woung et al., 1998)</td>
<td>7-12</td>
<td>34</td>
<td>Emm (–0.25 to +0.75 sph) EOM (–1.25 to –5.25 sph)</td>
<td>Infrared optometer</td>
<td>Internal asterisk @ 8 D for 2 min No refractive correction</td>
<td>No significant differences in adaptation EOM (0.50±0.36) &gt; Emm (0.39±0.37)</td>
</tr>
<tr>
<td>(Jiang and White, 1999)</td>
<td>22.4</td>
<td>15</td>
<td>Emm (±0.50 sph) LOM (–0.75 to –3.50 sph)</td>
<td>Infrared optometer</td>
<td>Near task at 6 D for 20 min</td>
<td>No significant differences in adaptation LOM (1.02) ≈ Emm (0.99)</td>
</tr>
</tbody>
</table>

Abbreviations: Hyp = hyperopes, Emm = emmetropes, EOM = early-onset myopes, LOM = late-onset myopes, N.A. = not available
<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Age (yr)</th>
<th>N</th>
<th>Refractive error criteria</th>
<th>Instrument</th>
<th>Near task conditions</th>
<th>Results (rate of decay)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(Strang et al., 1994)</em></td>
<td>23.2</td>
<td>20</td>
<td>Emm (−0.25 to +0.50 &amp; ≤0.50 cyl)</td>
<td>Infrared optometer</td>
<td>Maltese cross target 3 D above TA for 3 min</td>
<td>Emm &gt; LOM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOM (−1.00 to −3.25 sph &amp; ≤0.50 cyl)</td>
<td></td>
<td>Contact lens correction</td>
<td></td>
</tr>
<tr>
<td><em>(Fisher et al., 1986)</em></td>
<td>21-35</td>
<td>48</td>
<td>Hyp (&gt;+0.75 sph)</td>
<td>Hartinger optometer</td>
<td>Near task at accommodative amplitude for 10 min</td>
<td>Hyp &gt; Emm &gt; High myope ≈ Low myope</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emm (±0.75 sph)</td>
<td></td>
<td>Spectacle lens correction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low myope (&gt;−0.75 &amp; ≤−4.00 ph)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High myope (&gt;−4.00 sph)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Gilmartin and Bullimore, 1991)</em></td>
<td>19-25</td>
<td>30</td>
<td>Emm (plano to +0.50 sph &amp; ≤0.50 cyl)</td>
<td>Infrared optometer</td>
<td>Counting task at 0.2, 0.33 m for 10 min</td>
<td>Emm &gt; LOM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOM (−0.50 to −2.25 sph &amp; ≤0.50 cyl)</td>
<td></td>
<td>Contact lens correction</td>
<td></td>
</tr>
<tr>
<td><em>(Gilmartin and Winn, 1989)</em></td>
<td>N.A.</td>
<td>16</td>
<td>N.A.</td>
<td>Infrared optometer</td>
<td>Task at 3 D above TA for 3 min</td>
<td>Emm (5 s back to TA) &gt; LOM (20 s back to TA)</td>
</tr>
<tr>
<td><em>(McBrien and Millodot, 1988)</em></td>
<td>18-27</td>
<td>47</td>
<td>Hyp (&gt;+0.75 sph)</td>
<td>Infrared optometer</td>
<td>Counting task at 0.2, 0.37 m for 15 min</td>
<td>Hyp &gt; Emm ≈ EOM &gt; LOM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emm (−0.25 to +0.75 sph)</td>
<td></td>
<td>Contact lens correction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EOM (&gt;−0.25 sph &amp; &lt;1.00 cyl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOM (&gt;−0.25 sph &amp; &lt;1.00 cyl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Gilmartin et al., 1989)</em></td>
<td>N.A.</td>
<td>30</td>
<td>N.A.</td>
<td>Infrared optometer</td>
<td>Task at 1, 3, 5 D for 10 min</td>
<td>Emm (60 s back to TA) &gt; LOM (remained above base-line TA for 70 s)</td>
</tr>
</tbody>
</table>

Abbreviations: Hyp = hyperopes, Emm = emmetropes, EOM = early-onset myopes, LOM = late-onset myopes, N.A. = not available
v) Nearwork-induced transient myopia (NITM) (closed-loop conditions)

In addition to examining accommodative adaptation under open-loop conditions (i.e. in total darkness), some studies have examined adaptation effects under closed-loop viewing conditions (i.e. in the light) (Ciuffreda and Ordonez, 1995, Ong et al., 1996, Ciuffreda and Wallis, 1998). Figure 1.4 outlines the general experimental paradigm used in the assessment of accommodative adaptation under closed-loop conditions.

![Diagram of experimental paradigm](Figure 1.4)

**Abbreviation:** Distance refraction = DRx

Figure 1.4. The sequence and experimental paradigms for assessment of accommodative adaptation assessment under closed-loop conditions.

The transient myopic shift in the distance refraction following a period of nearwork has been termed nearwork-induced transient myopia (NITM) (Ong and Ciuffreda, 1995, Ong and Ciuffreda, 1997b, Ciuffreda and Wallis, 1998). It has been suggested that NITM is environmental in nature and an innervational and/or neuropharmacological origin has been postulated (Ciuffreda and Ordonez, 1995). If accommodative adaptation is considered to be a precursor to myopia development, its measurement and subsequent decay in the light rather than under open-loop conditions seems more relevant to the development of myopia, since nearwork is performed in the light and the open-loop accommodative adaptation effects may not translate directly to the more natural viewing environment. As normal defocus feedback mechanisms are allowed to operate under closed-loop conditions, accommodative adaptation effects observed under closed-loop
conditions are expected to be smaller than under open-loop conditions. Myopic shifts in distance refraction of 0.15 D to 0.6 D in magnitude have been reported (Table 1.7), whereas post-task myopic shifts in accommodation measured under open-loop conditions range from 0.24 D to 1.19 D (Table 1.5).

Myopes are reported to have enhanced susceptibility to NITM, whereas hyperopes and emmetropes are more resistant to this nearwork induced after-effect (Ciuffreda and Wallis, 1998, Ciuffreda et al., 2000, Ciuffreda and Lee, 2002). Following a 10-minute near task, Ciuffreda and Wallis (1998) found that LOMs demonstrated a greater amount of NITM, which took longer to return to the base-line refractive state than EOMs (63 s compared with 35 s), with some subjects remaining well above their base-line for the entire post-task period. Ciuffreda and Lee (2002) also extended the earlier investigation by adopting a longer nearwork period (i.e. four hours) and found a similar trend, i.e. myopes were highly susceptible to the nearwork after-effect. Ong and Ciuffreda (1997b) speculated that this transient myopia might provide substantial retinal defocus if the cycle were repeated many times over a period of weeks or months in particularly susceptible individuals, leading to myopia development or progression. A recent study has found NITM to be a feature of the progressive phase of myopia development (Vera-Diaz et al., 2002), however, longitudinal investigations may be necessary to prove whether NITM holds a cause and effect relationship with myopia development.
### Table 1.7. Findings of studies investigating NITM

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Age (yr)</th>
<th>No. of subjects</th>
<th>Instrument</th>
<th>Near task paradigm</th>
<th>Target/task details</th>
<th>Post-task monitoring period</th>
<th>Post-task decay time</th>
<th>NITM results (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Ehrlich, 1987)</td>
<td>18-30</td>
<td>15</td>
<td>Dioptron II Infrared optometer</td>
<td>Binocular 20 cm for 2 hr</td>
<td>6/9 number table /number search</td>
<td>1 hr</td>
<td>Decay incomplete after 1 hr</td>
<td>Mean NITM of 0.29 D</td>
</tr>
<tr>
<td>(Rosenfield and Ciuffreda, 1994)</td>
<td>21-25</td>
<td>12</td>
<td>Infrared optometer</td>
<td>Monocular 20 cm for 10 min</td>
<td>Matrix of numbers (N6)/adding</td>
<td>90 s</td>
<td>Time constant of 17 s</td>
<td>Mean NITM of 0.23 D</td>
</tr>
<tr>
<td>(Fisher et al., 1987a)</td>
<td>21-35</td>
<td>48-12 High myope 12 Low myope 12 Emm 12 Hyp</td>
<td>Hartinger optometer</td>
<td>Monocular Near point for 10 min</td>
<td>6/6 letters/ maintaining clarity</td>
<td>20 min</td>
<td>N.A.</td>
<td>Mean NITM of 0.20 D; no difference in NITM and its rate of decay between refractive error groups</td>
</tr>
<tr>
<td>(Rosenfield et al., 1992b)</td>
<td>23-32</td>
<td>27-9 Hyp 4 Emm 14 Myope</td>
<td>Infrared optometer</td>
<td>Binocular 20 cm for 20 min</td>
<td>Text/shading in letters</td>
<td>50 s</td>
<td>Time constant of 10-20 s</td>
<td>Mean NITM of 0.14 D</td>
</tr>
<tr>
<td>(Ciuffreda et al., 1996)</td>
<td>21-28</td>
<td>12 Emm</td>
<td>Infrared optometer</td>
<td>Binocular 20 cm for 0.25, 0.5, 1, 2, 4, 8 min</td>
<td>Matrix of numbers/ adding</td>
<td>100 s</td>
<td>Time constant of ≤ 40 s</td>
<td>Mean NITM of 0.30 - 0.60 D (after a 4 min task)</td>
</tr>
<tr>
<td>(Ong et al., 1996 1999)</td>
<td>21-31</td>
<td>16 LOM</td>
<td>Infrared optometer</td>
<td>Binocular 40 cm for 10 min</td>
<td>Matrix of numbers/ adding</td>
<td>N.A.</td>
<td>Time constant of 51 s</td>
<td>Mean NITM of 0.21 D</td>
</tr>
<tr>
<td>(Ciuffreda and Wallis, 1998)</td>
<td>21-30</td>
<td>44-9 Hyp 11 Emm 13 EOM 11 LOM</td>
<td>Infrared optometer</td>
<td>Binocular 20 cm for 10 min</td>
<td>6/9 Snellen letters /maintaining clarity</td>
<td>120 s</td>
<td>Time constant of 35 s (EOM) 63 s (LOM)</td>
<td>Myopes are most susceptible to nearwork aftereffects LOM (0.36) &gt; EOM (0.34) &gt; Emm (0.09) &gt; Hyp (0.01)</td>
</tr>
<tr>
<td>(Ciuffreda and Lee, 2002)</td>
<td>17-31</td>
<td>16-4 Hyp 4 Emm 4 EOM 4 LOM</td>
<td>Infrared optometer</td>
<td>Binocular Habitual working distance for 4 hr</td>
<td>Newspaper, lecture transcripts, novels etc.</td>
<td>20 min</td>
<td>Time constant of &lt; 8 min</td>
<td>Myopes are most susceptible to nearwork aftereffects LOM (0.36) &gt; EOM (0.34) &gt; Emm (0.09) &gt; Hyp (0.01)</td>
</tr>
<tr>
<td>(Vera-Diaz et al., 2002)</td>
<td>18-27</td>
<td>41-14 Emm 16 SM 13 PM</td>
<td>Infrared optometer</td>
<td>Binocular 20 cm for 10 min</td>
<td>6/9 Snellen letters /maintaining clarity</td>
<td>120 s</td>
<td>Time constant of &gt;120 s (PM) 42 s (SM) 35 s (Emm)</td>
<td>PMs are most susceptible to nearwork aftereffects PM (0.33±0.04) &gt; SM (0.17±0.03) &gt; Emm (0.16±0.03)</td>
</tr>
</tbody>
</table>

Abbreviations: Hyp = hyperopes, Emm = emmetropes, EOM = early-onset myopes, LOM = late-onset myopes, SM = stable myopes, PM = progressing myopes
1.4. Autonomic correlates: ciliary muscle innervation and accommodation

1.4.1. Introduction

The relative level of tonic accommodation, the degree of accommodative adaptation to near tasks and the characteristic regression pattern of adaptation effects represent potential indicators of myopia development and progression. The proposition that these accommodative responses may be precursors to myopia development implies an anomaly of the autonomic input to the ciliary muscle. The following section presents the working hypotheses of autonomic imbalance taken up in this thesis and as background to this issue, evidence of autonomic inputs to the ciliary muscle and relevant research of autonomic innervation and accommodation are discussed.

The autonomic nervous system (ANS) innervates the ciliary smooth muscles via its two branches: parasympathetic and sympathetic divisions. Figure 1.6 shows the central and peripheral pathways of the ANS to the ciliary muscle, the neurotransmitters involved in the synapses and the post-synaptic receptor types of the ciliary muscle.
Introduction

Figure 1.5. A diagram of the central and peripheral pathways for autonomic innervation of accommodation, the neurotransmitters and the post-synaptic receptors.

Accommodation for close objects is brought about by the combination of activation of the parasympathetic system and inhibition of the sympathetic system; conversely, focusing on distant objects requires an inhibition of the parasympathetic system accompanied by activation of the sympathetic system. As the role of the control processes of the ANS is to ensure an optimum balance, i.e. homeostasis between the parasympathetic and sympathetic inputs, the speculation that prolonged near vision may be a precursor to the development of myopia implies that some form of imbalance of the autonomic function could exacerbate an inherent genetic predisposition to myopia, in the presence of triggering environmental factors.
1.4.2. Hypotheses of autonomic imbalance and myopia development

The link between myopia and accommodation is likely to lie within the failure of the accommodation system to function adequately when presented with sustained near tasks. Optimal function could be achieved by the appropriate integration of parasympathetic and sympathetic components of accommodation (Rosenfield and Gilmartin, 1998a). Alternatively, high accommodation demands during near work could produce excessive accommodative adaptation, which then impedes accommodative relaxation to subsequent distance tasks. The following section summarizes the suggested hypotheses regarding the characteristics of the autonomic innervation that could precede myopia development.


A deficit in the sympathetic input could be reflected in enhanced accommodative adaptation effects and a prolonged period of regression due to an unantagonized parasympathetic tone (Gilmartin and Bullimore, 1987, McBrien and Millodot, 1988, Woung et al., 1993). If there is a deficit in the sympathetic input, myopia (particularly LOM as it has more association with nearwork) may result from the following progressive sequence: initial susceptibility to accommodative hysteresis effects due to a diminished ciliary muscle sympathetic input; cumulative retinal defocus from enhanced transient pseudomyopic changes in the distance refraction (NITM); accumulated retinal defocus reaching a critical level which triggers an increase in axial length (Gilmartin and Winfield, 1995).

Myopes could exhibit an overall reduced autonomic innervation, i.e. both sympathetic and parasympathetic innervation. This hypothesis is supported by the findings of Gilmartin and Bullimore (1987) that subjects with a reduced TA level (possibly mediated by a deficit in the parasympathetic input) had no difference in accommodation adaptation and regression time between timolol and saline trials. This suggests an absent or a reduced sympathetic facility. As sympathetic innervation is related to the concurrent level of the parasympathetic activity, this hypothesis of a dual infacility may physiologically be the most plausible. Furthermore, as an adaptive response to the environmental challenge of high accommodative demands in near vision (i.e. high parasympathetic activity), an optimum level of sympathetic inhibition may provide the facility required for an individual to maintain the emmetropic state whereas a deficit would predispose an individual to myopia.

1.4.3. Present understanding of ciliary smooth muscle dual innervation

Toates (1972) in his much-cited review first postulated the dual innervation system in the control of accommodation. It is well known that the parasympathetic system provides the dominant innervation to the ciliary muscle and that this is mediated by the action of acetylcholine on muscarinic receptors (Gupta et al., 1994, Pang et al., 1994). Parasympathetic input to the ciliary muscle mediates positive accommodation and it meets the need for rapid accommodative changes due to its fast onset of action (one to two seconds). The neural control of negative accommodation is less understood. It is now known that the ciliary muscle also receives sympathetic innervation, which is mediated by the action of noradrenaline on two subclasses of post-synaptic receptors, both of which are inhibitory: $\alpha_1$- and $\beta_2$-adrenoceptors (van
Alphen, 1976, Wax and Molinoff, 1987, Zetterström and Hahnenberger, 1988, Wilberg-Matsson et al., 2000); for reviews see Gilmartin (1986, 1992). The inhibitory accommodative effects of sympathetic inputs are small (<–2 D), slow (onset of action of 10 to 40 seconds), and directly related to the concurrent background parasympathetic activity (Törnqvist, 1967). These properties have led to the idea that the sympathetic input is more relevant to tasks requiring sustained accommodation rather than to tasks requiring a rapid change in the accommodation response. Evidence of dual innervation of the ciliary muscle will be reviewed from anatomical, physiological and pharmacological perspectives, with an emphasis on the sympathetic innervation.

i) Anatomical evidence

Using a range of adrenergic blocking agents, van Alphen (1965) identified both α- and β-adrenoceptors in cat ciliary muscle. It was also found that the receptors in rabbit ciliary muscle were predominantly of the α-subtype whereas only β-adrenoceptors were present in monkey ciliary muscle. In vivo and in vitro studies on human ciliary muscle are more difficult compared to those on animal species, due to the inaccessibility of tissue samples. Kern (1971) and van Alphen (1976) demonstrated by using adrenergic blocking agents that human ciliary muscle was predominantly populated by β-adrenoceptors.

More recent studies employing assay techniques and autonomic agents (Wax and Molinoff, 1987, Zetterström and Hahnenberger, 1988, Goyal, 1989, Pang et al., 1993, Gupta et al., 1994, Matsumoto et al., 1994, Pang et al., 1994) have given a better understanding of not only the presence, but the nature, distribution, and subtypes of both the muscarinic and adrenergic receptors. Techniques such as those involving the use of radioligands provide specific information on the subtypes of adrenergic receptors, however have limitations in terms of non-specific binding.
effects with melanin pigment in ocular structures (Hoffman and Lefkowitz, 1990, Wikberg-Matsson et al., 2000). Table 1.8 provides a summary of the various subtypes of receptors located in the human iris/ciliary body structures and their associated functions in the control of accommodation. Figure 1.6 illustrates the overall distribution of the receptors in the ocular structures and lists the drugs to which the receptors may respond.

ii) Physiological evidence

Physiological evidence of sympathetic inputs in the control of accommodation has largely come from nerve stimulation experiments on animal models. Olmsted et al. (1941) and Melton et al. (1955)(reviewed in (Gilmartin, 1986)) performed nerve stimulation experiments on animals such as cats and monkeys and demonstrated that sympathetic stimulation led to an inhibition of accommodation. Tornqvist (1967) demonstrated that cervical sympathetic nerve stimulation in monkeys led to hyperopic changes in their distance refraction. Conversely, in a more recent study, Hubbard (1999) found a 0.8 D myopic shift in the distance refraction in monkeys with superior cervical ganglionectomy. The shift in refraction was found to be independent of the vascular changes induced by stimulation of the α-adrenoceptors located in the blood vessels but a direct consequence of sympathetic innervation of the β-adrenoceptors present in the ciliary muscle (Törnqvist, 1967).
Table 1.8. A summary of the receptor types in the human iris/ciliary body structures.

<table>
<thead>
<tr>
<th>Autonomic branch</th>
<th>Receptor type</th>
<th>Receptor subtypes</th>
<th>Distribution in the human iris/ciliary body structures</th>
<th>Function of agonists in pupil size / accommodation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasym pathetic System</td>
<td>Muscarinic</td>
<td>M₁ M₄</td>
<td>✦ iris sphincter &gt; ciliary muscle &gt; ciliary epithelium</td>
<td>✦ contraction of the ciliary muscle (increase in accommodation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M₂</td>
<td>✦ longitudinal portion of the ciliary muscle, prejunctional iris, and trabecular meshwork</td>
<td>✦ contraction of the iris sphincter muscle (miosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M₃</td>
<td>✦ iris sphincter, ciliary muscle, ciliarybody, and trabecular meshwork ✦ 60-75% of receptors are the M₃ subtype</td>
<td></td>
</tr>
<tr>
<td>Sympathetic System</td>
<td>β-adrenoceptors</td>
<td>β₁</td>
<td>✦ β₁ accounts for 10% of the total β-adrenoceptors in the ciliary muscle</td>
<td>✦ relaxation of the ciliary muscle (decrease in accommodation) ✦ little effect on pupil size</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β₂</td>
<td>✦ meridional and circular portions of the ciliary muscle ✦ 90% of β-adrenoceptors in iris/ciliary body are β₂ subtype ✦ ciliary muscle (40%) &gt; ciliary processes (30%) ~ iris (30%) ✦ small amounts in iris sphincter muscle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>α-adrenoceptors</td>
<td>α₁</td>
<td>✦ radial muscle of the iris dilator, blood vessels ✦ a small number of α₁ receptors in ciliary muscle</td>
<td>✦ contraction of the iris dilator muscle (mydriasis) ✦ vascular changes leading to ciliary body volume changes (slight decrease in accommodation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α₂</td>
<td>✦ present in iris dilator muscle and sphincter muscle in equal amounts ✦ maybe present in ciliary muscle in a very small amount</td>
<td></td>
</tr>
</tbody>
</table>

(Figure 1.6 continues over page)
<table>
<thead>
<tr>
<th>Ciliary muscle</th>
<th>Receptor type</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>β₂*</td>
<td>isoprenaline (+)</td>
<td>timolol (−)</td>
</tr>
<tr>
<td>β₁</td>
<td>dobutamine (+)</td>
<td>betaxolol (−)</td>
</tr>
<tr>
<td>α₁</td>
<td>phenylephrine (+)</td>
<td>thymoxamine (−)</td>
</tr>
<tr>
<td>M₁, M₂</td>
<td>pilocarpine (+)</td>
<td>tropicamide (−)</td>
</tr>
<tr>
<td>M₃, M₄</td>
<td>pirenzepine (−)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iris sphincter muscle</th>
<th>Receptor type</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>M₁, M₂</td>
<td>pilocarpine (+)</td>
<td>tropicamide (−)</td>
</tr>
<tr>
<td>M₃, M₄*</td>
<td>pirenzepine (−)</td>
<td>isoprenaline (+)</td>
</tr>
<tr>
<td>β₂</td>
<td>timolol (−)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ciliary body</th>
<th>Receptor type</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>β₂*</td>
<td>isoprenaline (+)</td>
<td>timolol (−)</td>
</tr>
<tr>
<td>M₃</td>
<td>pilocarpine (+)</td>
<td>tropicamide (−)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iris dilator muscle</th>
<th>Receptor type</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁*</td>
<td>phenylephrine (+)</td>
<td>thymoxamine (−)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Afferent blood vessels</th>
<th>Receptor type</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁*</td>
<td>phenylephrine (+)</td>
<td>thymoxamine (−)</td>
</tr>
<tr>
<td>β₂</td>
<td>isoprenaline (+)</td>
<td>timolol (−)</td>
</tr>
</tbody>
</table>

Symbols: + = agonist
− = antagonist

Figure 1.6. Overall distribution of muscarinic, α- and β-receptors in the ocular structures and autonomic agents that act on them. The asterisk represents the receptor type in the largest number. Figure was adapted from Ocular Pharmacology (Neal, 2002). Data were collected from: (van Alphen, 1976, Nathanson, 1984, Wax and Molinoff, 1987, Zetterström and Hahnenberger, 1988, Gupta et al., 1994, Pang et al., 1994).
iii) Pharmacological evidence

The finding that instillation of cocaine produced a relaxation of the ciliary muscle was the earliest pharmacological clue to the inhibitory sympathetic innervation of human ciliary muscle in the late 1880s (reviewed in (Gilmartin, 1986). Sympathomimetics such as cocaine act on the ciliary muscle by preventing the uptake of the neurotransmitter, noradrenaline, at the neuro-effector junction and produce either α-activity (e.g. contraction of the iris dilator muscle having predominantly α-receptors) or β-activity (e.g. relaxation of the ciliary muscle having predominantly β-receptors).

As β₂-adrenoceptors predominate in human ciliary smooth muscle (Table 1.8), relaxation of the ciliary muscle would occur with non-selective β-agonists such as isoprenaline and hyperopic shifts in accommodation (particularly in TA) would be induced. Conversely, inhibition would occur with β-antagonists such as timolol, and to a much lesser extent with β₁-antagonists such as betaxolol, and produce myopic shifts in accommodation (Gilmartin and Hogan, 1985b, Gilmartin, 1986). Instillation of α-agonists and antagonists (e.g. phenylephrine and thymoxamine) would induce a decrease and an increase in accommodation respectively (particularly in the amplitude of accommodation) (Garner et al., 1983, Zetterström, 1988, Otsuka et al., 1998, Culhane et al., 1999). However, the induced changes by α-adrenergic agents in accommodation are believed to be due to changes in the ciliary body volume rather than a direct action on the ciliary muscle (Gilmartin, 1986). Additionally, Otsuka (1998) suggested that the α-adrenergic agents affect the amplitude of accommodation by modifying the parasympathetic activity rather than acting directly on the ciliary muscle.
1.4.4. Autonomic control of accommodation

The pharmacological events of autonomic innervation at the neuro-effector junction of the ciliary muscle are very complex. Most studies have used topical autonomic agents to stimulate or block respective muscarinic and adrenergic receptors of the ciliary muscle to investigate the effects on accommodation responses such as TA and accommodative adaptation (Gilmartin et al., 1992). Particular interest is directed to pharmacological intervention to the regression patterns of accommodative hysteresis following sustained near tasks to determine whether certain profiles of ANS function may in fact predispose an individual to myopia development.

Topical autonomic agents have been used to investigate the relative contributions of the parasympathetic and sympathetic inputs to TA levels. Based on the dual innervation theory of accommodation (Gilmartin, 1986, Gilmartin and Bullimore, 1987, Gilmartin et al., 1992), if a parasympathomimetic agent is applied to increase the parasympathetic component of accommodation, then TA should increase. Conversely, if a parasympatholytic agent is applied to decrease the parasympathetic system, then TA levels should decrease (Figure 1.7A). Similarly, a sympathomimetic agent would decrease TA whereas a sympatholytic agent would increase TA (Figure 1.7A). From the studies summarised in Figure 1.7B, it has been suggested that the variation in TA levels is a consequence of variations in parasympathetic inputs to the ciliary muscle (Gilmartin et al., 1984, Gilmartin and Hogan, 1985b, Gilmartin and Hogan, 1985a). The sympathetic system also has a significant role in TA but its contribution may be smaller (Gilmartin and Hogan, 1985c). Thus a low TA level may reflect a reduced parasympathetic input to the ciliary muscle (McBrien and Millodot, 1987, Woung et al., 1998), or an overall decrease from both the parasympathetic and sympathetic inputs (Ong and Ciuffreda, 1997a, Woung et al., 1998). The low parasympathetic tone may also account for lags of accommodation
during near tasks commonly observed in myopia development (McBrien and Millodot, 1986b) or myopia progression (Abbott et al., 1998, Vera-Diaz et al., 2000).

Figure 1.7. Schematic illustration of the predicted and actual effects of autonomic agents on TA. A. Predicted effect of autonomic agents on TA based on Toates’ (1972) model of accommodation. B. Results of studies investigating the effect of autonomic agents on TA (Garner et al., 1983, Gilmartin et al., 1984, Gilmartin and Hogan, 1985b, Gilmartin and Hogan, 1985a, Zetterström, 1988, Rosenfield et al., 1990, Otsuka et al., 1998). Experimental results are consistent with Toates’ model (1972). Abbreviations: P = parasympathetic, S = sympathetic (α or β receptors), + = stimulation, – = inhibition.
One proposed function of the sympathetic input, based on its inhibitory function, is to reduce the magnitude and duration of accommodative adaptation (Gilmartin and Bullimore, 1987, Gilmartin et al., 1992). During the course of a near task, the parasympathetic input required for sustained near vision stimulates and augments sympathetic input (Gilmartin and Bullimore, 1987). The two forces act in a state of equilibrium in order to maintain sustained single, clear binocular vision without excessive fatigue (Gilmartin, 1986, Gilmartin and Bullimore, 1987). After completion of the near task, a “sympathetic rebound phenomenon” may occur and attenuate the post-task accommodative adaptation effects (Woung et al., 1993).

This sympathetically mediated mechanism is thought to be responsible for the absence of adaptation in emmetropes or EOMs, as well as for inducing counter-adaptive shifts in the hyperopes (McBrien and Millodot, 1988). The regression pattern of the emmetropes reflects the decay characteristics of the interactive parasympathetic and sympathetic systems, while the regression pattern of myopes may primarily reflect the normal decay of parasympathetic activity alone (Gilmartin and Bullimore, 1991). A reduced sympathetic innervation would therefore result in less protection against accommodative adaptation. Based on this, a deficit in the sympathetic input may be responsible for the slow regression of adaptation effects in myopes and is thought to predispose an individual to myopia development or further myopia progression (McBrien and Millodot, 1988, Gilmartin and Bullimore, 1991, Gilmartin et al., 1992, Strang et al., 1994).

Susceptibility to nearwork-induced accommodative adaptation in myopia, as a consequence of reduced sympathetic input to the ciliary muscle, is also consistent with the accommodation response profile observed in the presence of adrenergic antagonism. Instillation of an adrenergic antagonist, such as timolol, has been found to increase accommodative adaptation in emmetropes (Gilmartin and Bullimore, 1987, Gilmartin and Winn, 1989, Culhane and Winn, 2000). Otsuka et al. (1998)
found that accommodative adaptation was increased by 0.36 D with timolol and decreased by 0.18 D with isoprenaline (an adrenergic agonist). In addition, Gilmartin and Bullimore (1987) found that timolol instillation resulted in a significant myopic shift in TA (approximately 0.4 D) following a near task and the regression time was increased to approximately 50 s (from typical values of 5-10 s). They also found that timolol produced a myopic shift in TA following a 5 D near task and a retarded decay to base-line TA levels in emmetropes with a pre-task TA level of greater than 0.75 D.

Timolol had no effect on accommodative adaptation in subjects with a pre-task TA level of less than 0.75 D. To explain this negative effect, it was suggested that the inhibitory sympathetic innervation was only activated when TA levels were greater than 0.75 D. An inadequate inhibitory sympathetic facility may mean that subjects with low TA levels are more susceptible to enhanced post-task hysteresis following relatively high levels of accommodative demand. Thus myopes who tend to have lower levels of TA than emmetropes may be more susceptible to accommodative hysteresis because of an anomalous inhibitory sympathetic facility. However, some studies (Rosenfield and Gilmartin, 1989, Gilmartin and Winfield, 1995) do not support the proposal that myopia (particularly LOM) is associated with a reduced sympathetic inhibitory facility and it is clear that further studies are required in this area.

Similar to enhanced accommodative adaptation of TA, an increased susceptibility to NITM might be a consequence of sympathetic insufficiency (Ciuffreda and Wallis, 1998, Ciuffreda et al., 2000, Ciuffreda and Lee, 2002). LOMs may have a deficit in the inhibitory sympathetic inputs to the ciliary muscle and therefore be more influenced by environmental factors such as nearwork. Information on this could be obtained by investigating the effects of autonomic agents on NITM in different refractive error groups. However, closed-loop measures of accommodation and
Introduction

factors pertaining to depth-of-focus are likely to mask the relatively small contribution from the sympathetic system.

1.5. Possible mechanisms linking autonomic input, accommodation and myopia development

Although accommodation has been thought of as a possible cause of myopia development for decades, early theories have largely relied on the mechanical effects of ciliary muscle contraction on scleral stretch rather than its impact of retinal image quality. The two main causative mechanisms linking an autonomic imbalance to anomalies of accommodation and the development of myopia are: i) retinal defocus, accommodation and myopia, and ii) ciliary muscle tonus, scleral stretching and myopia.

1.5.1. Retinal defocus, accommodation and myopia

Evidence from animal studies has revealed that in the presence of artificially imposed retinal defocus, by means of either positive or negative lenses, normal eye growth can be altered and this suggests that there are mechanisms in place which detect and compensate for the effect of induced retinal defocus (for reviews see (Goss and Wickham, 1995, Wildsoet, 1997)). In human, evidence of such a mechanism is less clear although imposing retinal defocus with undercorrection (Chung et al., 2002) or overcorrection (Goss, 1984) of myopia has been associated further myopia progression. If we assume that the retinal defocus associated with accommodative inaccuracy is a precursor for myopia development, then retinal defocus could arise either during sustained nearwork or immediately following the near task.
During nearwork, the quality of the retinal image may be compromised from the hyperopic retinal defocus that occurs in the presence of a large accommodative lag. Under such conditions, myopia may represent a physiological adaptation to this defocus, as the clarity of the image would be improved by an increase in axial length. Gwiazda et al. (1993b) and Abbott et al. (1998) proposed that it is the decrease in retinal image quality and the chronic defocus associated with nearwork, rather than the actual accommodative demand, that is the causative factor in myopia development. Alternatively, increased nearwork-induced accommodative adaptation may produce retinal defocus following nearwork on subsequent viewing of distant objects. Although the accommodative adaptation effects are transient, integration of such retinal defocus over time may lead to an increase in axial length. We suggest that in human, both myopic and hyperopic defocus have the potential to cause myopia and this is consistent with the overcorrection and undercorrection data (Goss, 1984, Chung et al., 2002). However, according to animal data, the imposed myopic retinal defocus associated with accommodative adaptation, should not be a stimulus for axial elongation (i.e. hyperopia occurs with imposed positive lenses)(Hung et al., 1995, Smith, 1998). Whether retinal defocus leads to myopia development and the importance of the type of defocus (myopic cf hyperopic) in causing human myopia is not clear.

Although animal studies have demonstrated the role of the retinal image in the process of refractive error development, the applicability of animal models in human refractive error development remains questionable (Zadnik and Mutti, 1995). In addition, there are several issues that need to be addressed.

1) As near work is never undertaken continuously, the hyperopic retinal defocus associated with an increased lag of accommodation during nearwork is never experienced continuously. A question then is: do intermittent periods of retinal defocus still have an effect on refractive error development? Animal
studies (Schmid and Wildsoet, 1996, Shaikh et al., 1999, Smith et al., 2002) have investigated the effect of intermittent blur on compensation to induced retinal defocus and found that brief periods of normal vision prevented the development of myopia in response to negative lenses. Periods of in-focus imagery as short as 20 min per day were found to be able to disrupt the development of myopia in chicks (Schmid and Wildsoet, 1997). Several short periods of normal vision per day were more effective in preventing the development of myopia than one single period of normal vision of the same duration (Napper et al., 1997). These findings therefore argue against the hypothesis of retinal defocus as myopes do experience substantial periods of clear vision. The presumption here may be that the amount of blur required to stimulate myopia development might be very small and less than the noticeable amount of blur and that integration of defocus over time leads to the development of refractive error.

2) Evidence that retinal image defocus produces myopia in humans has only come from cases of severe image degradation, i.e., conditions such as ptosis, haemangioma, congenital cataracts (Goss and Wickham, 1995). The degree of retinal image degradation in animal studies (e.g. with translucent occluders or lid sutures) provides a much greater degree of contrast reduction compared to that found in natural human visual experience. It seems unrealistic to equate the degree of image degradation produced by severe ocular conditions to the small hyperopic blur associated with the lags of accommodation during nearwork or the myopic blur due to the accommodative adaptation effects after nearwork.
1.5.2. Accommodation, ciliary muscle tonus, scleral stretching and myopia

Ramazzini in 1713 (reviewed in (Owens, 1991)) first suggested that the accommodative effort during nearwork would produce changes in tonus of the membranes and fibres of the eye. Shum et al. (1993) found that axial length increases during accommodation in both emmetropic and myopic subjects. Drexler et al. (1998) also investigated the changes in axial length associated with accommodation using a non-invasive and highly precise biometric technique, partial coherence interferometry, and found that during accommodation the ciliary muscle contracts and moves the choroid forward and inward, thus decreasing the circumference of the sclera and increasing the axial length. In fact, chronic accommodation has been demonstrated in chicks (Reiner et al., 1995) and kittens (Hendrickson and Rosenblum, 1985) to be sufficient to produce significant myopia. These findings provide tentative support for the idea that sustained accommodation could promote axial elongation and the development of myopia. Additionally, as ciliary muscle tonus is the mechanical component of accommodative adaptation effects (Rondeau et al., 1996), chronic accommodative adaptation from prolonged and excessive nearwork may also contribute to the axial elongation of the eye.

Van Alphen’s theory (1986) proposed that the ciliary muscle and choroid act as a continuous sheet of elastic capsule surrounding the globe and that choroidal tension is determined by the ciliary muscle tonus, which in turn regulates the amount of scleral stretch by resisting intraocular forces. The ability to resist intraocular forces and scleral stretch may be a function of the ciliary muscle tonus. Therefore, high ciliary muscle tone (high TA) would be predicted to offer increased resistance to stretching, and low ciliary muscle (low TA) would be predicted to offer less resistance to stretching and therefore predispose an eye to axial elongation and myopia development.
1.6. Myopia control treatments of relevance to accommodation and ANS

1.6.1. Myopia control using optical intervention

The ultimate aim of understanding the causes of myopia and the underlying mechanisms of the associated axial elongation is to develop ‘treatments’ to prevent myopia or arrest its progression. Various myopia “treatments” based on reducing the accommodative demand during nearwork have included bifocal/progressive addition lenses, spectacle intervention, and biofeedback visual training (Saw et al., 2002a, Saw et al., 2002b). The efficacy of these methods at preventing myopia or reducing its rate of progression is controversial.

i) Bifocal/progressive lenses

As one proposed mechanism of myopia development is the presence of retinal defocus during nearwork, bifocal lenses for young myopes were first advocated in the 1950s (reviewed in (Woo and Wilson, 1990)) to reduce the accommodation demand and the size of the retinal blur circle. However, reports on the efficacy of bifocals in reducing the rate of myopia progression are inconsistent (Curtin, 1985, Grosvenor, 1989), with more success for subjects who show esophoria at near (Goss, 1986, Goss, 1990, Goss and Grosvenor, 1990, Goss and Uyesugi, 1995, Fulk and Cyert, 1996, Fulk et al., 1998, Fulk et al., 2000, Brown et al., 2002, Fulk et al., 2002).

The use of progressive lenses in myopia control lies on the same premise of reducing the accommodation demand. Leung and Brown (1999) found that progressive lenses were effective in reducing the progression of myopia in Chinese children aged nine to 12 years. The mean myopic progression over the 2-year period was −1.23 D for single vision wearers, −0.76 D for +1.00 D addition and −0.66 D for +2.00 D addition progressive lenses wearers. The authors suggest that the success of these
Introduction

lenses may be due to better control of retinal image quality (a range of near additions is provided through the corridor) in addition to the reduction in accommodative demand required.

However, in a recent randomised masked study (Hong Kong Progressive Lens Myopia Control Study), Edwards et al. (2002) did not find that progressive lenses were effective in retarding myopia progression in Hong Kong myopic children. Myopia in children who wore the progressive lenses progressed at a similar rate as that in children wearing single vision lenses. The Correction of Myopia Evaluation Trial (COMET) was another randomised, double masked trial evaluating the effect of progressive lenses in children aged 6-11 years conducted in the United States at multiple sites (Hyman et al., 2001, Gwiazda et al., 2002). This study found that myopia progression of children wearing progressive lenses was only reduced by 0.2 D over a 3-year period and the authors thus concluded that myopia control with progressive lenses is limited (Gwiazda et al., 2003). However, children in the COMET study were not selected as progressing myopes, so it is unsurprising that relatively small effects were noted.

ii) Spectacle intervention

There is a variety of laboratory and clinical studies supporting the hypothesis that axial elongation and myopia develop by retinal image-mediated ocular growth (Goss and Wickham, 1995). In animal models, the eye can modify its growth to compensate for the effects of the lenses placed in front of the eye during development (Hung et al., 1995, Smith, 1998, Park et al., 2003). The axial length of the eye is presumed to adjust the location of the retina in order to minimize the degree of retinal defocus.
If myopia is an adaptive response to the accommodative demand which occurs during nearwork, then correction of myopia with minus lenses returns the need for accommodation at near. In the presence of chronic hyperopic retinal defocus during nearwork, the adaptive changes in axial length may be reinstated to compensate the effect of the lenses. A few models have predicted that full spectacle correction of myopia would lead to its exacerbation (Medina, 1987, Flitcroft, 1998). Ong et al. (1999) evaluated the rate of myopia progression in children over a three year period differentiated by their lens wear patterns (e.g. full time wear of distance correction cf. full distance correction for distance viewing only cf. no correction) and found that spectacle intervention had no effect on myopic progression rate. Pärssinen et al. (1989) also failed to find any differences in progression rate between myopic children who had continuous full correction, full correction for distant viewing only, and those who wore bifocal lenses. In fact, one recent study found that undercorrecting children enhanced rather than inhibited their myopia progression (Chung et al., 2002). With negative lenses as the routine management for myopia and myopia seemingly more prevalent, further evaluation of the relationship between myopia and its correction is needed.

iii) Biofeedback visual training

Biofeedback is another myopic control procedure with limited success. Its use is also based on the rationale that the accommodative demand during nearwork causes myopia to develop and progress (Woo and Wilson, 1990, Gilmartin et al., 1991). Typically, the feedback is in the form of an auditory signal that tells the patient if he or she is voluntarily changing his or her accommodation in the correct direction. After receiving seven training sessions using the Trachman procedure, subjects showed an improvement in visual acuity but no changes in refractive error were
found (Trachtman, 1986). As the training procedure requires repeated measures of visual acuity, the improvement in visual acuity is likely to be due to a learning effect rather than a true reduction in myopia (Grosvenor, 1989, Grosvenor, 1998). The improved visual acuity could also be explained by an improved ability to interpret a blurred retinal image (Gilmartin et al., 1991).

1.6.2. Myopia control treatments using topical autonomic agents

Apart from optically based treatments, pharmaceutical options are being pursued as a form of myopia control. The rationale behind the use of pharmaceutical agents lies in the premise of relaxing accommodation (muscarinic antagonists), lowering intraocular pressures (adrenergic antagonists) and reducing accommodative hysteresis effects (adrenergic agonists).

i) Muscarinic antagonists

The use of muscarinic antagonists such as atropine has been based on the hypothesis that excessive accommodation leads to increases in myopia. Atropine instillation is associated with a retarded rate of myopia progression (Hu, 1998, Shih et al., 1999, Kennedy et al., 2000), even in highly myopic children (–10 to –12 D) (Chou et al., 1997). The combination of atropine therapy with bifocal lenses (Romano and Donovan, 2000, Chiang et al., 2001, Syniuta and Isenberg, 2001) and progressive lenses (Shih et al., 2001) is also effective in slowing myopia progression. There is little information on the exact mechanisms of action of atropine although some animal studies demonstrate that it inhibits myopia by affecting scleral growth (Lind et al., 1998, Tigges et al., 1999). Problems with the use of atropine have been frequently reported. These include poor patient compliance, a high subject dropout rate, sustained cycloplegia, intense photophobia, and the possibility of toxic effects
associated with long-term use. Other weaker muscarinic antagonists, such as tropicamide, have been used in attempts to reduce the side effects and improve compliance, but they are less effective in reducing myopia progression rates (Chew et al., 1998, Grosvenor, 1998).

A promising therapeutic agent may be a muscarinic receptor antagonist without such severe cycloplegic and mydriatic side effects, and pirenzepine, a M₁ (and possibly M₄) subtype-specific muscarinic antagonist, appears to offer the prospect of influencing the signals that promote myopia without as many side effects. Pirenzepine has received much attention due to its effectiveness in reducing experimental myopia in animal models (Leech et al., 1995, Cottriall and McBrien, 1996, Cottriall et al., 1999, Tigges et al., 1999). The mechanism by which pirenzepine prevents myopia is also unclear, as it may work via the accommodation mechanism or at the retinal level (Cottriall et al., 1999). Several clinical trials on the efficacy of pirenzepine in slowing human myopia progression are currently underway in the United States (e.g. PIR-205 Myopia Clinical Trial, Collaborative Assessment of Myopia Progression with Pirenzepine (CAMPP) Study) and Singapore.

ii) Adrenergic antagonists

Based on the hypothesis that axial elongation associated with myopia results from scleral stretching in the presence of high intraocular pressures (IOP), β-adrenergic antagonists, such as timolol or labetalol, have been used for myopia control. With lowered IOP and tensile stress on the ocular coats, the subsequent axial expansion should be reduced. However, topical instillation of these agents daily in myopic children has proved ineffective (Hosaka, 1988, Jensen, 1991), and they also appear to be ineffective in animal models (Lauber, 1991, Schmid et al., 2000). In addition, children who become myopic do not show an elevated IOP before the onset of myopia when compared with those who remain emmetropic (Edwards and Brown,
Based on the accommodation models for myopia described here (i.e. a deficit in the sympathetic innervation may be associated with myopia), these agents may in fact exacerbate myopia progression.

iii) Adrenergic agonists

There is mounting evidence that in the absence of an adequate sympathetic input to the ciliary muscle, accommodative hysteresis effects produced by sustained near tasks and the cumulative effects of retinal defocus could induce axial elongation and myopia development. A longitudinal study using topical agents (such as isoprenaline), which stimulate sympathetic activity, to determine whether the reduction in myopia progression is due to their effects on TA and accommodative adaptation, would provide more insight (Gilmartin and Hogan, 1985b, Ciuffreda and Ordonez, 1995, Gilmartin, 1998).

1.7. Issues addressed

On the basis of the research reviewed, there is strong evidence that accommodation plays a role in the development of myopia, although the exact mechanism is yet to be determined. The collective results point to anomalous accommodation responses, possibly as a result of underlying anomalous autonomic inputs to the ciliary muscle being involved in myopia development and progression.

The specific objectives of this research were to:

1) Investigate the characteristics of accommodation in groups with different refractive errors, myopia progression rates and ethnic backgrounds and to
demonstrate the role of the sympathetic inputs to accommodation using topical β-adrenergic antagonists (Chapter 2).

2) Look for changes in tonic accommodation and accommodative adaptation over time and to investigate the effect of sympathetic stimulation on accommodation using salbutamol, a β-adrenergic agonist to confirm or otherwise the conclusions of Chapter 2 (Chapter 3).

3) Investigate accommodation functions and possible autonomic profiles using a topical β-adrenergic antagonist in a group of Hong Kong children with particularly high nearwork demands and an apparent genetic predisposition to myopia development (Chapter 4).

4) Investigate accommodation and convergence functions of school children in Hong Kong and to examine the role of sympathetic inputs in the accommodation and convergence interaction (Chapter 5).

5) Provide evidence for intrinsic physiological differences in accommodation characteristics and profiles of autonomic anomaly to the ciliary muscle in individuals with different myopia progression rates and ethnic backgrounds and to provide directions for further work involving autonomic agents and modelling of the accommodation system in myopia development (Chapter 6).

The present chapter has been accepted as a review paper by Ophthalmic and Physiological Optics. Manuscript #99281.
CHAPTER 2
EFFECT OF β-ADRENERGIC ANTAGONISM ON ACCOMMODATION IN DIFFERENT REFRACTIVE ERROR GROUPS

2.0. Summary

An anomaly of the autonomic system that controls accommodation has been suggested to be involved in myopia development and progression. The aims of this study were: i) to determine if the accommodation characteristics of myopes were different from those of other refractive error groups and ii) to demonstrate the role of the sympathetic inputs in accommodation using topical β-adrenergic antagonists. The effect of altering the sympathetic control of the ciliary muscle on tonic accommodation (TA) and nearwork-induced accommodative adaptation was investigated.

Accommodation measurements were made with an infrared Canon autorefractor before and after topical application of β-antagonists (timolol and control agent betaxolol). We predicted that nearwork-induced accommodative adaptation may be a feature of progressing myopia, particularly in myopes with an Asian background. We also predicted that timolol, a sympatholytic agent, would produce sympathetic blockade and increase accommodative adaptation in stable myopes, who presumably have a more robust sympathetic system to the ciliary muscle, but would have little effect in progressing myopes.

Consistent with the hypothesis, progressing myopes, particularly those with an Asian background, showed the highest TA levels and were highly susceptible to nearwork-induced accommodative adaptation, which showed no evidence of full decay. In contrast, stable myopes, particularly those with a Caucasian background exhibited
lower TA levels with minimal accommodative adaptation, which dissipated quickly. Timolol tended to have a greater sympathetic blocking effect in the stable myopes compared to the progressing myopes, presumably due to a more robust sympathetic system that could be inhibited. Asian stable myopes were most susceptible to the blocking effect of timolol.

Myopia progression rate and ethnic background were both important determinants of accommodation characteristics. The suggested autonomic imbalance model may explain differences in accommodation responses and the response profiles to $\beta$-antagonism in myopic individuals with different myopia progression rate and ethnic background. A genetic predisposition to alteration of the autonomic control of accommodation may cause myopia to manifest and progress and is of significance in terms of understanding the aetiology of myopia.

2.1. Introduction

While there is little doubt that myopia has a strong genetic component (Gwiazda et al., 1993a, Yap et al., 1993a, Zadnik et al., 1994, Goss and Jackson, 1996b, Pacella et al., 1999, Wu and Edwards, 1999), environmental influences such as nearwork may also play an important role in its development (Chow et al., 1990, Adams and McBrien, 1992, Midelfart et al., 1992, Zylbermann et al., 1993, Lin et al., 1996, McBrien and Adams, 1997, Rosenfield and Gilmartin, 1998b). Due to the association between nearwork and myopia, accommodation functions and pharmacological modifications of the accommodation system have been areas of great interest, study and conjecture. There is compelling evidence that myopic individuals demonstrate differences in their accommodation responses compared with their emmetropic counterparts (McBrien and Millodot, 1986b, Bullimore and Gilmartin, 1987a, McBrien and Millodot, 1988, Gilmartin and Bullimore, 1991).
As accommodation responses may reflect the inherent nature of the autonomic control of the ciliary muscle, which should have optimum balance between the parasympathetic and sympathetic inputs (Toates, 1972, Gilmartin, 1998), several investigators have suggested that an anomaly of the autonomic control of accommodation may be involved in the development of myopia (Gilmartin and Hogan, 1985b, McBrien and Millodot, 1986b, Gilmartin and Bullimore, 1987, Woung et al., 1993, Ciuffreda and Wallis, 1998, Culhane and Winn, 1999, Ciuffreda et al., 2000, Ciuffreda and Lee, 2002).

Particular autonomic innervation profiles may be genetically determined and may lead to an increased susceptibility to myopia development in the presence of environmental triggers such as increased nearwork. These profiles may include deficits in the parasympathetic or sympathetic system, or an overall reduction in both components of the autonomic inputs to the ciliary muscle. Differences in these autonomic profiles may explain why not all individuals performing substantial nearwork go on to become myopic. It is likely that only those with a genetic predisposition that may be modulated by the visual environment develop axial elongation and myopia. Ethnically based genetic differences in the susceptibility to environmental risk factors may also exist, given the rapid rate at which the prevalence of myopia is increasing in some countries (Rose et al., 2001).

Accommodation responses such as tonic accommodation (TA) and nearwork-induced accommodative adaptation effects (shifts in TA) as a function of refractive error have been studied in relation to an autonomic imbalance model. Previous studies have found that myopes have lower TA levels but a greater propensity for TA shifts after sustained nearwork (see section 1.3.1 for details). These accommodation responses have been investigated further by employing autonomic system modifying agents to determine the relative contributions of the parasympathetic and sympathetic inputs that produce them ((Gilmartin, 1986, Gilmartin et al., 1992, Gilmartin, 1998,
Winn et al., 2002); also see section 1.4.4). It has been demonstrated that TA levels reflect the parasympathetic input to accommodation and that myopes may have a parasympathetic deficit whereas attenuation of the nearwork-induced accommodative adaptation effects are related to the sympathetic contribution to accommodation and a deficit in the sympathetic accommodation input may render myopes more susceptible to accommodative changes following nearwork.

It is well known that accommodation is predominantly controlled by the parasympathetic innervation to the ciliary muscle and that this is mediated by the action of acetylcholine on muscarinic receptors (Gupta et al., 1994, Pang et al., 1994). The neural control of the sympathetically mediated accommodation is less understood. It is now known that the ciliary muscle receives sympathetic innervation, mediated by the action of noradrenaline on two subclasses of $\alpha_1$ and $\beta_2$ adrenoceptors ((van Alphen, 1976, Wax and Molinoff, 1987, Zetterström and Hahnenberger, 1988, Wikberg-Matsson et al., 2000); for reviews see Gilmartin (1986, 1992)). The inhibitory accommodative effects of sympathetic inputs are small ($<-2$ D), slow (onset of action of 10 to 40 seconds), and directly related to the concurrent background parasympathetic activity (Törnqvist, 1967). These properties have led to the idea that the sympathetic input is more relevant to tasks requiring sustained accommodation rather than to tasks requiring a rapid change in the accommodation response and is related to how an individual adapts to sustained nearwork (Gilmartin and Hogan, 1985c, Gilmartin, 1986, Gilmartin and Bullimore, 1987).

To understand the sympathetic control of accommodation, Gilmartin and Winfield (1995) investigated the effect of topical $\beta$-adrenergic antagonists on accommodation in 16 young adults. Nearwork-induced accommodative adaptation was measured following topical applications of timolol, an adrenergic antagonist, and the control agent betaxolol. Response profiles to $\beta$-adrenergic antagonism were similar in
emmetropes, early-onset myopes (EOMs) and late-onset myopes (LOMs) and it was thus concluded that a propensity for LOM was not associated with a deficit in the sympathetic input to the ciliary muscle. A more recent study (Gilmartin et al., 2002) also showed that there are significant inter-subject variations in the response to β-adrenergic antagonism with timolol. It was also suggested that only 30 to 40% of individuals are likely to have access to a sympathetic inhibitory facility during sustained nearwork and this is not confined to a particular refractive error group.

In this study, we sought to confirm or otherwise the findings of Gilmartin and Winfield (1995) by using a larger sample of subjects. As the myopia classification system based on the age of myopia onset did not differentiate the accommodation responses modified by β-adrenergic antagonism, we also sought to investigate other myopia classification systems. Myopic progression rate and ethnic background may be important factors to consider, in studies of accommodation and myopia.
2.2. Methods

The following section describes the experimental protocol for measurements of the two accommodation responses. Tonic accommodation and nearwork-induced accommodative adaptation and its regression were measured in myopic and non-myopic adults, following topical instillations of saline, betaxolol, and timolol.

2.2.1. Subjects

Forty-five subjects (24 males and 21 females) aged between 18 to 27 years (mean = 21.8±2.0) were recruited from the student population at Queensland University of Technology (QUT) and patients attending its Optometry Clinic. Monocular visual acuities were 6/6 or better using the Bailey-Lovie acuity chart (Bailey and Lovie, 1976) and all of the subjects were free of ocular disease or oculomotor imbalance. Biometric data were collected using A-scan ultrasonography (Storz). Subjects with greater than 0.50 D of cylindrical corrections, anisometropia of greater than 1.00 D and a history of current or past cardiac or respiratory conditions were excluded from participation.

Based on non-cycloplegic subjective refraction results, subjects were divided into three groups, non-myopes (n = 15), early-onset myopes (EOMs, n = 15) and late-onset myopes (LOMs, n = 15). The non-myopic group consisted of 13 emmetropes and two low hyperopes with spherical equivalent refractive error (SERE) (i.e. spherical component + half of the cylindrical component) ranging from –0.375 to +1.375 D (mean SERE = 0.05±0.49 D). Subjects with SERE ≥ –0.75 D were categorized as being myopes. Information from a questionnaire asking about subject’s past refractive history and family ocular history was collected (See Appendix 1). According to the approximate age of myopia onset, subjects were subdivided into EOMs (age of myopia onset prior to 14 years) and LOMs (myopia
onset after 15 years of age). Information on progression rate was obtained from past clinic records or from the subject’s optometrist. Myopes were considered to be progressing if they had a myopic shift of –0.50 D or more over the past two years. This rate of myopia progression criterion was based on a study by McBrien and Adams (1997) where myopia in adult myopes “progressors” increased by –0.58 D on average. Subjects were also asked to report their ethnic background on a questionnaire and were divided into Caucasians or Asian subgroups. Of the subjects who classified themselves as Asians, two were from Taiwan, two from Hong Kong, three from Malaysia, one from China, two from Vietnam and two from Korea. All had been residing in Australia for more than three years. The study was conducted in accordance with the requirements of the Queensland University of Technology Human Research Ethics Committee. All subjects were given a full explanation of the experimental procedures and informed consent was obtained.

2.2.2. Measurements of accommodation

_Tonic accommodation_

A 3-minute period in the dark was used to allow accommodation to regress to a baseline tonic level. Darkroom accommodation readings (~30 readings) were taken for one minute and averaged. The tonic accommodation value was taken as the difference between the average of the darkroom readings and the initial baseline far reading (i.e. with the subjects looking at the far target).

_Nearwork-induced accommodative adaptation effects and regression_

Subjects were directed to fixate on the far target for a 3-minute period. They were asked to keep the letters as clear as possible at all times and to inform the examiner if this was not achievable (Stark and Atchison, 1994). They were also instructed to exert (for the near target), the same level of accommodative attention as that
normally employed when reading a book. The level of accommodation exerted during the 3-minute task was assessed and recorded at 30-second intervals to assure accuracy and stability of the accommodation response. Six measurements were taken and the mean spherical equivalent accommodation response was calculated.

Immediately after task completion, lights were extinguished and accommodation regression towards the base-line pre-task TA level was measured over a 90-second period at 2-second intervals (from time 240-330s with a total of 45 readings). A 5-minute break was given before repeating the procedure for the near target distance. Figure 2.1 illustrates the schematic representation of the accommodation task and measurement protocol.

![Figure 2.1](image.png)

**Figure 2.1.** A schematic representation of the experimental protocol. Shaded parts represent the dark room condition. Darkroom accommodation readings (30 readings) were taken for one minute and averaged. Subjects then viewed the target (distant or near target) for a 3-minute period. The lights were then extinguished and accommodation regression towards the base-line pre-task TA level was measured over a 90-second period (45 readings).
2.2.3. Apparatus

Refractive errors were corrected with soft disposable contact lenses (CIBA Focus Night & Day) for the duration of the experimental trial. The use of contact lenses ensured that the accommodative demand for each subject was virtually identical at each task distance. Accommodation was measured using a Canon Autoref R-1 autorefractor (McBrien and Millodot, 1985). This instrument allows objective measurement of the refractive state of the eye, requiring no judgement or response by the subject. It also provides an unrestricted binocular field of view by means of a semi-silvered mirror, allowing viewing at a range of distances. As the instrument uses infra-red light, it measures refractive states under light (e.g. normal distance refraction) or dark (e.g. tonic accommodation) conditions. A video system was used to monitor the subject’s eye position during measurements to ensure proper fixation and alignment.

All measurements were made on the right eye while the left eye was occluded with an eye patch. The autorefractor was used in a static mode and an interface was used to connect the printer port of the autorefractor to a computer so that accommodation could be recorded successively at approximately 2-second intervals. Invalid autorefractor readings characterized by large cylindrical components or error display, due to blinking or fixation losses, were disregarded. Sphere and cylinder powers were recorded to an accuracy of 0.12 D with all powers being referred to the corneal plane and the SERE was used. The instrument’s calibration level was checked and a correction factor of +0.20 D was applied to all data (Baker et al., 1983).
2.2.4. Target details

The far target consisted of a single line of 6/9 high contrast letters (90%) on a Bailey-Lovie acuity chart. The near target (laser print N5) was equivalent to the far target in terms of angular letter size and contrast. The far and near target viewing distances were set at 0.2 D (4.75 m) and 4.0 D (0.25 m) respectively. The luminance of the task was controlled to give approximately equal luminance at each target distance (~320 cd/m²). The target was positioned along the subject’s line of sight and the autorefractor aligned with the pupil centre.

2.2.5. Drug treatments

Each subject repeated the experimental procedure on two separate occasions with each visit lasting approximately 90 minutes. The two experimental trials were separated by at least two days to ensure total wash-out of the drug. In order to reduce the number of visits required, the drug trials were not double-blind nor randomized. Testing was performed 30 minutes following the instillation of timolol maleate 0.5% (Timoptol, Merck, Sharp and Dohme) on the first visit. The experimental protocol was conducted following saline application as the first trial on the second visit, and betaxolol S HCL 0.25% (Betoptic, Alcon) application was used as the second trial. Prior to instillation, benoxinate HCL 0.4% was used to inhibit reflex lacrimation and increase corneal permeability (Bartlett and Jaanus, 2001).

As timolol maleate 0.5%, a non-selective β-adrenergic antagonist, reduces intraocular pressures, it has been suggested that betaxolol may serve as a better control than saline to account for possible interaction effects, if any, between intraocular pressures and accommodation responses (Gilmartin and Winfield, 1995, Winn et al., 2002). Betaxolol S HCL 0.25% is equi-potent as betaxolol HCl 0.5% (MIMS, 2002). One drop was used for the saline and timolol trials and two drops for
the betaxolol trial, with a separation period of 5 minutes. Previous studies have shown that these dosages of timolol and betaxolol produce similar reductions of intraocular pressures (Stewart et al., 1986, Gilmartin and Winfield, 1995). Drugs were applied to the right eye only using a precision micropipette and each instillation comprised 20 µl of drug. The volume size of 20 µl was chosen to maximize ocular absorption (Appendix 2). Eyelid closure and punctal occlusion techniques were carried out for two minutes to minimize systemic absorption. To monitor the ocular hypotensive effects of timolol and betaxolol, IOP was measured both at the beginning and the end of the experimental trial using a non-contact tonometer (American Optical, U. K.). Drug effects on amplitudes of accommodation and pupil sizes were monitored using the push-up method and a Rosenbaum pupillometer respectively. To determine interaction effects between iris colour and drug response, the subject’s iris colour was graded on a 1-5 scale (1: light blue/grey, 2: medium blue/hazel/light brown, 3: green, 4: medium brown, 5: dark brown)(Seddon et al., 1990).

Contact lenses fitting was carried out 15 minutes after drug instillation and subjects were given 15 minutes to adapt to their soft contact lenses before measurements of accommodation commenced. Subjects were asked to refrain from performing sustained near tasks for a period of 30 minutes preceding the commencement of the experimental trial.
2.2.6. Data analysis

Statistical analysis of the stored data was conducted using Statistical Packages for Social Sciences (SPSS). All subjects had TA measured on two occasions for each drug condition. The two measurements were highly correlated ($r = 0.962, P < 0.001$) thus the average TA value was used for all further analysis. None of the measures were significantly different from the normal distribution (Kolmogorov-Smirnov, $P > 0.05$) and parametric tests were used. One-way analysis of variance was used to determine whether tonic accommodation levels were different among groups with different refractive error, myopic progression rate, and ethnic background. Paired t-tests were used to compare timolol and control trials. Correlation tests were used to establish if there were statistically significant relationships between variables such as tonic accommodation and refractive error. Repeated measures analysis of variance (three factors: drug, time, and subject group) was used to assess the effects of the drugs on regression patterns of accommodative adaptation. Differences in regression patterns between groups of different refractive error, myopia progression rate and ethnic background were also analysed using repeated measures analysis of variance.

Analysis of regression patterns was performed using two methods: i) standard analysis, ii) regression quotient (%) analysis. Standard analysis of accommodative regression patterns uses pre-task TA level as the reference, to determine the magnitude and duration of the relative shifts in TA induced by nearwork. Due to the possible extraneous factors which may influence TA and the uncertainty of its short-term stability, Gilmartin et al. (1995, 2002) used a procedure which eliminates inter-individual variability and takes account of the lag and lead of accommodation that may occur with different tasks (Schaeffel et al., 1993). In this case, the accommodative regression pattern resulting from the far task is taken as the control condition. Differences in far and near regression data points are then expressed as a percentage of regression (regression quotient %) using the difference between mean
levels of near and far accommodation level (e.g. accommodative effort for the near and far tasks respectively) as the reference. Regression quotient of 100 represents no regression while zero represents full regression back towards the base-line level.

2.2.7. Control treatments: saline vs betaxolol

The two control agents used (betaxolol and saline) gave results which were highly correlated. No statistical differences between TA measurements taken after saline cf. after betaxolol were observed ($t_{44} = -0.215, P = 0.831$). Nor were there differences between TA shifts with timolol when either was used as control (e.g., timolol-saline, timolol-betaxolol) ($t_{44} = -0.215, P = 0.831$). There were no differences in the effect of saline and betaxolol on accommodative adaptation (simple contrast, $F = 0.162, df = 1, P = 0.689$). To simplify interpretation, in the results section betaxolol is the drug referred to when discussing the effect of the control agent on accommodation.

2.3. Results

2.3.1. Subject characteristics

The EOMs had refractive errors between $-1.75$ to $-10.50$ D (mean SERE = $-4.32\pm2.08$ D) and the LOMs had refractive errors between $-0.875$ to $-3.375$ D (mean SERE = $-2.29\pm0.78$ D)(Table 2.1 over page). EOMs tended to have greater magnitude of myopia than LOMs by 2.03 D. There were no differences in subject characteristics between stable and progressing myopes except in their myopic progression rate (see Table 2.2 over page). Myopia progression rate was found to be independent of the age of myopia onset or magnitude of myopia.
Table 2.1. Subject characteristics based on separating myopes according to the age of myopia onset.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Refractive error groups</th>
<th>ANOVA/t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-myopes</td>
<td>EOMs</td>
</tr>
<tr>
<td>No. (males, females)</td>
<td>15 (8M, 7F)</td>
<td>15 (9M, 6F)</td>
</tr>
<tr>
<td>No. stable myopes</td>
<td>N.A.</td>
<td>10</td>
</tr>
<tr>
<td>No. progressing myopes</td>
<td>N.A.</td>
<td>5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>21.3±2.4</td>
<td>21.8±2.1</td>
</tr>
<tr>
<td>Age of myopia onset (years)</td>
<td>N.A.</td>
<td>11.8±1.9</td>
</tr>
<tr>
<td>Best sphere refraction (D)</td>
<td>0.05±0.49</td>
<td>-4.32±2.08</td>
</tr>
<tr>
<td>Myopic progression rate (D/year)</td>
<td>N.A.</td>
<td>-0.19±0.23</td>
</tr>
<tr>
<td>Vitreous chamber length (mm)</td>
<td>16.24±0.84</td>
<td>17.90±1.23</td>
</tr>
<tr>
<td>Axial length (mm)</td>
<td>23.08±0.90</td>
<td>24.79±1.32</td>
</tr>
</tbody>
</table>

N.A. = not applicable
Table 2.2. Subject characteristics based on separating myopes according to the myopia progression rate.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Refractive error groups</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stable myopes</td>
<td>Progressing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>myopes</td>
</tr>
<tr>
<td>No. (males, females)</td>
<td>16 (9M, 7F)</td>
<td>14 (7M, 7F)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>21.8±2.1</td>
<td>21.1±1.5</td>
</tr>
<tr>
<td>Age of myopia onset (years)</td>
<td>13.7±3.6</td>
<td>15.3±2.9</td>
</tr>
<tr>
<td>Best sphere refraction (D)</td>
<td>-3.40±2.41</td>
<td>-3.20±1.00</td>
</tr>
<tr>
<td>Myopic progression rate (D/year)</td>
<td>-0.05±0.10</td>
<td>-0.55±0.27</td>
</tr>
<tr>
<td>Vitreous chamber length (mm)</td>
<td>17.63±1.32</td>
<td>17.57±0.82</td>
</tr>
<tr>
<td>Axial length (mm)</td>
<td>24.68±1.44</td>
<td>24.36±0.68</td>
</tr>
</tbody>
</table>

N.A. = not applicable
2.3.2. Tonic accommodation

In the absence of any visual stimuli, the accommodation system adopted an intermediate resting position (Figure 2.2). The average TA level of all 45 subjects was 0.86±0.99 D, which is comparable to the average value of 1.0 – 1.5 D reported in previous literature (see Table 1.4). However, there was a large range of TA values, from –0.59 D (hyperopic) to 3.67 D (myopic). Large individual variations in TA have been previously reported (Gilmartin and Hogan, 1985b, Gilmartin and Hogan, 1985a, McBrien and Millodot, 1988).

Correlation coefficients between TA and refractive error have ranged from 0.61 (Charman, 1982), to 0.48 (Maddock et al., 1981) to 0.24 (McBrien and Millodot, 1987). No direct linear relationship between TA and refractive error was observed in our data ($r = 0.06, P = 0.696$; Figure 2.3). There was no association between TA and myopic progression rate ($r = –0.258, P = 0.168$; Figure 2.4).

Figure 2.2. Frequency distribution of tonic accommodation for all 45 subjects. Positive values represent myopic TA and negative values represent hyperopic TA. Mean TA was equal to 0.86 D.
Figure 2.3. A scattergram of the relationship between tonic accommodation and ocular refraction for 45 subjects. There appeared to be no direct relationship between tonic accommodation and ocular refraction.

Figure 2.4. A scattergram of the relationship between tonic accommodation and myopia progression rate. There appeared to be no direct relationship between tonic accommodation and the amount of myopia progression per year.
TA and refractive error, myopia progression rate and ethnic background

Both EOMs (0.68 ±0.91 D) and LOMs (0.79±1.04 D) had lower TA levels than non-myopes (1.11±1.03 D) but the difference was not statistically significant (F2, 42 = 0.768, P = 0.471; Figure 2.5A). When the myopic subjects were classified according to their myopic progression rate, differences in base-line TA levels were revealed (F2, 42 = 5.516, P = 0.007; Figure 2.5B). Stable myopes had significantly lower TA levels than the non-myopes (Bonferroni, P = 0.037) and progressing myopes (Bonferroni, P = 0.012). Differences in TA levels were also found when the myopic subjects were grouped based on their myopia progression rate and ethnic background (F4, 40 = 4.526, P = 0.004; Figure 2.5C). Caucasian stable myopes had the lowest TA levels whereas Asian progressing myopes had the highest TA levels (Bonferroni, P = 0.003). When only the myopes were considered, there was a significant relationship between ethnic background and base-line TA levels (r = 0.511, P = 0.004), i.e. myopes with an Asian ethnic background have higher TA levels (1.37±1.27 D) than Caucasian myopes (0.37±0.45 D).
Figure 2.5. Differences in mean base-line TA levels when separating subjects based on **A**: refractive error, **B**: myopic progression rate, and **C**: myopic progression rate/ethnic background. Stable myopes have lower TA levels compared with non-myopes and progressing myopes. Asian progressing myopes have the highest TA level whereas Caucasian stable myopes have the lowest TA. Asterisks represent statistically significant differences at **\( P < 0.01 \), ***\( P < 0.005 \) level, one-way analysis of variance. The number in brackets represents the number of subjects in each group. Error bars show one standard deviation.
2.3.3. Lag of accommodation and TA

The lags of accommodation during the 4 D near task of non-myopes (0.20±0.30 D), EOMs (0.11±0.25 D), and LOMs (0.25±0.39 D) were similar (F2, 42 = 0.791, P = 0.46). The lag of accommodation did not vary with myopic progression rate (F2, 42 = 0.05, P = 0.951) or myopic progression rate/ethnic background (F4, 40 = 1.202, P = 0.325). Although the difference did not reach a statistically significant level, Asian myopes exhibited a smaller amount of accommodative lag compared to the non-myopes and their Caucasian counterparts. There appeared to be a negative correlation between the lag and resting state of accommodation, i.e. the higher the TA, the smaller the lag of accommodation (r = −0.318, P = 0.033; Figure 2.6)

![Figure 2.6](image)

Figure 2.6. A scattergram of the relationship between TA and lag of accommodation for 45 subjects. There appeared to be a negative relationship, i.e. the higher the TA, the smaller the lag of accommodation at near.
2.2.4. Changes in TA induced by timolol

Timolol instillation produced mean hyperopic shifts in TA in non-myopes (0.21±0.38 D), EOMs (0.39±1.1 D) and LOMs (0.17±0.9 D)(F$_2$, 42 = 0.272, $P$ = 0.763; Figure 2.7A). When the myopic subjects were divided based on myopic progression rate, significant differences in timolol-induced TA shifts were found (F$_2$, 42 = 5.131, $P$ = 0.01; Figure 2.7B). Progressing myopes showed a significantly more hyperopic shift in TA (0.76±1.17 D) compared to the small myopic shift of the stable myopes (0.14±0.59D)(Bonferroni, $P$ = 0.008). Significant differences were also found when the myopic subjects were divided on the basis of myopia progression and ethnic background (F$_4$, 40 = 5.566, $P$ = 0.001; Figure 2.7C). The Asian progressing myopic group exhibited the most substantial hyperopic shift in TA with timolol (mean = 1.34±1.40 D) and post-hoc analysis (Bonferroni) showed significant differences between this particular group and every other group at a 0.05 level (Figure 2.7C).

When looking at the number of subjects in the non-myopic, EOM and LOM group who demonstrated a hyperopic shift in TA compared to those who showed a myopic shift, no remarkable pattern was observed. When the myopic subjects were divided on the basis of myopic progression rate, the majority of subjects in the stable myopic group showed a myopic shift in TA (11/16), whereas most of the progressing myopes showed a hyperopic shift (9/14)(Table 2.3). Using the classification system involving myopia stability and ethnic background, all of the Asian progressing myopes exhibited a hyperopic shift in TA (7/7) whereas 8/12 of Caucasian stable myopes showed a myopic shift in TA with timolol application (Table 2.3).
Figure 2.7. Differences in timolol-induced TA shift when subjects were separated based on A: refractive error, B: myopic progression rate, and C: myopic progression rate/ethnic background. Progressing myopes showed a greater hyperopic TA shift compared with stable myopes. Asian progressing myopes showed a statistically significant greater hyperopic TA shift than every other group. Asterisks represent statistically significant differences at * $P < 0.05$, ** $P < 0.01$, one-way analysis of variance. The number in brackets represents the number of subjects in each group. Error bars show one standard deviation.
Table 2.3. Number of subjects who demonstrated myopic vs hyperopic changes in TA following timolol instillation.

<table>
<thead>
<tr>
<th>Timolol-induced change in TA</th>
<th>Non-myopes</th>
<th>EOMs</th>
<th>LOMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopic shift</td>
<td>3/15</td>
<td>5/15</td>
<td>6/15</td>
</tr>
<tr>
<td>Hyperopic shift</td>
<td>8/15</td>
<td>8/15</td>
<td>5/15</td>
</tr>
<tr>
<td>No shift</td>
<td>4/15</td>
<td>2/15</td>
<td>4/15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timolol-induced change in TA</th>
<th>Non-myopes</th>
<th>Stable myopes</th>
<th>Progressing myopes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopic shift</td>
<td>3/15</td>
<td>11/16 (68.75%)</td>
<td>2/14</td>
</tr>
<tr>
<td>Hyperopic shift</td>
<td>8/15</td>
<td>4/16</td>
<td>9/14 (64%)</td>
</tr>
<tr>
<td>No shift</td>
<td>4/15</td>
<td>1/16</td>
<td>3/14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timolol-induced change in TA</th>
<th>Non-myopes</th>
<th>Caucasian stable myopes</th>
<th>Caucasian progressing myopes</th>
<th>Asian stable myopes</th>
<th>Asian progressing myopes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopic shift</td>
<td>3/15</td>
<td>8/12 (67%)</td>
<td>1/7</td>
<td>3/4 (75%)</td>
<td>0/7</td>
</tr>
<tr>
<td>Hyperopic shift</td>
<td>8/15</td>
<td>2/12</td>
<td>3/7</td>
<td>1/4</td>
<td>7/7 (100%)</td>
</tr>
<tr>
<td>No shift</td>
<td>4/15</td>
<td>2/12</td>
<td>3/7</td>
<td>0/4</td>
<td>0/7</td>
</tr>
</tbody>
</table>
The hyperopic shift in TA induced by timolol was directly proportional to the base-line level of TA, i.e. the higher the base-line TA level, the greater the hyperopic shift (Figure 2.8). This linear relationship supports the notion that sympathetic inputs are involved in determining the variations in TA levels, although the direction of shift was opposite to that previously reported (e.g. myopic direction)(Gilmartin and Hogan, 1985b). In addition, timolol instillation eliminated the previously observed differences in the base-line TA measurements between stable and progressing myopes ($F_{2, 42} = 2.292, P = 0.114$) and between groups of different myopia progression and ethnic backgrounds ($F_{4, 40} = 1.140, P = 0.239$).

![Figure 2.8. A scattergram of the relationship between base-line TA and the change in TA induced by the instillation of timolol. The plot showed a negative linear relationship between base-line TA and the hyperopic shift in TA, i.e. the higher the base-line TA, the greater the hyperopic shift induced by timolol application.](image-url)
2.3.5. Effect of timolol on IOP, pupil size and amplitude of accommodation

Paired t-tests with regard to the ocular hypotensive effects of timolol and betaxolol showed a trend towards lower IOPs (Table 2.4). However, betaxolol S HCL 0.25% failed to achieve the same ocular hypotensive effects as timolol 0.5%. The change in TA did not appear to have any correlation with the change in IOP which occurred concurrently with timolol instillation ($r = -0.00021$, $P = 0.999$). The change in TA induced by timolol was not related to the iris colour of the subject ($F_{4,40} = 1.067$, $P = 0.385$). No subjects reported any blurring or fluctuating vision with the instillation of timolol. Pupil diameter and amplitudes of accommodation were not significantly affected by timolol (Table 2.4). The slight reduction in pupil diameter induced by timolol and betaxolol may suggest the presence of inhibitory β-receptors on the sphincter pupillae (van Alphen, 1976).

| Table 2.4. Mean change in IOP, pupil diameter, and amplitude of accommodation following betaxolol and timolol instillation. |
|-------------------------------------------------|--------------------|--------------------|
| **betaxolol** | **timolol** | **Paired t-test** |
| **trial** | **trial** | |
| Change in IOP (mm Hg) | 2.1±1.2 | 4.3±1.9 | $t_{44} = 6.753$, $P < 0.001$ |
| Change in pupil diameter (mm) | -0.19±0.49 | -0.30±0.61 | $t_{44} = 0.904$, $P = 0.371$ |
| Change in amplitude of accommodation (D) | 0.10±0.37 | 0.04±0.37 | $t_{44} = 0.783$, $P = 0.438$ |
2.3.6. Accommodative adaptation effects and regression following nearwork

*Non-normalised accommodation data*

A split-plot ANOVA (factors: drug, time, subject group) was carried out on non-normalised accommodation data (i.e. without taking pre-task TA as the reference level). There were no statistically significant differences in the accommodation data following nearwork between refractive error groups ($F_{2, 42} = 0.53, P = 0.593$). There was a clear delineation of accommodation regression patterns when myopic subjects were re-categorised according to their myopic progression rate ($F_{2, 42} = 6.364, P = 0.004$). Stable myopes achieved a faster decay of the accommodative measures and reached a lower endpoint than the non-myopes and progressing myopes (Figures 2.9A). There were also differences in the non-normalised accommodation measures between groups with different myopia progression and ethnic background ($F_{4, 40} = 4.451, P = 0.005$; Figure 2.10A). Asian progressing myopes had the highest accommodation endpoint than all other groups whereas the Caucasian stable myopes had the lowest final level (Bonferroni, $P = 0.002$).

2.3.7. Accommodative adaptation – standard analysis

To investigate the regression of adaptation effects following the near task, the standard analysis involves subtracting the respective individual pre-task TA level from each of the 45 data points (i.e. post-task accommodation measure – pre-task TA level). The magnitude of accommodative adaptation was calculated by averaging the 45 data points. LOMs (0.65±1.06 D) had greater adaptation levels than the non-myopes (0.23±0.52 D) and EOMs (0.14±1.19 D) but the difference was not significantly different ($F_{2, 42} = 1.184, P = 0.316$). No differences were observed between non-myopes (0.23±0.53 D), stable myopes (0.33±0.45 D) and progressing
myopes (0.47±1.63 D)(F_2, 42 = 0.214, \( P = 0.808 \)) or in groups of different myopic progression rate/ethnic background (F_4, 40 = 0.254, \( P = 0.906 \)). After taking the pre-task TA levels into account, differences in the regression patterns of accommodation shifts following nearwork diminished. Thus it could be concluded that differences in the regression patterns of the non-normalised accommodative measures following nearwork were due to differences in the pre-task TA levels. Figures 2.9A, 2.10A illustrate the regression patterns of non-normalised accommodation data when pre-task TA levels were not taken into account compared to normalised TA shifts in Figures 2.9B, 2.10B.

2.3.8. Accommodative adaptation – standard analysis (timolol vs betaxolol)

As expected, variation in accommodation over time was significant for both drug conditions (F = 65.970, df = 45, \( P < 0.001 \)). Polynomial contrasts indicated that the regression pattern of accommodation following nearwork was of a higher order polynomial. The interaction effect between drugs and time was statistically significant (F = 1.726, df = 45, \( P < 0.001 \))(i.e. effect of the drug on accommodation over time was significantly different). No significant three-way interaction effects between drug, time and subject groups were found. The subject’s iris colour had no effect in the drug response to either timolol (F_{4, 40} = 0.611, \( P = 0.657 \)) or betaxolol (F_{4, 40} = 0.978, \( P = 0.43 \)).
Figure 2.9. A: Regression patterns of non-normalised accommodation measures following nearwork of non-myopes, stable and progressing myopes. Base-line pre-task TA levels were not subtracted from the accommodation measures. There was a clear delineation of accommodation responses between the three groups. B: Regression patterns of accommodative adaptation effects (normalised TA shifts) following nearwork. In this instance, base-line pre-task TA levels were taken into account. No statistically significant differences in the regression patterns between groups were then observed. Error bars represent one standard error of the mean. Standard errors for stable myopes and non-myopes were approximately of the same order and have been omitted for clarity.
Figure 2.10. A: Regression of non-normalised accommodation measures following nearwork in groups with different myopic progression rate and ethnic background. Base-line pre-task TA levels were not subtracted from the accommodation measures. Regression patterns between Caucasian stable myopes and Asian progressing myopes were distinctly different. B: Regression patterns of accommodative adaptation effects (normalised TA shifts) were similar between the groups. Base-line pre-task TA levels were taken into account in this instance. Differences in the regression patterns of non-normalised accommodative measures following nearwork were therefore due to differences in the pre-task TA levels. Errors bars have been omitted for clarity.
Standard analysis: comparison of accommodative adaptation of timolol vs betaxolol trials

While nearwork-induced accommodative adaptation effects for the control trial of different refractive error groups were similar, β-antagonism with timolol produced different patterns ($F_{2,42} = 6.674, P = 0.003; \text{Figure } 2.11$). Under this condition, non-myopes failed to demonstrate enhanced magnitude and duration of accommodative adaptation that is commonly observed with timolol (Gilmartin and Bullimore, 1987, Gilmartin and Winfield, 1995, Winn et al., 2002) and showed a small hyperopic shift in TA compared with EOMs and LOMs ($\text{Bonferroni, } P = 0.024$). EOMs had some increased adaptation effects with timolol while there were no differences observed with LOMs. Differences in the effect of timolol on regression patterns of accommodative adaptation in groups with different myopic progression rate were observed ($F_{2,42} = 7.651, P = 0.001; \text{Figure } 2.12$). Stable myopes exhibited fast regression patterns for both control and timolol trials. Unlike the stable myopes, accommodation responses in progressing myopes showed more variability and the regression pattern with timolol was retarded in the first 40s of the post-task monitoring period.

Significant differences in accommodative adaptation for both drug conditions were also observed between groups with different myopic progression rate and ethnic background ($F_{4,40} = 5.291, P = 0.002; \text{Figure } 2.13$). Asian stable and progressing myopes exhibited considerable individual variability of the accommodation responses and were susceptible to the blocking effect of timolol. Caucasian progressing myopes also had variable accommodation responses and similar regression profiles to the Asian progressing myopes. By contrast, there was minimal variability of the accommodation responses in the Caucasian stable myopes and timolol did not produce any differences in the pattern of regression compared to the control trial.
Figure 2.11. Accommodation regression patterns for timolol and betaxolol trials of
A: non-myopes, B: EOMs, C: LOMs. LOMs had greater adaptation effects than non-
myopes and EOMs in the betaxolol trial. There were no significant differences in the
response to timolol application between the groups.
Figure 2.12. Accommodation regression patterns for timolol and betaxolol trials of A: non-myopes, B: stable myopes, and C: progressing myopes. Progressing myopes demonstrated greater adaptation effects and response variability compared to the stable myopic counterparts.
**β-Adrenergic Antagonism of Accommodation in Myopia**

(Figure 2.13 continues over page)
Figure 2.13. Accommodation regression patterns for timolol and betaxolol trials of 
A: non-myopes, B: Caucasian stable myopes, C: Caucasian progressing myopes, D: 
Asian stable myopes, and E: Asian progressing myopes. Non-myopes and Caucasian 
stable myopes had fast decay of the adaptation effects and similar responses under 
both drug conditions. Accommodation responses of Caucasian and Asian progressing 
myopes were more variable compared to those of non-myopes and stable myopes. 
Asian stable myopes had small adaptation effects but were most susceptible to the 
blocking effect of timolol.
2.3.9. Accommodative adaptation - regression quotient (%) analysis

Consistent with previous reports, regression patterns of accommodative adaptation effects presented marked inter-subject variations (Ebenholtz, 1983, Gilmartin and Bullimore, 1987). Variation in accommodation over time was significant (F = 33.37, df = 45, P < 0.001). Polynomial contrasts indicated that the regression pattern of nearwork-induced accommodative adaptation was highly non-linear and appeared to be of a higher order polynomial (P < 0.001 for linear, quadratic, cubic and 4 -13th order polynomials).

2.3.10. Accommodative adaptation - regression analysis (timolol vs betaxolol)

Using the regression quotient (%) analysis (Gilmartin et al., 2002), LOMs had the greatest amount of accommodative adaptation with a regression quotient of 16.4±10.2 % compared with the EOMs (with 13.0±10.7 % of non-dissipated adaptation) and non-myopes (with 10.5±8.1 % of non-dissipated adaptation). The difference in percentage of regression between the groups was not statistically significant (F2, 42 = 0.483, P = 0.62; Figure 2.14). Timolol had no significant effects on accommodative adaptation, i.e. regression patterns for both timolol and control trials of non-myopes, EOMs and LOMs were similar (F2, 42 = 1.518, P = 0.231; Figure 2.14).

Progressing myopes showed more accommodative adaptation effects which decayed slowly towards the base-line levels (21.1±11.0 % of adaptation effects remained non-dissipated) compared to the non-myopes (10.5±8.1 % of adaptation effects non-dissipated) and stable myopes (9.1±10.0 % of adaptation effects non-dissipated) in the control trial (F2, 42 = 2.472, P = 0.09; Figure 2.15). Differences in regression patterns of non-myopes, stable myopes and progressing myopes in timolol and control trials approached statistical significance (F2, 42 = 3.119, P = 0.055). The
largest difference in the regression profiles between betaxolol and timolol trials was between 34 to 64 second of the post-task monitoring period for the progressing myopes. Non-myopes and stable myopes achieved a high percentage of accommodative regression under both drug conditions.

Statistically significant differences in the percentage of regression in groups with different myopic progression rate and ethnic background were also found ($F_{4, 40} = 2.709, P = 0.044$). Regression patterns for the control trial of non-myopes, Caucasian stable myopes and progressing myopes overlay each other (with only ~10 % non-dissipated adaptation effects) whereas myopes with Asian ethnic background showed distinctively different patterns (Figure 2.16). Asian progressing myopes exhibited the poorest regression pattern in the control trial (29.5±12.0 % of non-dissipated adaptation effects) and timolol reduced the amount of adaptation following nearwork. In contrast, Asian stable myopes for the control trial showed some counter-adaptive effects and timolol produced enhanced adaptation, suggesting the blocking effect of timolol was taking place.
Figure 2.14. Accommodative regression patterns in timolol and betaxolol trials of A: non-myopes, B: EOMs, C: LOMs. LOMs had greater accommodative adaptation effects than the non-myopes and EOMs in the control trial. Timolol did not produce any significant differences in the regression profiles.
Figure 2.15. Accommodative regression patterns in timolol and betaxolol trials of A: non-myopes, B: stable myopes, and C: progressing myopes. Progressing myopes demonstrated greater accommodative adaptation effects compared to the stable myopic counterparts. Timolol produced a small increase in adaptation in the stable myopes.
β-Adrenergic Antagonism of Accommodation in Myopia

(Figure 2.16 continues over page)
Figure 2.16. Percentage regression quotients for timolol and betaxolol trials of A: non-myopes, B: Caucasian stable myopes, C: Caucasian progressing myopes, D: Asian stable myopes, and E: Asian progressing myopes. Non-myopes and Caucasian stable myopes had fast decay of adaptation effects and similar responses under both drug conditions. Accommodation responses of Caucasian and Asian progressing myopes were more variable and timolol produced different regression profiles compared to the control trial. Asian stable myopes on average had minimal adaptation effects for the control trial but were most susceptible to the blocking effect of timolol.
2.3.11. Relationship between base-line TA and accommodative adaptation

Based on the base-line TA level, subjects were divided into two groups: one group comprised 23 subjects with pre-task base-line TA levels > 0.6 D and the other comprised 22 subjects with base-line TA levels ≤ 0.6 D. TA level of 0.6 D was chosen as it was the median for the 45 subjects. Accommodative adaptation for the group with lower base-line TA levels was significantly greater compared to the high TA group in the regression quotient (%) analysis (F\(_1, 43\) = 5.367, \(P = 0.025\); Figure 2.17B) and marginally significant in the standard analysis (F\(_1, 43\) = 3.966, \(P = 0.053\); Figure 2.17A). For the group with higher base-line TA, timolol produced increased accommodative adaptation, suggesting the presence of sympathetic inhibition with timolol (Figure 2.18A). The regression patterns for the lower pre-task TA group showed no significant differences between timolol and control betaxolol trials (Figure 2.18B). However, differences in the response profiles to \(\beta\)-adrenergic antagonism between the two groups did not reach a statistically significant level. (F\(_1, 43\) = 2.410, \(P = 0.128\)).
Figure 2.17. Comparison of nearwork-induced accommodative adaptations of A: standard analysis, and B: regression quotient (%) analysis when subjects were separated based on their pre-task base-line TA levels. One group comprised subjects with base-line pre-task TA levels greater than 0.60 D and another group with base-line pre-task TA levels less than 0.60 D. The lower base-line TA group was more susceptible to accommodative adaptation effects in both analysis methods. Accommodative adaptation returned towards base-line level more quickly in the group with higher pre-task TA level.
Figure 2.18. Accommodative regression patterns in timolol and betaxolol trials of A: subjects with base-line TA > 0.60 D, B: subjects with base-line TA ≤ 0.60 D. The group with higher base-line TA was more susceptible to the blocking effect of timolol in the first 40s of the post-task period. However, there were no statistically significant differences in the response profiles to β-adrenergic antagonism between the two groups.
2.4. Discussion

2.4.1. TA - refractive error, myopia progression and ethnic background

The relationship between TA and refractive error has been investigated extensively, and the most consistent finding is that myopes (particularly LOMs) have lower TA levels than emmetropes by approximately 0.4 D (see Table 1.4). EOMs and LOMs in our study had lower levels of TA than non-myopes but the difference was not statistically significant. When myopic subjects were divided on the basis of their myopic progression rate rather than the age of myopia onset, larger differences were observed. Progressing myopes exhibited higher levels of TA than non-myopic individuals, which is opposite to the lower TA reported by Adams and McBrien (1993) and Owens et al. (1989). Stable myopes did have lower levels of TA, which is consistent with a more recent finding by Vera-Diaz et al. (2000).

Ethnic background was found to be an important factor for classifying myopic individuals. Progressing myopes with an Asian background had the highest TA levels and they were substantially higher than that of non-myopes, Caucasian myopes (both stable and progressing), as well as Asian stable myopes. The astoundingly high prevalence of myopia in Asian countries have been attributed to the excessive nearwork demand (Tan et al., 2000, Wu et al., 2001, Fan et al., 2002, Saw et al., 2002c) and to our knowledge, no studies have attempted to investigate whether differences in the accommodation system exist in myopic individuals with different ethnic background. As variation in the TA data is interpreted as reflecting differences in the autonomic input to the ciliary muscle (Gilmartin et al., 1984, Gilmartin and Hogan, 1985b, Gilmartin and Hogan, 1985c, Gilmartin, 1986), our results may suggest differences in the underlying autonomic input that controls TA in myopes with different ethnicity and they may be part of racial or genetic susceptibility to myopia development.
2.4.2. Accommodative adaptation - refractive error, myopia progression and ethnic background

Enhanced susceptibility to nearwork-induced accommodative adaptation has been suggested as a possible precursor to myopia development or progression (see section 1.3.1). If this is the case, it would be predicted that myopes would show larger accommodative adaptation effects after nearwork than non-myopes; progressing myopes being more likely to undergo hysteresis effects compared to those whose myopia is stable. In this study, LOMs (0.65±1.06 D; 16.4±10.2 % regression quotient) and EOMs (0.14±1.19 D; 13±10.7 % regression quotient) did not show statistically greater accommodative adaptation effects than non-myopes (0.23±0.53 D; 10.5±8.1 % regression quotient). Thus classifying myopes based on age of myopia onset may not be the best way to differentiate susceptibility to nearwork-induced accommodative adaptation as some have found LOMs to show greater effects (McBrien and Millodot, 1988, Woung et al., 1993) while others have not (Morse and Smith, 1993, Jiang and White, 1999).

However, consistent with our hypothesis, progressing myopes showed a marginally significantly greater adaptation effects which decayed slowly towards the base-line level (0.47±0.63 D; 21.1±11.0 % regression quotient) while non-myopes (0.23±0.53 D; 10.5±8.1 % regression quotient) and stable myopes (0.33±0.45 D; 9.1±10.0 % regression quotient) had minimal accommodative adaptation that dissipated quickly. Also, in support of our hypothesis, Caucasian progressing myopes (0.66±0.69 D; 12.8±12.3 %) and Asian progressing myopes (0.27±2.27 D; 29.5±12.0 % regression quotient) exhibited large adaptation effects while Caucasian stable myopes (0.38±0.48 D; 11.7±8.1 % regression quotient) had similar accommodative regression profiles compared to non-myopes. Asian stable myopes (0.20±0.36 D; 1.6±17.6 % regression quotient) demonstrated a counter-adaptive change in TA. Counter-adaptation has been observed previously by McBrien et al. (1988) in a group
of hyperopes, who suggested that this was indicative of strong sympathetic inputs or facility to the ciliary muscle.

Both methods of analysis of accommodative adaptation (i.e. standard analysis vs. regression quotient (%) analysis) produced similar results, except in the case of Asian progressing myopes. Using the regression quotient (%) analysis (Gilmartin et al., 2002), Asian progressing myopes demonstrated significant adaptation effects (29.5 % regression quotient) and this appears to be greater than the 0.27 D of adaptation effects calculated using the standard analysis with pre-task TA as the reference level. This discrepancy may be due to the high pre-task TA level of the Asian progressing myopes or the slight lead of accommodation observed during the near task. Standard analysis may be an adequate method for data analysis as TA is a relatively stable accommodative measure (Miller, 1978, Rosenfield et al., 1993) while the regression quotient (%) method (Gilmartin and Winfield, 1995) may be preferred as it takes into account the lag or lead of accommodation during near and far tasks respectively and extraneous factors that may influence the stability and the final resting level of the accommodation system. The following discussion was based on the regression quotient (%) data analysis method.

2.4.3. Effect of β-antagonism on accommodation

The effect of β-antagonism with timolol on regression profiles of accommodative adaptation of non-myopes, EOMs and LOMs was similar and timolol failed to induce any enhanced accommodative adaptation effects in any of the refractive error groups. This is consistent with the earlier study by Gilmartin (1995) that a sympathetic deficit is not associated with the development of LOM. A recent study (Gilmartin et al., 2002) further showed that access to sympathetic inhibition is not confined to a particular refractive error group and may be restricted to only about 30-40% of individuals. Myopic progression rate however appeared to be an important factor in
determining the effect of timolol. Timolol appeared to induce sympathetic blockade and produce myopic shifts in TA in the stable myopes, but a hyperopic shift in the progressing myopes and emmetropes. This hyperopic shift in accommodation is opposite to the predicted effect of timolol and has been suggested to be due to a vascular change in the ciliary body induced by timolol (Gilmartin et al., 1984).

When myopia progression rate and ethnic background were both taken into account, significant differences in the effect of timolol were also found. Timolol produced the greatest sympathetic blocking effect in Asian stable myopes who showed rapid and full regression of adaptation effects for the control trial and increased adaptation with timolol application. This suggests that adequate sympathetic activity was present in this particular group for the blocking effect of timolol to take place. Further evidence for the inhibitory sympathetic facility during nearwork could also be deduced from the rapid regression pattern in the control trial. On the contrary, Asian progressing myopes exhibited significant accommodative adaptation and the poorest regression pattern, with no evidence of full decay towards the base-line level and a hyperopic shift in TA with timolol application. Exacerbation of myopia may be mediated by this enhanced susceptibility of accommodative adaptation effects following nearwork, resulting possibly from a deficit in the sympathetic input to accommodation.

2.4.4. Possible autonomic imbalances in myopia

What do our results tell us about the autonomic control of accommodation in myopes? Based on the theory connecting autonomic inputs and accommodation (Gilmartin et al., 1984, Gilmartin and Hogan, 1985b), TA is described as the position reflecting relative contributions of the parasympathetic and sympathetic inputs to the ciliary muscle. The degree of β-antagonism with timolol may also be used to determine the role of sympathetic input in accommodation and it is assumed that
timolol had induced maximal blocking effect of the ciliary muscle associated with \( \beta \)-receptors.

Based on low TA levels and the response to \( \beta \)-antagonism with timolol, we propose that stable myopes may have a reduced parasympathetic tonus but a more robust sympathetic input to the ciliary muscle (Table 2.5). A large number of stable myopes (eg.11/16) were susceptible to the blocking effect of timolol presumably due to the adequate amount of sympathetic input that could be inhibited. Fast regression to base-line from small nearwork-induced accommodative adaptation also support the proposal of adequate sympathetic activity. In contrast, progressing myopes had higher TA levels and were more susceptible to nearwork-induced accommodative adaptation effects. This may suggest adequate parasympathetic input yet a deficit in the underlying sympathetic facility (Table 2.5). It is interesting to speculate as to whether this reduced sympathetic facility is an environmental or genetic trait.

Table 2.5. Main findings and indicated autonomic imbalance model of stable and progressing myopia. This is based on the assumption of normal autonomic inputs to accommodation in non-myopes.

<table>
<thead>
<tr>
<th>Main findings</th>
<th>Stable myopia</th>
<th>Progressing myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low base-line TA</td>
<td>Myopic shift in TA with timolol</td>
<td>Hyperopic shift in TA with timolol</td>
</tr>
<tr>
<td>Minimal adaptation effects</td>
<td>Greater adaptation effects</td>
<td></td>
</tr>
<tr>
<td>Fast regression profile</td>
<td>Retarded regression profile</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible autonomic characteristics</th>
<th>Stable myopia</th>
<th>Progressing myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic dominance or autonomic balance</td>
<td></td>
<td>Parasympathetic dominance and relative sympathetic deficit</td>
</tr>
</tbody>
</table>
The most substantial difference in terms of TA levels, nearwork-induced accommodative adaptation and response profiles to β-antagonism with timolol was observed between Caucasian stable myopes and Asian progressing myopes. The suggested autonomic imbalance model in stable and progressing myopes (Table 2.5) could also represent Caucasian stable myopes and Asian progressing myopes respectively. Asian stable myopes in comparison may have the strongest sympathetic facility, based on the findings of counter-adaptation and the enhanced sympathetic blocking effect of timolol. Table 2.6 shows the suggested autonomic imbalance model in myopes with different ethnic background. Non-myopes may have a relatively balanced autonomic innervation, based on the findings of normal TA values and fast regression patterns of the minimal adaptation effects following nearwork. One could argue that as the majority of non-myopic subjects demonstrated small but hyperopic shifts in TA with timolol, it may indicate a deficit in the sympathetic system in these subjects. This is conceivable as these non-myopes may have undergone a myopic shift in their refraction (eg. from hyperopia) over the past years or they may be subjects who are more susceptible to becoming myopic in the future. This assumption is difficult to ascertain, as refraction progression rates were not obtained for these non-myopes.
**Table 2.6.** Main findings and indicated autonomic imbalance model of stable and progressing myopia for individuals with Asian or Caucasian backgrounds. This is based on the assumption of normal autonomic input in non-myopes.

<table>
<thead>
<tr>
<th></th>
<th>Caucasian stable myopia</th>
<th>Asian stable myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main findings</strong></td>
<td>Similar to Emm</td>
<td>Similar to Emm</td>
</tr>
<tr>
<td></td>
<td>Small myopic shift in TA with timolol</td>
<td>Small myopic shift in TA with timolol</td>
</tr>
<tr>
<td></td>
<td>Minimal adaptation effects</td>
<td>Counter-adaptation effects</td>
</tr>
<tr>
<td></td>
<td>Fast regression profile</td>
<td>Fast regression profile</td>
</tr>
<tr>
<td><strong>Possible autonomic characteristics</strong></td>
<td>Sympathetic dominance or autonomic balance</td>
<td>Sympathetic dominance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Caucasian progressing myopia</th>
<th>Asian progressing myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main findings</strong></td>
<td>Similar to Emm</td>
<td>High base-line TA</td>
</tr>
<tr>
<td></td>
<td>Similar to Emm</td>
<td>Hyperopic shift in TA with timolol</td>
</tr>
<tr>
<td></td>
<td>Moderate adaptation effects</td>
<td>Significant adaptation effects</td>
</tr>
<tr>
<td></td>
<td>Retarded regression profile</td>
<td>Retarded regression profile</td>
</tr>
<tr>
<td><strong>Possible autonomic characteristics</strong></td>
<td>Parasympathetic dominance and relative sympathetic deficit</td>
<td>Parasympathetic dominance and relative sympathetic deficit</td>
</tr>
</tbody>
</table>

Abbreviations: Emm = emmetropes

2.4.5. Mechanism of autonomic imbalance in myopia

Differences in accommodation characteristics between non-myopes, stable and progressing myopes and between different ethnic groups provide some insight into the possible mechanisms linking autonomic imbalance and myopia development. Jiang (1995) proposed that high TA levels, instead of low TA levels, should be regarded as a risk factor for the development of myopia. High TA levels observed in the progressing myopes may be potentially detrimental, as the combined tonic, blur-driven and vergence-driven components of accommodation would tend to result in over-accommodation (Fisher et al., 1987b). This is in agreement with our findings.
that Asian progressing myopes, who had the highest levels of TA, had a tendency towards over-accommodation during the near task.

Increased susceptibility to nearwork-induced accommodative adaptation, resulting possibly from a sympathetic deficit, may be another predisposing factor for further myopia progression. Nearwork-induced hysteresis effects are related to blurred distance vision (Owens and Wolf-Kelly, 1987) and accumulation of such retinal defocus over time may stimulate axial elongation and myopia development. Jiang (1995) also suggested that prolonged accommodative hysteresis may result in higher TA levels, which may in turn lead to over-accommodation at near. Figure 2.19 represents a conceptual flowchart and shows how nearwork, high TA levels and accommodative hysteresis may lead to inaccurate accommodation response and result in myopia development. This hypothesis is more applicable to the Asian progressing myopes who showed high TA levels, a tendency towards over-accommodation at near, and greater susceptibility to accommodative adaptation.

Subjects with lower base-line TA levels ($\leq 0.60$ D) showed greater accommodative adaptation effects than those with higher TA levels ($> 0.60$ D) and this is consistent with previous studies (Gilmartin and Bullimore, 1987, Rosenfield and Gilmartin, 1989) which found that the ability of the sympathetic system to modify the post-task regression patterns was restricted to those having high TA levels. The inference is that if parasympathetic inputs are reduced (i.e. low TA levels), the ability to attenuate nearwork-induced accommodative adaptation effects derived from sympathetic activity is likely to be reduced too (Gilmartin and Bullimore, 1987). Figure 2.20 represents a conceptual flowchart and shows how nearwork, low TA levels and accommodative hysteresis may lead to inaccurate accommodation response and result in myopia progression. This is more applicable to the case of Caucasian progressing myopes given the findings of lower TA levels and moderate accommodative adaptation effects in this group.
Figure 2.19. A conceptual block diagram of the possible factors involved in myopia progression. This model is most applicable to the Asian progressing myopes. This model was based on the hypothesis of retinal defocus being one of the important cues in regulating eye growth and that defocus signals that a change in eye growth is required. In addition, the assumption that small amounts of chronic retinal defocus, regardless of the direction lead to myopia development and progression has been made.
Figure 2.20. A conceptual block diagram of the possible factors involved in myopia progression. This model is more applicable to Caucasian progressing myopes. As for Figure 2.19, this model was based on the assumption that retinal defocus is an important factor in human myopia development and that the change in defocus magnitude, rather than the sign of defocus, is the critical factor in terms of myopia development and progression.
2.4.6. Comparison to findings of previous research

The measured hyperopic shift in TA with timolol observed in emmetropes and progressing myopes was opposite to the predicted effect of timolol and there are several possible explanations for this finding. Firstly, the complexity of pharmacological studies should be appreciated. Sympathetic and parasympathetic forces are known to interact in a very complex manner and when neural activity in one of the two autonomic branches is pharmacologically blocked, the result may not reflect the expected behaviour of the remaining branch. In addition, potential cross-linkage interactions need to be taken into account as there is anatomical evidence to suggest that adrenergic and muscarinic nerve terminals often lie together (Rang and Dale, 1995). Such pre-synaptic inhibition at the parasympathetic terminal from the sympathetic terminal inhibited by timolol may be a possible mechanism by which timolol produced the hyperopic shift in TA.

Secondly, the hyperopic shift produced by timolol has been suggested to be vascular in nature as the accumulated transmitters of noradrenaline produce vasoconstriction of the ciliary body vasculature and reduce the volume of the ciliary body (Gilmartin et al., 1984). Tension of the zonular fibres would then increase, flattening the anterior central portion of the crystalline lens and producing a hyperopic shift. However, this timolol-induced vascular change is unlikely as α-receptor agents, such as phenylephrine, have minimal effect on TA (Garner et al., 1983, Zetterström, 1988, Otsuka et al., 1998).

A smaller dosage (20 µl) of monocular timolol application was used in our study compared to binocular instillation of 30 µl used in the study by Gilmartin et al. (1995). It is possible that the smaller dosage was less effective at causing receptor blockade in the presence of strong sympathetic innervation. However, a study we
conducted comparing the effect monocular and binocular instillation of timolol on TA found no significant differences (see Appendix 2). The control agent, betaxolol S HCL 0.25%, did not reduce IOP to the same extent as timolol, possibly due to the lower concentration or the suspension form used, and the possible interaction between IOP and accommodation may need to be considered when comparing results of the timolol and betaxolol trials.

Variation of the results may also be explained by the fact that some previous studies have only used emmetropic subjects (Gilmartin et al., 1984, Gilmartin and Bullimore, 1987, Zetterström, 1988, Gilmartin and Winn, 1989, Otsuka et al., 1998). As we found that myopia stability was an important determinant in accommodation responses, differentiating between stable or progressing myopes has enabled differences in accommodation responses to be observed. Using a larger sample size and classifying myopes according to stability of their myopia were the main reasons that differences in the accommodative responses and response profiles to timolol were found in our study. In addition, studies which have found timolol-induced myopic shifts in TA have used a Badal laser optometer, an instrument which has been found to stimulate more accommodation than an infrared optometer, due to the required judgement of the speckle motion direction (Post et al., 1985, Rosenfield, 1989, Rosenfield et al., 1993).
2.5. Conclusion

Myopes with different myopia progression rate and ethnic background were differentiated by their resting levels of accommodation, susceptibility to nearwork-induced adaptation and response profiles to $\beta$-antagonism with timolol. The findings suggest that stable myopes may have sympathetic dominance or a more balanced autonomic innervation while progressing myopes may have parasympathetic dominance and a relative deficit in the sympathetic input to the ciliary muscle. A genetic predisposition to alteration of this system may cause myopia to manifest and is of significance in terms of understanding the aetiology of myopia. Longitudinal studies investigating the potential relation between these accommodation response profiles and myopia development would be useful.
CHAPTER 3
EFFECT OF β-ADRENERGIC STIMULATION ON ACCOMMODATION – A FOLLOW-UP STUDY

This chapter describes a follow-up experiment to that described in Chapter 2 (Effect of β-adrenergic Antagonism on Accommodation in Different Refractive Error Groups) to further investigate the hypothesis that an imbalance in the autonomic control of the accommodation system may underlie myopia development and progression. The experiment was designed to provide longitudinal data on the relationship between accommodation responses, drug response profiles and refractive error change. The experiment was also designed to confirm or otherwise the conclusion of the experiment reached in Chapter 2. Data is presented on the effect of a β-adrenergic agonist, salbutamol, on tonic accommodation (TA) and nearwork-induced accommodative adaptation in a sub-set of subjects from the experiment of Chapter 2.

3.0. Summary

The function of the sympathetic inputs, due to their inhibitory nature, may be related to the attenuation of accommodative adaptation induced by sustained nearwork. If a deficit of the sympathetic inputs to the ciliary muscle was associated with myopia development and progression, it may be predicted that myopes would show greater nearwork-induced accommodative adaptation than non-myopes and that progressing myopes would show greater accommodative hysteresis than those whose myopia was stable. Slow regression of nearwork-induced accommodative adaptation observed in some subjects (mostly progressing myopes), may be restored to the rapid dissipation of accommodative adaptation of non-myopes or stable myopes by sympathetic stimulation. The purpose of the study was to i) reassess a sub-set of subjects to investigate the relationship between changes in accommodation and refractive error...
over time, and ii) to examine the effect of sympathetic stimulation on accommodation using salbutamol, a β-adrenergic agonist. There was a myopic shift in refraction on average for the 12 subjects available for follow-up. However, there was no significant change in base-line TA levels, or nearwork-induced accommodative adaptation between subjects who showed myopic shifts in the refraction compared to those whose refraction was stable. Salbutamol application appeared to have a greater effect in attenuating the magnitude and duration of accommodative adaptation of the myopes who were progressing. The rapid dissipation of accommodative adaptation effects of the stable myopes was not further enhanced by salbutamol application. Further investigation using a larger sample size would be useful in substantiating the role of sympathetic inputs in myopia progression.

3.1. Introduction

The concept of the sympathetic control of accommodation has largely come from anatomical evidence, demonstrating the presence of adrenoceptors in human ciliary muscle (Kern, 1971, van Alphen, 1976, Lograno and Reibaldi, 1986, Wax and Molinoff, 1987, Zetterström and Hahnenberger, 1988, Wikberg-Matsson et al., 2000). Early animal nerve stimulation studies and drug investigations into the autonomic control of accommodation indicate that the sympathetic input to the ciliary muscle mediates negative accommodation via the function of the inhibitory β2-adrenoceptors (Törnqvist, 1966, Hurwitz et al., 1972b, Hurwitz et al., 1972a). It is now well known that the sympathetic control of accommodation is mediated predominantly by inhibitory β2-adrenoceptors, while α1-adrenoceptors may also be responsible for controlling the accommodation response to a smaller extent ((Culhane et al., 1999); for reviews see Gilmartin (1986, 1998)). While the exact role of the sympathetic inputs in the control of accommodation is unclear, it appears to be
related to how a person adapts to sustained accommodation rather than to rapidly changing accommodative demands (Gilmartin et al., 2002).

The role of the sympathetic inputs to accommodation has been investigated extensively using β-adrenergic antagonists such as timolol (Gilmartin et al., 1984, Rosenfield and Gilmartin, 1987a, Gilmartin and Winfield, 1995, Gilmartin et al., 2002, Winn et al., 2002). However, few studies have used β-stimulation with adrenergic agonists to investigate the role of the sympathetic system in accommodation, as they are not readily available in eye drop form. Results of the few experiments using β-agonists show large variations of the effect of sympathetic stimulation on tonic accommodation (TA). Gilmartin et al. (1985b) found that 3% isoproterenol (a non-selective β-agonist) produced a significant hyperopic shift in TA while other studies (Zetterström, 1988, Otsuka et al., 1998) reported no significant effect (Table 3.1).

The varied results may relate to methodological differences in the assessment of TA, i.e. laser compared with infrared optometer, and the type of subjects used in the studies, i.e. emmetropes compared with corrected but visually normal ametropes. The isoproterenol induced hyperopic shift in TA produced by β-adrenoceptor stimulation reported by Gilmartin et al. (1985b) is consistent with the reported timolol induced myopic shifts in TA produced by β-adrenoceptor inhibition (Gilmartin et al., 1984). Data collected using these two agents support the idea that the contribution of the sympathetic input mediated via the β-adrenoceptors of the ciliary muscle determines TA levels. Selective α-adrenergic agents do not appear to play a role in determining the TA position but have a greater effect on the amplitude of accommodation (Garner et al., 1983, Zetterström, 1988, Culhane et al., 1999). However, Zetterström (1988) using a laser optometer for the assessment of TA reported that the instillation of phenylephrine produced a myopic shift of 0.9 D. It has been suggested that the laser optometer technique may affect the measurement of
TA due to the mental effort required to judge the direction of the laser speckle motion (Post et al., 1985, Bullimore et al., 1986, Rosenfield, 1989) and this may have contributed to the result.

The function of the sympathetic input to the ciliary muscle may be to attenuate any accommodative adaptation effects induced by sustained near tasks (Winn et al., 2002). Based on the hypothesis of a sympathetic deficit in myopia development and progression (see section 2.4 for detailed discussions), it may be predicted that myopes would show greater accommodative adaptation after nearwork than non-myopes and that progressing myopes would be more likely to show hysteresis effects than those whose myopia was stable. Instillation of a β-agonist should stimulate the sympathetic inputs to the ciliary muscle and enhance the dissipation of any accommodative adaptation effects induced by sustained nearwork. This would act to restore the regression pattern of accommodative adaptation of myopic individuals, i.e. the regression pattern of myopes would then be similar to those of non-myopes.

The purpose of this experiment was to compare the effect of β-stimulation with salbutamol on accommodation with that of β-antagonism using timolol. We hypothesized that salbutamol would have the opposite effect of timolol, and that it would have a greater effect on subjects who demonstrated greater accommodative adaptation effects, i.e. the progressing myopes, compared to those who showed minimal changes in accommodation following nearwork.
Table 3.1. A summary of the effects of sympathetic stimulation using sympathomimetics on TA

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>N</th>
<th>Age (yr)</th>
<th>Refractive error criteria</th>
<th>Instrument</th>
<th>Topical autonomic agents</th>
<th>Selectivity</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Gilmartin and Hogan, 1985b)</td>
<td>10</td>
<td>23</td>
<td>visually normal</td>
<td>Badal laser optometer</td>
<td>3% isoprenaline sulphate</td>
<td>non-selective</td>
<td>A statistically significant hyperopic shift of 0.47D – a constant shift across all TA levels</td>
</tr>
<tr>
<td>(Zetterström, 1988)</td>
<td>10</td>
<td>19-31</td>
<td>visually normal</td>
<td>Badal laser optometer</td>
<td>10% phenylephrine</td>
<td>α1</td>
<td>A myopic shift of 0.9±0.2 D in TA – effect possibly due to the mydriatic action of the drug</td>
</tr>
<tr>
<td>(Otsuka et al., 1998)</td>
<td>52</td>
<td>19-28</td>
<td>emmetropes</td>
<td>Infrared optometer</td>
<td>5% phenylephrine hydrochloride</td>
<td>α1</td>
<td>A non-significant myopic shift of 0.32 D in TA</td>
</tr>
<tr>
<td>(Garner et al., 1983)</td>
<td>3</td>
<td>N.A.</td>
<td>visually normal</td>
<td>Badal laser optometer</td>
<td>10% phenylephrine hydrochloride</td>
<td>α1</td>
<td>A non-significant myopic shift of 0.05 D in TA</td>
</tr>
<tr>
<td>(Rosenfield et al., 1990)</td>
<td>7</td>
<td>18-21</td>
<td>emmetropes</td>
<td>Infrared optometer</td>
<td>2.5% phenylephrine</td>
<td>α1</td>
<td>No significant change in TA</td>
</tr>
</tbody>
</table>
3.2. Methods

The following section describes the experimental protocol for measurements of the two accommodation responses. Tonic accommodation and nearwork-induced accommodative adaptation and its regression were measured in myopic and non-myopic adults, following topical instillations of salbutamol and control agent saline.

3.2.1. Subject details

Twelve (six females, six males) of the 45 subjects from Chapter 2 were used in this follow-up study. The mean period between the timolol and salbutamol measurements was 16.25 months (range 12-21 months). Based on non-cycloplegic subjective refraction results and age of myopia onset, subjects were divided into three groups, non-myopes, early-onset myopes (EOMs; age of myopia onset prior to 14 years) and late-onset myopes (LOMs; myopia onset after 15 years of age). Subjects with SERE (i.e. spherical component + half of the cylindrical component) ≥ −0.75 D were categorized as being myopes. Two non-myopes (mean SERE = −0.44±0.09 D), seven EOMs (mean SERE = −4.04±1.27 D) and three LOMs (mean SERE = −2.25±0.99 D) were available for follow-up. Myopia progression rate over the past 16 months was calculated using the subjective refraction results from Chapter 2. Myopes were considered to be progressing if their SERE had decreased by −0.50 D or more over the past two years.

Monocular visual acuities of the subjects were 6/6 or better using the Bailey-Lovie acuity chart (Bailey and Lovie, 1976) and all of the subjects were free of ocular disease or oculomotor imbalance. Subjects with greater than 0.50 D of cylindrical corrections, anisometropia of greater than 1.00 D and a history of current or past cardiac or respiratory conditions were excluded from participation. Subjects were also excluded if they had any of the following contraindications to salbutamol
instillation: diabetes, hypertension, hyperthyroidism, myocardial insufficiency, use of beta-blockers, steroids or diuretics (MIMS, 2002). All subjects were given a full explanation of the experimental procedures and informed consent was obtained. The study was conducted in accordance with the requirements of the Queensland University of Technology Human Research Ethics Committee.

3.2.2. Accommodation measurements

Tonic accommodation

A 3-minute period in the dark was used to allow accommodation to regress to a baseline tonic level. Darkroom accommodation readings (~30 readings) were taken for one minute and averaged. The tonic accommodation value was taken as the difference between the average of the darkroom readings and the initial baseline far reading (i.e. with the subjects looking at the far target).

Nearwork-induced accommodative adaptation effects and regression

Subjects were directed to fixate on the far target for a 3-minute period. They were asked to keep the letters as clear as possible at all times and to inform the examiner if this was not achievable (Stark and Atchison, 1994). They were also instructed to exert (for the near target), the same level of accommodative attention as that normally employed when reading a book. The level of accommodation exerted during the 3-minute task was assessed and recorded at 30-second intervals to assure accuracy and stability of the accommodative response. Six measurements were taken and the mean SERE was calculated.
Immediately after task completion, lights were extinguished and accommodation regression towards the base-line pre-task TA level was measured over a 90-second period at 2-second intervals (from time 240-330s with a total of 45 readings). A 5-minute break was given before repeating the procedure for the near target distance (see section 2.2 for more details and Figure 2.1 for the schematic representation of the accommodation task and measurement protocol).

3.2.3. Target details

The far target consisted of a single line of 6/9 high contrast letters (90%) on a Bailey-Lovie acuity chart. The near target (laser print N5) was equivalent to the far target in terms of angular letter size and contrast. The far and near target viewing distances were set at 0.2 D (4.75 m) and 4.0 D (0.25 m) respectively. The luminance of the task was controlled to give approximately equal luminance at each target distance (~320 cd/m²). Great care was taken to ensure that the optical axis of the autorefractor and the subject’s visual axis were coincident. The fixation target was positioned such that the measurement pattern image of the autorefractor was aligned with the centre of the target. Proper alignment was achieved when the pupil and the reflected corneal image were positioned inside the reticle marks.

3.2.4. Drug treatments

Salbutamol, a selective β₂-agonist, is usually administered systemically as an inhaler for the relief of bronchospasm (asthma, chronic bronchitis, emphysema)(MIMS, 2002). For this study, 3% salbutamol sulphate was prepared as 1 ml ophthalmic solutions (prepared by Dr. Bob Soszinski, Central Pharmacy, Royal Brisbane Hospital, QLD, Australia). A 3% concentration of isoprenaline sulfate, a non-selective β-agonist, was used in the study of Gilmartin and Hogan (1985b). The drug was applied topically to the right eye only using a precision micropipette, which
delivered 20 µl of drug. One drop of benoxinate HCL 0.4% (Allergan) was applied topically prior to salbutamol instillation to inhibit reflex lacrimation and increase corneal permeability (Bartlett and Jaanus, 2001). Eyelid closure and punctal occlusion were carried out for two minutes to minimize systemic absorption.

Contact lenses (Ciba Focus Night & Day) were fitted 15 minutes following drug instillation and the subjects were given 15 minutes to adapt to their soft contact lenses before measurements of accommodation commenced. The experimental procedure was run first for the saline control trial and repeated 30 minutes following the instillation of salbutamol. IOP was measured both before and after the instillation of salbutamol using a non-contact tonometer (American Optical, U. K.). Drug effects on amplitudes of accommodation using the push-up method and pupil sizes using a Rosenbaum pupillometer and a Burton lamp were also monitored.

3.2.5. Apparatus

Refractive errors were corrected with soft disposable contact lenses for the duration of the experimental trial. The use of contact lenses ensured that the accommodative demand for each subject was virtually identical at each task distance. Accommodation responses were measured using the open-field Shin-Nippon SRW-5000 autorefractor (Japan). All measurements were made on the right eye while the left eye was occluded with an eye patch. The accuracy and repeatability of this instrument has been found comparable with the Canon Autoref R-1 (Mallen et al., 2001). The autorefractor is objective and allows unrestricted viewing of targets at any distance through an infrared-reflecting mirror. Accommodation readings measured with the Shin-Nippon autorefractor have been found accurate and repeatable in both adults (Mallen et al., 2001) and children (Chat and Edwards, 2001). The autorefractor was used in a static mode and an interface was used to connect the printer port of the autorefractor to a computer so that accommodation
could be recorded successively at approximately 2-second intervals. A built-in visual
display unit was used to monitor the subject’s eye position during measurements.
Invalid autorefractor readings which are characterized by large cylindrical
components or error displays were disregarded. Sphere and cylinder powers were
recorded to an accuracy of 0.125 D with all powers being referred to the corneal
plane and the SERE was used.

3.2.6. Data analysis

Statistical analysis of the collected data was conducted using Statistical Packages for
Social Sciences (SPSS). None of the measures were significantly different from the
normal distribution (Kolmogorov-Smirnov, *P* > 0.05) and parametric tests were used.
Paired t-tests were used to compare the effect of salbutamol and saline applications
on TA, IOP, amplitude of accommodation and pupil size. Correlation tests were used
to establish if there were statistically significant relationships between variables such
as tonic accommodation and refractive error. One-way analysis of variance was used
to determine whether tonic accommodation levels were different among groups with
different refractive errors, myopia progression rate, and ethnic background. Repeated
measures analysis of variance (three factors: drug, time, and refractive error group)
was used to assess the effect of salbutamol on regression patterns of accommodative
adaptation. Due to the small sample size of subjects, the effect of myopia progression
and ethnic background could not be analysed statistically, instead subjects with
similar regression profiles and drug responses were grouped and descriptive analysis
utilised.
3.3. Results

3.3.1. Refraction change over 16 months

On average, subjects showed a refractive error change between the first (timolol, Chapter 2) and second (salbutamol, Chapter 3) measurement points (separated by a 16-month period). Mean refraction for all 12 subjects increased from $-2.88\pm1.82$ to $-2.99\pm1.76$ D and this change in refraction was statistically significant ($t_{11}=2.303, P = 0.042$). Five subjects (two non-myopes, two EOMs and one LOM) showed a myopic shift greater than $-0.25$ D and were grouped into ‘the Rx change group’ (mean refraction change $=-0.313$ D). The remaining seven subjects showed no change in refraction and were grouped into the ‘No Rx change group’. Table 3.2 presents the details of the 12 subjects divided into three groups based on refractive error and age of myopia onset.

Table 3.2. Characteristics of the 12 subjects separated into groups of different refractive error and age of onset of myopia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-myopes (2)</th>
<th>EOMs (7)</th>
<th>LOMs (3)</th>
<th>ANOVA/t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>18.9±0.5</td>
<td>21.6±2.5</td>
<td>21.4±0.4</td>
<td>F$_{2, 9} = 1.37, P = 0.302$</td>
</tr>
<tr>
<td>Age of myopia onset (years)</td>
<td>N.A.</td>
<td>12.6±1.1</td>
<td>16.7±2.1</td>
<td>t$_{8} = -4.147, P = 0.003$</td>
</tr>
<tr>
<td>Best sphere refraction (D) (Year 2000)</td>
<td>$-0.19\pm0.09$</td>
<td>$-3.95\pm1.29$</td>
<td>$-2.17\pm1.05$</td>
<td>F$_{2, 9} = 8.779, P = 0.008$</td>
</tr>
<tr>
<td>Best sphere refraction (D) (Year 2002)</td>
<td>$-0.44\pm0.09$</td>
<td>$-4.04\pm1.27$</td>
<td>$-2.25\pm0.99$</td>
<td>F$_{2, 9} = 8.598, P = 0.008$</td>
</tr>
<tr>
<td>Refraction change over 16 months (D)</td>
<td>$-0.25\pm0.18$</td>
<td>$-0.09\pm0.19$</td>
<td>$-0.08\pm0.14$</td>
<td>F$_{2, 9} = 0.702, P = 0.521$</td>
</tr>
</tbody>
</table>

N.A. = not applicable
3.3.2. TA change over 16 months

There was no significant change in base-line TA level over the 16 months period ($t_{11} = 0.721$, $P = 0.486$). Mean base-line TA for the 12 subjects was $0.78 \pm 0.82$ D in 2000 and $0.67 \pm 0.98$ D in 2002. Figure 3.1 illustrates the distribution of base-line TA levels for the 12 subjects at the two time points. Six subjects showed a decrease in base-line TA, and two subjects showed an increase while four subjects showed no change. Overall, there was no significant difference in base-line TA distribution over the 16-month period. There were no significant differences in base-line TA change over time between the group which showed no refraction change and those who showed a myopic shift in their refraction (Figure 3.2). The No Rx change group had higher base-line TA levels of $0.93 \pm 1.04$ D in year 2000 compared to the group which showed a myopic shift in refraction and the base-line TA decreased to $0.70 \pm 1.16$ D in year 2002 but the difference was not statistically significant. Similarly, the Rx change group had no significant changes in base-line TA levels over time ($0.57 \pm 0.33$ D to $0.63 \pm 0.78$ D)(Figure 3.2).

![Figure 3.1. The effect of the passage of time on the distribution of tonic accommodation for a group of 12 subjects. The mean base-line TA was $0.78 \pm 0.82$ D in year 2000 and $0.67 \pm 0.98$ D in year 2002 respectively. There were no significant differences in base-line TA distribution over the 16-month period.](image-url)
Figure 3.2. The base-line TA levels in year 2000 were similar between the group which showed no refraction changes compared to those whose refraction showed a myopic shift. There were no significant differences in base-line TA change over time between the Rx change group and the No Rx change group. Error bars show one standard deviation.

3.3.3. Nearwork-induced accommodative adaptation change over 16 months

Similarly, there was no significant change in nearwork-induced accommodative adaptation over the 16 months period ($t_{11} = -0.373$, $P = 0.716$). Mean accommodative adaptation for the 12 subjects was $0.29 \pm 0.68$ D in 2000 and $0.22 \pm 0.50$ D in 2002. Both of the non-myopes who showed myopic shifts in their refraction demonstrated a larger amount of nearwork-induced accommodative adaptation ($0.67 \pm 0.15$ D) compared to EOMs ($0.11 \pm 0.53$ D) and LOMs ($0.17 \pm 0.51$ D). However the difference was not statistically significant ($F_{2, 9} = 0.98$, $P = 0.412$). The Rx change group showed a greater magnitude of accommodative adaptation ($0.29 \pm 0.59$ D) compared to the group whose refraction was unchanged ($0.17 \pm 0.46$ D) but again the difference did not reach a statistically significant level ($t_{11} = -0.378$, $P = 0.713$). As with the results on TA, there was no significant change in the magnitude of adaptation over the 16-month period between the two groups ($t_{11} = -0.373$, $P = 0.716$; Figure 3.3)(See Appendix 7 for power analysis).
3.3.4. Effect of salbutamol

Salbutamol application did not have significant effects on TA \( (t_{11} = 0.422, P = 0.681) \) and accommodative adaptation \( (t_{11} = 1.625, P = 0.132) \)(Table 3.3). TA and accommodative adaptation were similar to those measured following application of this agent. Similarly, salbutamol application did not have significant effects on pupil size or the amplitude of accommodation. The only measurable effect of salbutamol was a significant reduction in IOP by 1.9 mmHg (Table 3.3). The reduction in IOP was possibly due to an increase in aqueous flow rate and uveoscleral outflow (Coakes and Siah, 1984). The reduction in IOP had a significant correlation with the base-line IOP, i.e. the higher the base-line IOP, the greater the decrease induced by salbutamol application (Figure 3.4).
Table 3.3. Accommodation responses, IOP, pupil diameter pre- and post-salbutamol instillation

<table>
<thead>
<tr>
<th>Salbutamol instillation</th>
<th>Pre-</th>
<th>Post-</th>
<th>Paired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic accommodation (D)</td>
<td>0.67±0.98</td>
<td>0.62±0.90</td>
<td>t₁₁ = 0.422, P = 0.681</td>
</tr>
<tr>
<td>Accommodative adaptation (D)</td>
<td>0.22±0.50</td>
<td>0.01±0.50</td>
<td>t₁₁ = 1.625, P = 0.132</td>
</tr>
<tr>
<td>Near accommodation response (D)</td>
<td>3.56±0.31</td>
<td>3.56±0.32</td>
<td>t₁₁ = –0.043, P = 0.996</td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>13.1±2.8</td>
<td>11.2±1.7</td>
<td>t₁₁ = 3.682, P = 0.004</td>
</tr>
<tr>
<td>Pupil diameter (mm)</td>
<td>4.11±0.63</td>
<td>4.08±0.47</td>
<td>t₁₁ = 2.602, P = 0.25</td>
</tr>
<tr>
<td>Amplitude of accommodation (D)</td>
<td>10.51±1.63</td>
<td>10.22±1.69</td>
<td>t₁₁ = 1.751, P = 0.108</td>
</tr>
</tbody>
</table>

Figure 3.4. The scattergram between base-line IOP and the reduction in IOP induced by salbutamol application. There was a significant negative relationship, i.e. the higher the base-line IOP, the greater the amount of IOP reduction induced by salbutamol. The average percentage of reduction in IOP was 14.5%.
3.3.5. Standard analysis: comparison of accommodative adaptation of salbutamol vs control trials

As we found previously (Chapter 2), the variation in accommodation over time was significant for both salbutamol and saline trials ($F = 13.378$, $df = 45$, $P < 0.001$). The interaction between drugs and time was not statistically significant ($F = 0.909$, $df = 45$, $P = 0.641$) and neither was the effect of salbutamol compared to the control agent (simple contrast, $F = 0.823$, $df = 1$, $P = 0.388$).

When subjects were grouped based on their refractive error and age of myopia onset, the regression profiles of accommodative adaptation of non-myopes, EOMs and LOMs following saline application were similar ($F_{2,9} = 1.018$, $P = 0.4$; Figure 3.5). While salbutamol appeared to have a greater effect on LOMs in stimulating the sympathetic input and minimizing nearwork-induced accommodative adaptation and even resulted in counter-adaptation from time 40-90 seconds, overall, the response profiles to salbutamol application were similar between the groups ($F_{2,9} = 2.392$, $P = 0.147$; Figure 3.5). There was no interaction between the effect of the drug and the refractive error group ($F = 0.011$, $df = 1$, $P = 0.920$) and no significant three-way interaction effects between drug, time and refractive error group were found ($F = 0.675$, $df = 45$, $P = 0.947$). Similarly, salbutamol application did not have a significant effect on the regression profiles of accommodative adaptation of subjects who showed a myopic shift in their refraction compared to those with a stable refraction ($F_{1,10} = 0.251$, $P = 0.627$; Figure 3.6).
Figure 3.5. Accommodation regression patterns for salbutamol and control trials of A: non-myopes, B: EOMs, C: LOMs. Salbutamol appeared to have a greater effect on LOMs, minimizing accommodative adaptation effects and even producing counter-adaptation from time 40-90 seconds. However, there were no statistically significant differences in response profiles to salbutamol between the refractive error groups.
Figure 3.6. Accommodation regression patterns for salbutamol and control trials of A: No Rx change group, B: Rx change group. There were no statistically significant differences in regression patterns of accommodative adaptation between subjects who showed a myopic shift in refraction compared to those whose refraction was stable. Response profiles to salbutamol application were also similar between the groups.
3.3.6. Regression quotient (%) analysis: comparison of accommodative adaptation of salbutamol vs control trials

Using the regression quotient (%) analysis (Gilmartin et al., 2002), the two non-myopes who showed myopic shifts in their refraction demonstrated a larger amount of nearwork-induced accommodative adaptation with a regression quotient of 26.7±5.6 %, compared with the EOMs (with 8.9±12.6 % of non-dissipated adaptation effects) and LOMs (with 13.4±4.0 % of non-dissipated adaptation effects). However, the difference in percentage of regression between the groups was not statistically significant (F_{2, 9} = 2.189, P = 0.168; Figure 3.7). Salbutamol application had no significant effects on accommodative adaptation, i.e. regression patterns for both salbutamol and control trials of non-myopes, EOMs and LOMs were similar (F_{2, 9} = 2.797, P = 0.114; Figure 3.7).

When the subjects were divided into the No Rx change group (12.4±10.3 %) and Rx change group (13.8±14.7 %), the regression profiles of accommodative adaptation of the control trial were similar (F_{1, 10} = 0.04, P = 0.846; Figure 3.8). Salbutamol application appeared to have a greater effect, i.e. attenuating the amount of nearwork-induced accommodative adaptation, on subjects who showed a myopic shift in their refraction than the No Rx change group. However, the difference in the response profiles to salbutamol between the groups was not statistically significant (F_{1, 10} = 0.088, P = 0.773; Figure 3.8).
Figure 3.7. Accommodative regression patterns in salbutamol and control trials of A: non-myopes, B: EOMs, C: LOMs. Non-myopes who showed myopic shifts in refraction over the past 16 months had greater accommodative adaptation effects than EOMs and LOMs in the control trial. Salbutamol did not produce any statistically significant differences in the regression profiles between the groups.
Figure 3.8. Accommodative regression patterns in salbutamol and control trials of A: No Rx change group, B: Rx change group. There were no statistically significant differences in regression patterns of accommodative adaptation between those who showed a myopic shift in refraction compared to those whose refraction was stable. Response profiles to salbutamol application were also similar between the groups.
3.3.7. Scenarios of possible autonomic imbalance

Subject numbers were too small to enable analysis based on refractive error, myopia progression rate and ethnic background. Subjects were grouped based on accommodative regression profiles and drug responses and there were three main scenarios of possible autonomic imbalance (Figures 3.9, 3.10, 3.11). The graphs included regression patterns of the timolol trials (year 2000) and salbutamol trials (year 2002). Saline and timolol trials (year 2000) were results of Chapter 2.

Accommodation profile 1: **Progressing myopia** (possible sympathetic deficit – susceptibility to sympathetic stimulation)

Progressing myope, TK, demonstrated moderate accommodative adaptation following nearwork for the saline control trials, which dissipated slowly, and this regression profile fits our hypothesis of a relative sympathetic deficit. Two other cases of progressing myopia (subjects NAC and TN) demonstrated a lesser degree of accommodative adaptation compared to subject TK. Accommodation responses of all three subjects were more variable compared with those of the stable myopes. Stimulation of the sympathetic system with salbutamol in all subjects resulted in a faster dissipation of adaptation, i.e. accommodative regressions of subjects TK and TN, reached baseline in less than 10 s while subject NAC had an accommodation endpoint ~2 D below the baseline TA level (counter-adaptation). Figure 3.9 illustrates the accommodative regression profiles of these subjects.
Figure 3.9. Regression patterns of the timolol trial (year 2000) and salbutamol trial (year 2002) of progressing myopes. Accommodation responses of all three subjects were variable. Stimulation of the sympathetic system with salbutamol in all subjects resulted in a faster dissipation of accommodative adaptation.
Accommodation profile 2: **Progressing → Stable myopia** (possible improvement of the sympathetic facility)

Subjects JC and AMP, both EOMs, were classified as progressing myopes for the timolol study described in Chapter 2. During that period, myopia of both subjects was progressing rapidly at a rate of –0.5 D/year and both demonstrated significant nearwork-induced accommodative adaptation. Timolol failed to induce any significant sympathetic blocking effect, possibly due to a relative sympathetic deficit to the ciliary muscle. However, myopia of these two subjects stabilised over the past 21 months and less nearwork-induced accommodative adaptation effects were demonstrated compared to the base-line saline regression pattern for the timolol study (year 2000). Salbutamol did not further enhance the rapid dissipation of the adaptation effects (Figure 3.10).

Accommodation profile 3: **Stable myopia** (Robust sympathetic input to the ciliary muscle – susceptibility to sympathetic blockage)

Subjects KH and AB (EOMs) both demonstrated minimal accommodative adaptation effects for the saline trials (both in year 2000 and 2002), suggestive of adequate sympathetic facility for relaxing accommodation following sustained nearwork. Salbutamol and control saline trials were similar in terms of the rapid regression patterns which resulted. Subject KH however had a more pronounced susceptibility to the sympathetic blocking effect of timolol compared to subject AB and demonstrated enhanced magnitude and duration of accommodative adaptation (Figure 3.11).
Figure 3.10. Regression patterns of the timolol trial (year 2000) and salbutamol trial (year 2002) of progressing myopes-turned-stable myopes. Less nearwork-induced adaptation effects were demonstrated once myopia stabilised. Salbutamol had no significant effects on the already rapid regression pattern of accommodative adaptation effects.
Figure 3.11. Regression patterns of the timolol trial (year 2000) and salbutamol trial (year 2002) of stable myopes. Both myopes demonstrated rapid dissipation of the minimal accommodative adaptation effects. Subject KH was more susceptible to timolol compared to subject AB.
3.4. Discussion

3.4.1. Changes in accommodation over time

The time frame between timolol and salbutamol studies provided an opportunity to study the accommodation system in a longitudinal fashion. Through this follow-up, our results suggest that changes in refraction are not related to changes in TA levels and nearwork-induced accommodative adaptation. Following subjects in a longitudinal fashion provided the opportunity to gather information on the concurrent change of refractive error and accommodation profile, and the possible imbalance of the autonomic inputs to the ciliary muscle. Due to the low subject availability, the effect of myopia progression rate and ethnic background could not be studied. A longitudinal study of a larger sample where proportionately more subjects show a rapid change in refraction may give further insight into the relationship between accommodation and refractive error change.

3.4.2. Sympathetic input

The descriptive analysis indicates that distinct differences in accommodation responses between stable and progressing myopes may be present. Myopes with a stable refraction demonstrated minimal nearwork-induced accommodative adaptation and a rapid, smooth pattern of regression while progressing myopes tended to have more fluctuations in their accommodation responses. It is not known whether the fluctuations are a result of instability of the accommodation system, or a poor integration of the parasympathetic and sympathetic inputs to the accommodation response. Myopia of two myopes who were progressing rapidly during the timolol experiment stabilized and they subsequently showed an improvement in their accommodation responses, i.e. less nearwork-induced adaptation was demonstrated, consistent with the stabilisation of their myopia. Susceptibility to nearwork-induced
accommodative adaptation may therefore be one of the features of progressing myopia and may be absent once myopia stabilises.

Consistent with our hypothesis, salbutamol application had a greater effect on accommodative adaptation of progressing myopes compared to stable myopes, i.e. salbutamol resulted in a faster dissipation of the adaptation effects of progressing myopes while it did not further enhance the rapid accommodative regression profile demonstrated by the stable myopes. Thus the effect of sympathetic stimulation with salbutamol application was only evident in the progressing myopes, whom we hypothesized may have a parasympathetic dominance and a relative sympathetic deficit type of autonomic imbalance. In some cases of progressing myopia, salbutamol not only dissipated the accommodative adaptation effects rapidly, but also produced a counter-adaptive decrease in TA, i.e. the accommodation endpoint was below the base-line pre-task level. Otsuka (1998) reported similar counter-adaptive changes in accommodation after the instillation of isoprenaline in a sample of 52 subjects and reasoned that stimulation of the sympathetic system with adrenergic agents may modify the parasympathetic activity at the ciliary muscle.

Recent work (Winn et al., 2002) has demonstrated that certain individuals have less sympathetic facility, and this may render them more susceptible to nearwork-induced accommodative adaptation and environmentally induced myopia. If accommodative adaptation and the associated retinal defocus trigger myopia development and progression, pharmacological control of myopia with the use of topical adrenergic agonists may be of benefit. However, this hypothesis needs to be tested with a longitudinal study.

We predicted that salbutamol would have an opposite effect on intraocular pressures (IOP) compared to timolol however salbutamol also produced a reduction in IOP. The most likely explanation for both salbutamol (β2-agonist) and timolol (non-
selective β-antagonist) both lowering the IOP is that there are multiple sites for the adrenergic drugs acting as ocular hypotensive agents. Adrenergic agonists (β₂) such as salbutamol reduce IOP by increasing trabecular and uveoscelral outflow whereas adrenergic antagonists such as timolol reduce IOP by decreasing aqueous formation (Hiett and Carlson, 1991).

3.5. Conclusion

Our results suggest that changes in refraction are not related to changes in TA levels and nearwork-induced accommodative adaptation. A longitudinal study of a larger sample where proportionately more subjects demonstrate significant myopia progression may further our knowledge of the relationship between accommodation characteristics and refractive error change. There were differences in the effect of salbutamol on accommodation responses between stable myopes and progressing myopes and this supports the hypothesis of differing sympathetic inputs to the ciliary muscle between stable and progressing myopia. These results suggest that stable myopes may have sympathetic dominance while progressing myopes may have parasympathetic dominance with a relative deficit in the sympathetic input to the ciliary muscle. The potential therapeutic benefits of sympathetic stimulation with adrenergic agonists as myopia control agents could be investigated with a longitudinal study.
CHAPTER 4
THE EFFECT OF β-ADRENERGIC ANTAGONISM
ON ACCOMMODATIVE ADAPTATION IN
HONG KONG CHINESE CHILDREN

Results from Chapter 2, which investigated the effect of β-adrenergic antagonism on accommodation in a young adult population, indicated that differences of accommodation responses may exist in myopes with different ethnic background (Caucasian vs Asians). This thus led us to explore further the role of accommodative adaptation in myopia development in school-aged Chinese children in Hong Kong where the prevalence of myopia is very high.

4.0. Summary

Nearwork-induced accommodative adaptation has been suggested as a possible risk factor for myopia development. Susceptibility of individuals to accommodative adaptation and the implications of this for myopia development have been studied extensively in young adult populations. There is a paucity of such information in children of school age, the age group most susceptible to the acquisition and progression of early-onset myopia.

The prevalence of myopia in Hong Kong children is particularly high, at 60% for the 7-12 age group (Edwards, 1999) and it is not known if this is due to the effects of nearwork. The purpose of this experiment was to investigate whether nearwork-induced accommodative adaptation may explain in part, the high prevalence of myopia in Hong Kong children and examines whether the sympathetic inputs to the ciliary muscle may be involved in accommodative adaptation, using timolol maleate
0.5%, an adrenergic antagonist. We predicted that timolol would produce increased accommodative adaptation in stable myopes, who presumably have normal sympathetic inputs to the ciliary muscle, but not in the progressing myopes. Tonic accommodation (TA) was measured in 30 children aged eight to 12 years, using the Shin-Nippon autorefractor, both before and after five minutes of video game playing. Measurements were repeated 30 minutes after timolol application.

Progressing myopic children demonstrated the largest amount of accommodative adaptation following the near task, while stable myopes showed counter-adaptive changes in their accommodation. Timolol increased the magnitude of adaptation in the stable myopes, but had little effect in the progressing myopes or emmetropes. The results suggested a possible deficit of sympathetic inputs to the ciliary muscle in progressing myopia.

4.1. Introduction

In the majority of studies on accommodation and myopia, Caucasian or Northern European subjects have predominated. As significant differences in the prevalence of myopia across ethnic groups exist, investigating specific ethnic groups in terms of their genetic predisposition to myopia or susceptibility to nearwork-induced myopia is important. How children’s eyes become myopic is a much debated public health issue in countries such as Hong Kong (Lam and Goh, 1991, Yap et al., 1993b, Edwards, 1999, Lam et al., 1999), Taiwan (Lin et al., 1998, Lin et al., 1999), Singapore (Tan et al., 2000, Zhang et al., 2000, Wu et al., 2001), and Japan (Matsumura and Hirai, 1999, Watanabe et al., 1999). Prevalence of myopia in Hong Kong is among one of the highest in the world and children develop myopia as early as six years of age (Lam et al., 1999). Ten percent of children are myopic at age seven years, 60% at age ten (Edwards, 1999), and the prevalence level increases to
70% at age of 16-17 (Lam and Goh, 1991, Lam et al., 1999). Goldschmidt (1998) has also reported myopia prevalence of 95% in a group of Hong Kong medical students he examined.

The relationship between nearwork and myopia has prevailed in the myopia literature; however, the link is still not well defined. The notion that excessive and sustained nearwork predisposes a child to myopia is supported by several studies that found increased nearwork is associated with increased risk of myopia development (Tan et al., 2000, Hepsen et al., 2001, Fan et al., 2002, Saw et al., 2002c) although some studies have only found a weak association between nearwork and myopia (Saw et al., 2000, Goldschmidt et al., 2001).

Several studies have demonstrated differences in accommodation parameters between myopic and non-myopic individuals (McBrien and Millodot, 1986b, Bullimore and Gilmartin, 1987a, McBrien and Millodot, 1988, Gilmartin and Bullimore, 1991, Woung et al., 1993). If we assume that myopia development in childhood is a complex adaptation to nearwork, then it may be possible to demonstrate changes in accommodation functions before changes in refractive error occur. The resting state of accommodation, referred to as tonic accommodation (TA), has attracted considerable interest in recent years as possible a risk factor for myopia development (Rosenfield et al., 1993). Similar to the trend observed for young adults, myopic children have lower TA levels compared with emmetropic or hyperopic children (Table 4.1) although it is unclear whether reduced TA causes myopia or occurs secondary to myopia development. Results of two longitudinal studies (Yap et al., 1998, Zadnik et al., 1999) in children support the interpretation of reduced TA as a consequence of myopia development, rather than a cause.
It has been demonstrated that the magnitude of TA may change transiently (usually shifting in the myopic direction) following a period of sustained nearwork. This apparent post-task shift in TA relative to the pre-task level has been described as nearwork-induced accommodative adaptation (Ebenholtz, 1983). There is limited information on accommodative adaptation as a function of refractive error in children. Owens et al. (1991) reported that emmetropic children were more susceptible to accommodative adaptation compared with emmetropic young adults, although Rosenfield et al. (1994a) disputed this. Myopic children tend to exhibit greater nearwork-induced accommodative adaptation effects compared to emmetropic children (Table 4.2). Gwiazda et al. (1995b) found that all children demonstrated accommodative adaptation after playing video games, with myopic children showing the largest myopic shift in TA compared to emmetropes and hyperopes. It was thus suggested that accommodative adaptation may be a possible risk factor for school-age myopia.

According to the theory connecting accommodation and autonomic balance of the parasympathetic and sympathetic inputs to the ciliary muscle (Toates, 1972), the resting state of accommodation is a consequence of variations in parasympathetic inputs (Gilmartin et al., 1984, Gilmartin and Hogan, 1985b, Gilmartin and Hogan, 1985a), with a smaller contribution from the sympathetic system (Gilmartin and Hogan, 1985c). Thus a low TA level may reflect a reduced parasympathetic input to the ciliary muscle, (McBrien and Millodot, 1987, Woung et al., 1998), or an overall decrease from both the parasympathetic and sympathetic components of autonomic control (Ong and Ciuffreda, 1997a, Woung et al., 1998).

The inhibitory nature of the sympathetic control of accommodation, mediated via $\beta_2$-adrenergic receptors, is of more relevance to accommodative adaptation, i.e. how an individual adapts to near tasks, and it has been speculated that an increased susceptibility to accommodative adaptation may be associated with a deficit in the
sympathetic input to the ciliary muscle (Gilmartin and Bullimore, 1987, Gilmartin et al., 1992). Research on $\beta$-receptor activity at the ciliary muscle therefore provides a possible route for a clearer understanding of autonomic control of sustained accommodation.

The purpose of this study was to investigate accommodation functions, in a group of children with particularly high nearwork demands and an apparent genetic predisposition to myopia development. To our knowledge, this is the first study in children, utilizing autonomic agents to deduce the role of the autonomic inputs in accommodation responses and examine autonomic profiles operating during sustained near vision. We hypothesized that a sympathetic deficit may be involved in increased susceptibility to nearwork-induced accommodative adaptation and play a role in progressing myopia and predicted that timolol, an adrenergic antagonist, would therefore produce increased accommodative adaptation in stable myopic children, who presumably have a more robust sympathetic input to the ciliary muscle, but would have little effect in progressing myopic children.
Table 4.1. Summary results of studies investigating tonic accommodation in children

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Age (yr)</th>
<th>N</th>
<th>Refractive error criteria</th>
<th>Instrument</th>
<th>Testing conditions</th>
<th>TA results (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Rosner and Rosner, 1989)</td>
<td>6-14</td>
<td>113</td>
<td>Hyp (&gt;+0.75 sph) Emm (–0.25 to +0.75 sph) EOM (&gt;–0.25 sph)</td>
<td>Dynamic retinoscopy</td>
<td>Gaussian target @ 40 cm Spectacle lens correction</td>
<td>EOMs have lower TA levels Hyp (1.73±0.40) &gt; Emm (1.54±0.49) &gt; EOM (1.36±0.46)</td>
</tr>
<tr>
<td>(Gwiazda et al., 1995b)</td>
<td>6.5-16.5</td>
<td>87</td>
<td>Hyp (+1.00 to +4.12 sph) Emm (–0.25 to +0.75 sph) EOM (–0.25 to –7.00 sph)</td>
<td>Infrared optometer</td>
<td>Darkness Spectacle lens correction</td>
<td>EOMs have lower TA levels Hyp (0.94) &gt; Emm (0.75) &gt; EOM (0.30)</td>
</tr>
<tr>
<td>(Woung et al., 1998)</td>
<td>7-12</td>
<td>34</td>
<td>Emm (–0.25 to +0.75 sph) EOM (–1.25 to –5.25 sph)</td>
<td>Infrared optometer</td>
<td>Internal asterisk @ 8 D No refractive correction</td>
<td>EOMs have lower TA levels Emm (1.37±0.33) &gt; EOM (1.03±0.36)</td>
</tr>
<tr>
<td>(Yap et al., 1998)</td>
<td>7-16</td>
<td>210</td>
<td>Hyp (≥+0.75 sph) Emm (–0.50 to +0.75 sph) EOM (≥–0.50 sph)</td>
<td>Infrared optometer</td>
<td>Darkness No refractive correction</td>
<td>EOMs have lower TA levels Hyp (0.67±0.36) &gt; Emm (0.69±0.31) &gt; EOM (0.44±0.31)</td>
</tr>
<tr>
<td>(Zadnik et al., 1999)</td>
<td>6-11</td>
<td>790</td>
<td>Hyp (≥+1.00 sph) Emm (–0.50 to +0.75 sph) EOM (–0.75 sph)</td>
<td>Infrared optometer</td>
<td>Empty-field condition</td>
<td>EOMs have lower TA levels Hyp (2.25±1.78) &gt; Emm (1.92±1.59) &gt; EOM (1.02±1.18)</td>
</tr>
</tbody>
</table>

Abbreviations: Hyp = hyperopes, Emm = emmetropes, EOM = early-onset myopes
Table 4.2. Summary results of studies investigating accommodative adaptation in children

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Age (yr)</th>
<th>N</th>
<th>Refractive error criteria</th>
<th>Instrument</th>
<th>Testing conditions</th>
<th>Results (D)</th>
</tr>
</thead>
</table>
| (Gwiazda et al., 1995b) | 6.5-16.5 (mean = 11.5) | 87 | Hyp (+1.00 to +4.12 sph) Emm (+0.75 to –0.25 sph) EOM (–0.25 to –7.00 sph) | Infrared optometer | Spectacle correction Video game playing @ 4 D for 15 min | **EOMs showed the greatest accommodative adaptation in all refractive error groups**  
  EOM (1.15) > Emm (0.68) > Hyp (0.24)   |
| (Owens et al., 1991) | mean = 9.5           | 20 | visually normal                             | Infrared optometer | Video game playing @ ~6.5 D for 20 min    | Children exhibited grater accommodative adaptation (0.75) compared to adults (0.21) |
| (Rosenfield et al., 1994a) | 5-13 (mean = 10.1)  | 15 | visually normal                             | Infrared optometer | Habitual spectacle correction Near task @ 5 D for 5 min | No difference in accommodative adaptation between children and adults (~1.0) |

Abbreviations: Hyp = hyperopes, Emm = emmetropes, EOM = early-onset myopes
4.2. Methods

TA and accommodative adaptation were measured in emmetropic and myopic children. Measurements were repeated following the instillation of timolol and the effect of timolol on accommodation was investigated.

4.2.1. Subjects

Thirty children aged eight to 12 years (mean±sd = 10.6±1.4 yr) were recruited from the optometry clinic at The Hong Kong Polytechnic University. The following steps were used to determine the subjective refraction: i) non-cycloplegic autorefraction (Shin-Nippon, Japan); ii) subjective monocular refraction with blur-back (+0.50 D to blur the 6/9 line); iii) binocular balance; and iv) final prescription. All subjects had at least 6/6 visual acuity in each eye on the Bailey-Lovie acuity chart (Bailey and Lovie, 1976) and all of the subjects were free of ocular disease and oculomotor imbalance. No child had anisometropia or astigmatism greater than 1.5 D. The subjective refraction was used to correct refractive error during measurement and to classify the child into a refractive error group.

Subjects were divided into three groups, based on the refraction results: emmetropes (spherical equivalent refractive error (SERE) (i.e. spherical component + half of the cylindrical component) between –0.25 D and +0.50 D), stable myopes and progressing myopes (SERE ≥ –0.75 D). Information on myopia progression rate was obtained from past clinic records or the subject’s optometrist. Myopes were considered to be progressing if their myopia had worsened by –0.50 D or more over the past two years. Past refraction data over the previous three years or more was available for all myopic children, while no refraction data was available for the emmetropic ones. The study was conducted in accordance with the requirements of both the Queensland University of Technology Human Research Ethics Committee
and The Hong Kong Polytechnic University Human Subjects Ethics Sub-Committee. All children were given a full explanation of the experimental procedures and verbal agreement from the children and written informed consent of the parents was obtained before commencement of the study.

4.2.2. Accommodation measurements

*Tonic accommodation*

The child was first directed to the distance target (6/9 letters on a Bailey-Lovie chart at 6 m) and initial base-line far readings were taken at 2-second intervals for one minute (~30 readings). A 3-minute period in the dark was used to allow accommodation to regress to the base-line tonic level. Darkroom accommodation readings (~30 readings) were measured for one minute with the child being instructed to look straight ahead. The tonic accommodation value was taken as the difference between the average of the darkroom readings and the average of the initial base-line far readings.

The child was then asked to spend the next 5 minutes playing the video game Tetris (Gameboy, Japan). The 5-minute task duration was selected because it has previously been shown to produce consistent accommodative adaptation (Rosenfield and Gilmartin, 1989, Fisher et al., 1990, Rosenfield et al., 1992a). It also allowed the experiment to be completed within a reasonable period of time. We felt that longer task duration such as in Gwiazda’s study (1995b)(i.e. 15 mins) may induce fatigue effects and affect the child’s attention span and concentration level.

Instructions on how to play Tetris were given to children who had never played the game before. Children played the game binocularly and the child’s position was held constant at 33 cm from the monitor with the eyes levelled with the centre of the
screen. Throughout the 5-minute period, the child was monitored by the examiner periodically to ensure that eyes were always directed to the game on the screen.

Regression of accommodative adaptation

Immediately following the period of video game playing, lights were extinguished and the child was repositioned in front of the autorefractor. Accommodation regression towards the base-line pre-task TA level was measured over a 90-second period at 2-second intervals (from time 240-330s with a total of 45 readings). A summary of the accommodation task and measurement protocol is represented schematically in Figure 4.1.

![Figure 4.1](https://example.com/figure41.png)

**Figure 4.1.** A schematic representation of the experimental protocol. Darkroom accommodation readings (30 readings) were measured for one minute and averaged. The children then played the video game for a 3-minute period. The lights were then extinguished and accommodation regression towards the base-line pre-task TA level was measured over a 90-second period (45 readings). Shaded parts represent the dark room condition.
4.2.3. Apparatus

Trial frames and lenses were used to correct the child’s refractive error as determined by subjective refraction. The frame was fitted with a pantoscopic tilt of 15 degrees to reduce reflections from the anterior surface of the lens to prevent interference with the operation of the autorefractor.

Accommodation responses were measured using the open-field Shin-Nippon SRW-5000 infrared (IR) autorefractor (Japan). The autorefractor is objective and allows unrestricted viewing of targets at any distance and measures accommodation state by image analysis of an infrared ring of light reflected from the retina. Accommodation readings measured with the Shin-Nippon autorefractor have been found accurate and repeatable in both adults (Mallen et al., 2001) and emmetropic and myopic children (Chat and Edwards, 2001). The autorefractor was used in a static mode and accommodation could be recorded successively at approximately 2-second intervals. A built-in visual display unit provided an image of the pupil to allow alignment of the instrument head with respect to the subject’s visual axis and was used to monitor the child’s eye position during measurements. Invalid autorefractor readings which are characterized by large cylindrical components or error displays were disregarded. The vertex distance of the autorefractor was set to 12 mm. Sphere and cylinder powers were recorded to an accuracy of 0.125 D and the SERE was used in later analysis.

4.2.4. Drug treatments

Testing was performed twice: i) after binocular topical saline application, and ii) 30 minutes after binocular timolol maleate 0.5% (Timoptol, Merck, Sharp & Dohme) application. In order to complete all testing in one visit the drug trials were neither double-blind nor randomized.
Prior proxymetacaine hydrochloride 0.5% (Alcaine, Alcon) application was used to inhibit reflex lacrimation and increase corneal permeability (Bartlett and Jaanus, 2001). To standardize drug volumes, drugs were instilled using a precision micropipette (20 µl of drug per eye). Eyelid closure and punctal occlusion were carried out for two minutes to minimize systemic absorption. To measure the ocular hypotensive effects of timolol, pre- and post-instillation IOP was measured using a non-contact tonometer (Nikon, Japan). Children with a history of current or past cardiac or respiratory conditions were excluded from participation.

4.2.5. Data analysis

Statistical analysis of the stored data was conducted using Statistical Packages for Social Sciences (SPSS). No measures differed significantly from the normal distribution (Kolmogorov-Smirnov, P > 0.05) and parametric tests were used. One-way analysis of variance was used to determine whether TA levels were different among groups of different refractive error, myopic progression rate, and ethnic background. Paired t-tests were used to compare timolol and control trials. Correlation tests were used to establish if there were statistically significant relationships between variables such as TA and refractive error. Differences in regression patterns between groups of different refractive error, myopia progression rate were analysed using repeated measures analysis of variance. Analysis of accommodative regression patterns used pre-task TA level as the reference, to determine the magnitude and duration of the relative shifts in TA induced by nearwork, i.e. zero dioptre thus representing the baseline TA level. Repeated measures analysis of variance (three factors: drug, time, and subject group) was also used to assess the effects of timolol on regression patterns of accommodative adaptation. All data are presented as mean±sd unless otherwise indicated.
Accommodative Adaptation in HK Children

Lens effectivity was taken into account in all measurements. The ocular accommodation demand (D) was calculated using the formula: 

\[ \frac{-L}{(1-d*Rx)[1-d*(L+Rx)]} \]

where \( L \) = accommodation stimulus (D) at the spectacle plane; \( d \) = vertex distance (m); \( Rx \) = spectacle correction (D) (Bennett and Rabbetts, 1989, Rosenfield, 1997). The ocular accommodation response (D) was calculated as: \( \frac{L_1}{1+d*L_1} \), where \( L_1 \) = spectacle accommodation response (D) (Rosenfield, 1997).

The accommodation stimulus for the spectacle-corrected myopes, when compensated for lens effectivity, varied from 2.71 D for the highest myope (SERE = –7.00 D) to 3.11 D for the lowest myope (SERE = –0.875 D). The average stimulus for myopes was 2.89 D for the average myopic refraction of –4.15 D whereas the stimulus remained at 3.3 D for the emmetropes.

4.3. Results

4.3.1. Subject characteristics

Ten emmetropes, 20 myopes (five stable myopes and 15 progressing myopes) were tested (see Table 4.3 over page). Young stable myopes were difficult to find in the Hong Kong population, as young myopes tend to progress (Edwards, 1999, Fan et al., 2002). Emmetropes were younger by an average of 2.3 and 1.6 years than the stable and progressing myopes respectively (Table 4.4 over page). The progressing myopes in this sample appeared to have become myopic at an earlier age (by an average of 2.2 years) and exhibited a higher degree of myopia (by an average of 2.1 D) compared with their stable counterparts. There was a significant correlation between the age of myopia onset and amount of myopia (\( r = 0.584, P = 0.003 \)), i.e. the earlier the myopia onset, the larger the magnitude of myopia.
Table 4.3. Characteristics of the Hong Kong children separated into emmetropes and myopes based on their refractive error

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Refractive error groups</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Emmetropes</td>
<td>EOMs</td>
</tr>
<tr>
<td>No. (males, females)</td>
<td>10 (8M, 2F)</td>
<td>20 (10M, 10F)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.26±1.43</td>
<td>10.99±1.11</td>
</tr>
<tr>
<td>Age of myopia onset (years)</td>
<td>N.A.</td>
<td>7.03±1.64</td>
</tr>
<tr>
<td>Spherical equivalent refractive error (D)</td>
<td>−0.06±0.42</td>
<td>−4.15±1.59</td>
</tr>
<tr>
<td>Myopia progression rate (D/yr)</td>
<td>N.A.</td>
<td>−0.69±0.39</td>
</tr>
<tr>
<td>Baseline IOP (mmHg)</td>
<td>15.38±2.22</td>
<td>14.63±2.59</td>
</tr>
</tbody>
</table>

N.A. = not applicable
Table 4.4. Subject characteristics when myopic children were separated based on myopia progression rate

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Refractive error groups</th>
<th>ANOVA/t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Emmetropes</td>
<td>Stable myopes</td>
</tr>
<tr>
<td>No. (males, females)</td>
<td>10 (8M, 2F)</td>
<td>5 (3M, 2F)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.26±0.51</td>
<td>11.52±0.52</td>
</tr>
<tr>
<td>Age at myopia onset (years)</td>
<td>N.A.</td>
<td>8.77±1.42</td>
</tr>
<tr>
<td>Spherical equivalent refractive error (D)</td>
<td>−0.06±0.42</td>
<td>−2.53±1.24</td>
</tr>
<tr>
<td>Myopia progression rate (D/yr)</td>
<td>N.A.</td>
<td>−0.23±0.16</td>
</tr>
<tr>
<td>Baseline IOP (mmHg)</td>
<td>15.38±2.22</td>
<td>15.3±2.08</td>
</tr>
</tbody>
</table>

N.A. = not applicable
4.3.2. Tonic accommodation

TA for each child was defined as the difference between the averages of the dark readings and initial base-line far readings. The average TA level for all 30 children was 0.57±0.44 D. Figure 4.2 shows the frequency distribution. Base-line TA of emmetropes (0.66±0.65 D) and myopes (0.54±0.35 D) were similar (t_{28} = 0.688, P = 0.497; Figure 4.3A). There were no statistically significant differences in base-line TA levels between emmetropes (0.66±0.65 D), stable myopes (0.35±0.45 D) and progressing myopes (0.59±0.32 D)(F_{2, 27} = 0.828, P = 0.447; Figure 4.3B). Base-line TA was significantly correlated with the age of myopia onset (r = −0.570, P = 0.004; Figure 4.4) and duration of myopia (r = 0.621, P = 0.002; Figure 4.5); myopes who had recently become myopic had reduced TA levels, and TA gradually increased with myopia duration.

![Figure 4.2](image.png)

Figure 4.2. Frequency distribution of tonic accommodation for all 45 subjects reported in the study. Positive values represent myopic TA and negative values represent hyperopic TA. Mean TA was equal to 0.57 D.
Figure 4.3. Differences in mean base-line TA levels when separating subjects based on A: refractive error, B: myopic progression rate. There were no statistically significant differences emmetropic and myopic children. Base-line TA of emmetropes, stable myopes and progressing myopes were similar. Error bars represent one standard deviation.
**Figure 4.4.** A scattergram of the relationship between TA and the age of myopia onset. Myopes who had become myopic at a later age had lower TA than those who became myopic earlier.

**Figure 4.5.** A scattergram of the relationship between TA and myopia duration. Children who had recently become myopic had lower TA than those who had been myopic for a longer period of time.
4.3.3. Accommodative adaptation

Following the near task, the post-task shift was calculated by subtracting the pre-task TA value and the myopic shift in TA represents accommodative adaptation expressed as a positive value. The pattern of regression back to the pre-task TA level was also used to assess the degree of adaptation generated by the task. Accommodative adaptation for emmetropes and myopes were $0.10 \pm 0.45$ and $-0.01 \pm 0.52$D respectively; myopic children failed to demonstrate a greater degree of accommodative adaptation compared with the emmetropes ($t_{28} = 0.53$, $P = 0.6$; Figure 4.6A). However, when the myopes were separated into stable and progressing myopes, a split plot analysis of variance (two factors: refractive error, time) revealed significant differences in accommodative adaptation following nearwork ($F_{2,27} = 3.953$, $P = 0.031$; Figure 4.6B).

Over the entire 90-second post-task period, progressing myopes showed the largest accommodative adaptation effects ($0.13 \pm 0.38$ D), while stable myopes showed counter-adaptive changes ($-0.51 \pm 0.71$D), i.e., TA regressed below the pre-task baseline level and this difference was statistically significant (Bonferroni, $P = 0.012$). Accommodative adaptation of emmetropes and progressing myopes were however similar. The interaction effects between time and refractive error ($F = 1.028$, df = 45, $P = 0.422$) or time and myopic progression rate ($F = 0.935$, df = 45, $P = 0.596$) were not statistically significant. Base-line TA level was not a factor in determining the degree of adaptation induced by the near task ($r = 0.231$, $P = 0.212$) nor was the age of myopia onset ($r = 0.309$, $P = 0.152$).
Figure 4.6. Regression of accommodative adaptation effects (normalised TA shifts) of A: emmetropes and myopes, B: emmetropes, stable myopes and progressing myopes. There were no statistically significant differences in the magnitude of accommodative adaptation and its regression to base-line TA level between emmetropes and myopes. Differences emerged when myopes were separated into stable and progressing myopes. Progressing myopes showed some adaptation effects while stable myopes demonstrated counter-adaptive changes in their accommodation (i.e. TA shifting in the hyperopic direction).
4.3.4. Beta-antagonism

The changes induced by timolol in the magnitude of accommodative adaptation of emmetropes (–0.23±0.36 D) and myopes (0±0.61 D) were similar (t28 = –1.012, P = 0.32). When myopes were separated based on myopic progression rate, there were significant differences in timolol-induced changes in the magnitude of adaptation of emmetropes (–0.23±0.36 D), stable myopes (0.53±0.73 D), and progressing myopes (–0.15±0.51 D)(F2, 27 = 4.038, P = 0.029; Figure 4.7). Post-hoc analysis revealed that the increased accommodative adaptation with timolol in the stable myopes was significantly different from the minimal changes in the emmetropes and progressing myopes (Bonferroni, P = 0.043).

![Figure 4.7](image-url)

**Figure 4.7.** Mean timolol-induced change in the magnitude of accommodative adaptation effects of emmetropes, stable myopes and progressing myopes. Timolol induced a statistically significant greater amount of accommodative adaptation in the stable myopes compared with the progressing myopes and emmetropes. Asterisks represent statistically significant differences at * P < 0.05, one-way analysis of variance. Error bars show one standard deviation.
Timolol had similar effects on the regression patterns of adaptation of emmetropes and myopes ($F_{1,28} = 0.657, P = 0.424$; Figure 4.8). The response profiles following timolol application were significantly different between the emmetropes, stable myopes and progressing myopes (split-plot ANOVA (factors: drug, time, and refractive error) ($F_{2,27} = 3.792, P = 0.035$; Figure 4.9). Timolol only modified the regression pattern in the stable myopes but had little effect in the emmetropes or progressing myopes, i.e. timolol eliminated the counter-adaptive shift in TA and with timolol application, the regression pattern of the stable myopes returned to the baseline regression patterns of emmetropes and progressing myopes. The interaction effect between drug and myopic progression grouping was also statistically significant ($F_{2,27} = 3.528, P = 0.043$).
Figure 4.8. Mean accommodative adaptation for saline and timolol trials of A: emmetropes, B: myopes. Accommodative adaptation is zero when TA is unchanged before and after video game playing. Timolol failed to induce any significant changes in the regression patterns of emmetropes whereas it induced increased accommodative adaptation in the myopes. However, there were no statistically significant differences in the effect of timolol on accommodation in emmetropes and myopes.
Figure 4.9. Mean accommodative adaptation for saline and timolol trials of A: emmetropes, B: stable myopes, C: progressing myopes. Accommodative adaptation is zero when TA is unchanged before and after video game playing. Timolol produced a significantly greater degree of accommodative adaptation in the stable myopic children, but had little effect in the emmetropes and progressing myopes.
4.4. Discussion

4.4.1. TA – refractive error and myopia progression

TA levels of Hong Kong children were lower than those reported in Caucasian children (Gwiazda et al., 1995b, Zadnik et al., 1999) but more comparable to those reported by Yap et al. (1998) in a group of Nepalese children. All the above-mentioned studies used an infrared optometer and the same open-loop condition (i.e. darkness) for the measurement of TA except that of Zadnik et al. (1999), which used an empty-field condition, thus variation of the TA results may be attributed to the differences in ethnic background, an interpretation that echoes with the results of Chapter 2.

We did not find that TA levels varied with refractive error or myopia progression rate and the results of the relationship between TA and myopia stability from Chapter 2 were not reproduced here. The Hong Kong progressing myopic children did not have higher TA levels than the non-myopes as the Asian progressing myopic adults; stable myopic children did not have lower TA levels than non-myopes as the Asian stable myopic adults. The finding that recent myopes had lower TA levels compared with those who became myopic at an earlier age suggests that reduced TA accompanies myopia onset or may be a consequence of myopia development. Longitudinal studies are necessary to investigate whether reduced TA can predispose an emmetropic child to myopia and be identified as a risk factor for myopia development. However, to date, two longitudinal studies in children have disputed the role of lower TA as a predictor of myopia development (Yap et al., 1998, Zadnik et al., 1999).
4.4.2. Accommodative adaptation – refractive error and myopia progression

The magnitude of nearwork-induced accommodative adaptation in Hong Kong children is smaller compared to that reported by Gwiazda et al. (1995b) in a group of Caucasian children although both studies used similar near task conditions (e.g. video game playing). The shorter task duration used in our study may have contributed to the smaller magnitude of accommodative adaptation. In addition, Gwiazda et al. (1995b) found that all myopic children were susceptible to accommodative adaptation following nearwork than the emmetropes and hyperopes while we found no differences between the Hong Kong emmetropic and myopic children. The fact that the accommodation stimuli in the spectacle-corrected myopic children were reduced compared to the emmetropic children may have been a factor in myopes not demonstrating a greater degree of accommodative adaptation than the emmetropes.

However, clear differences in nearwork-induced accommodative adaptation between Hong Kong stable and progressing myopic children were observed. The progressing myopic children demonstrated myopic shifts in TA while the stable myopes underwent a ‘counter-adaptive’ shift in TA (i.e. hyperopic shift). It has been suggested that differences in accommodation responses may be related to the characteristics of the autonomic inputs to the ciliary muscle (Gilmartin, 1986, Gilmartin et al., 1992, Gilmartin, 1998). During nearwork, parasympathetic inputs required for sustained near vision also produces concurrent sympathetic activation. As the sympathetic control is related to how an individual adapts to sustained near task, reduced sympathetic inputs would therefore result in less protection against accommodative adaptation. Based on this hypothesis, our results indicate that the progressing myopes may have a reduced sympathetic input or facility to the ciliary muscle while stable myopes may have a strong sympathetic input. This counter-adaptive change in TA has been reported by McBrien et al. (1988) in a group of
Accommodative Adaptation in HK Children

hyperopes and it was suggested to be indicative of strong sympathetic inputs or facility to the ciliary muscle.

4.4.3. Effect of β-antagonism on accommodation

Increased susceptibility to nearwork-induced accommodative adaptation in progressing myopic children as a consequence of a weaker sympathetic innervation to the ciliary muscle may also be deduced from the response profile following β-adrenergic antagonism with timolol application. Timolol application failed to modify the regression pattern of accommodative adaptation of the progressing myopes, presumably due to insufficient sympathetic input to the ciliary muscle. The stable myopic children in contrast demonstrated increased accommodative adaptation with timolol, presumably as there was adequate sympathetic input to be inhibited. Therefore, an underlying sympathetic deficit may play a role in myopia progression in these children. These results suggest that stable myopes may have sympathetic dominance while progressing myopes may have parasympathetic dominance with a relative deficit in the sympathetic input to the ciliary muscle. The potential therapeutic benefits of stimulating the sympathetic inputs to the ciliary muscle with adrenergic agonists as a means to slow down myopia progression may be investigated by conducting a longitudinal study.

Emmetropic children in this study could not be differentiated from the progressing myopes in terms of the degree of nearwork-induced accommodative adaptation and the response to β-adrenergic antagonism. Edwards (1999) found in a 5-year longitudinal study that the mean refraction of Hong Kong children was +0.32 D at age seven, remained around emmetropia between 8-9 years, with the greatest shift towards myopia between the ages of 9 and 11 years. The average age of the emmetropic children in our study was 9.26 years and it is thus highly likely that the refractive errors of some of these presently emmetropic children were in the process
of shifting towards myopia. This made even more plausible by the effect that 30% of Hong Kong children at age 6-7 years and about 70% by the age of 17 years are myopic (Lam and Goh, 1991).

Furthermore, reliability with the autorefractor in young subjects has been found to be better when accommodation measures were made following cycloplegia (Chat and Edwards, 2001). Non-cycloplegic refraction was used in this study and this may have been a factor that confounded the classification between emmetropic and myopic children, particularly in the case of low myopia.

4.4.4. Comparison to Asian myopic adults

We have shown that the ethnic background of a myopic individual is an important factor to consider when investigating accommodative responses (Chapter 2). For example, Caucasian stable myopes exhibited considerably different regression patterns of nearwork-induced accommodative adaptation compared with the Asian counterparts (Figure 2.13). Given that the Hong Kong children in this study have similar ethnic background to the Asian myopic subjects in Chapter 2, here we compared the accommodation characteristics and response profiles to β-adrenergic antagonism between children and adults. Despite differences in methodology of the two studies, the Hong Kong stable myopic children in this experiment demonstrated counter-adaptive changes and also timolol response profiles consistent with those of the adult Asian stable myopes, i.e. timolol produced enhanced accommodative adaptation effects in both groups (Figure 2.13). Both groups of the Asian progressing myopic children and adults showed greater accommodative adaptation than the stable myopes and similar response profiles to β-adrenergic antagonism, i.e. timolol failed to modify either pattern of regression. Table 4.5 presents the suggested autonomic imbalance model of stable and progressing myopia in Asian myopes.
Table 4.5. Main findings and the indicated autonomic imbalance model of stable and progressing myopia in Asian myopes (children and adults). This is based on the assumption of normal autonomic inputs in non-myopes/emmetropes.

<table>
<thead>
<tr>
<th></th>
<th>Asian stable myopes</th>
<th>Asian progressing myopes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main findings</strong></td>
<td>Minimal adaptation effects</td>
<td>Greater accommodative adaptation effects</td>
</tr>
<tr>
<td><strong>common to both</strong></td>
<td>(counter-adaptation in some cases)</td>
<td></td>
</tr>
<tr>
<td><strong>adults and children</strong></td>
<td>Fast regression profile</td>
<td>Retarded regression profile</td>
</tr>
<tr>
<td></td>
<td>Enhanced accommodative adaptation with timolol</td>
<td>No significant change in adaptation effects with timolol</td>
</tr>
<tr>
<td><strong>Possible autonomic</strong></td>
<td>Sympathetic dominance</td>
<td>Parasympathetic dominance and relative sympathetic deficit</td>
</tr>
<tr>
<td><strong>imbalance</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ethnic background is important in the aetiology of disease and developmental processes because it is one of the expressions of genetic constitution, and certain ethnic groups show strong susceptibility to certain conditions. Hong Kong children, along with those in Taiwan, Singapore and Japan are exposed to competitive school systems from a young age. Despite the lack of concrete evidence on the relationship between nearwork and myopia onset or progression, this increased duration and intensity of nearwork activity and the racial susceptibility to nearwork effects may be the factors in question. As high prevalences of myopia are confined to particular ethnic groups, it seems highly likely that myopia development is related to environmental exposure in genetically susceptible individuals. Investigations of accommodation changes induced by nearwork in Hong Kong stable myopic children, an apparently susceptible ethnic population to myopia development, may help devise methods to reduce accommodative adaptation as means to retard myopia progression.
Figure 4.10 continues over page
Figure 4.10. Regression patterns for timolol and control trials of **A**: Asian stable myopic young adults, **B**: Asian stable myopic children, **C**: Asian progressing myopic young adults, **D**: Asian progressing myopic children. Stable myopic children demonstrated counter-adaptive changes in accommodation and also timolol response profiles consistent with those of the adult Asian stable myopes, i.e. enhanced accommodative adaptation effects with timolol. Both Asian progressing myopic children and adults showed more accommodative adaptation than the stable myopes and similar responses to adrenergic antagonism, i.e. timolol failed to modify either pattern of regression.
4.5. Conclusion

Although the relationship between nearwork-induced accommodative adaptation and refractive error has not been reproduced in all investigations, our results suggest an association between accommodative adaptation and myopia progression rate. Nearwork-induced accommodative changes are a characteristic of Hong Kong children with progressing myopia. Our results support the hypothesis of differing sympathetic inputs to the ciliary muscle in stable and progressing myopia. Further work will be required to find out if Caucasian children with progressing myopia are also susceptible to nearwork-induced accommodative adaptation and share similar autonomic innervation characteristics with the Hong Kong children.

The present chapter has been published as an ARVO abstract.

CHAPTER 5
EFFECT OF β-ADRENERGIC ANTAGONISM ON AC/A RATIOS IN MYOPIC AND EMMETROPIC HONG KONG CHINESE CHILDREN

5.0. Summary

It has been suggested that the relationship between myopia and nearwork may not only involve the accommodation system but also the vergence system. If convergence is involved in myopia development, then the interaction between accommodation and vergence (described by the accommodative vergence to accommodation ratio, AC/A) is an important factor to consider. Caucasian children with myopia have elevated response AC/A ratios (Gwiazda et al., 1999, Mutti et al., 2000). The prevalence of myopia in Hong Kong is very high and if the reason for this involved the accommodation and convergence systems then AC/A ratios would also be expected to be elevated in Hong Kong Chinese myopic children.

This chapter investigated if response AC/A ratios varied with refractive error and with myopia progression rate and examined the effect of β-adrenergic antagonism on AC/A ratios in 30 Hong Kong Chinese children aged eight to 12 years. Accommodation responses were measured using a Shin-Nippon autorefractor and concurrent changes in vergence were assessed using a vertical prism and a Howell-Dwyer card at 3 and 0.33 m. Accommodation demand was altered using ±2 D lenses and lens- and distance-induced response AC/A ratios were calculated. Measurements were repeated 30 minutes following the instillation of topical timolol maleate (0.5%). Progressing myopes had the highest response AC/A ratios although there were no statistically significant differences between emmetropes, stable myopes and progressing myopes. Timolol application reduced accommodative convergence (AC) in the stable myopes but not in the emmetropes or progressing myopes, and this
difference between refractive groups was statistically significant. However, timolol did not produce any significant change in the accommodation response to positive or negative lenses or response AC/A ratios.

AC/A ratios of Hong Kong Chinese myopic children were not significantly elevated from those of emmetropic children, and it is therefore unlikely that elevated AC/A ratios are responsible for the high levels of myopia that occur in Hong Kong. The finding that timolol reduced AC in the stable myopes suggests that the autonomic control of AC in these children may be different from that in emmetropic children and those with progressing myopia.

5.1. Introduction

In addition to the involvement of the accommodation system, the association between myopia and nearwork may also involve the vergence system (Goss and Zhai, 1994, Goss and Rosenfield, 1998, Norton and Gamlin, 1999). Authors of clinical studies have reported that the onset of myopia in children is associated with increased esophoria at near (Table 5.1). Myopic children with near esophoria also demonstrate greater rates of myopia progression than those with orthophoria or exophoria (Goss, 1986, Goss, 1990, Goss and Grosvenor, 1990, Brown et al., 2002). Increased esophoria has also been found to be associated with higher amounts of myopia (Chung and Chong, 2000).

If convergence is involved in myopia development, then the interaction between accommodation and vergence, i.e. the accommodative vergence to accommodation (AC/A) ratio (the amount of accommodative convergence (AC) per unit of accommodative (A) response) becomes an important factor to consider. Caucasian children with myopia have elevated response AC/A ratios (Table 5.2) and it has been
suggested that this elevated ratio is the result of reduced accommodation response at near or enhanced accommodative convergence (Gwiazda et al., 1999). Gwiazda et al. (1999) proposed that AC/A ratios in myopes might reduce once the myopia stabilizes, presumably due to an improved accommodation response or an exophoric shift in the near phoria. The latter has been observed by Goss (1999) who found a tendency for near phoria to show an exophoric shift following the cessation of childhood myopia progression. As myopic children may accommodate less accurately than emmetropic children (Gwiazda et al., 1993b), particularly progressing myopic children with esophoria (Gwiazda et al., 1996), response AC/A ratios calculated on the basis of the measured accommodation response rather than the accommodation stimulus and assumed response (stimulus AC/A) would be more appropriate.

**Table 5.1. Summary of near heterophorias (Δ) associated with the onset of myopia.**

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Age (yr)</th>
<th>No. of subjects</th>
<th>Phoria measurement technique</th>
<th>‘remain emmetropic’ group</th>
<th>‘became myopic’ group</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Goss, 1991)</td>
<td>6-15</td>
<td>122</td>
<td>Von Graefe</td>
<td>2±6 exo</td>
<td>1±6 eso</td>
</tr>
<tr>
<td>(Drobe and de Saint-André, 1995)</td>
<td>&lt;40</td>
<td>46</td>
<td>N.A.</td>
<td>2.3±4.2 exo</td>
<td>0.6±6.7 eso</td>
</tr>
<tr>
<td>(Goss and Jackson, 1996a)</td>
<td>10.8-11.3</td>
<td>87</td>
<td>Von Graefe</td>
<td>1.5±4.6 exo</td>
<td>2.3±4.5 eso</td>
</tr>
<tr>
<td>(Gwiazda et al., 2001)</td>
<td>6-18</td>
<td>80</td>
<td>Maddox rod &amp; Risley prism</td>
<td>1.26 exo</td>
<td>4.03 eso</td>
</tr>
</tbody>
</table>
In the light of the differences in accommodation response between refractive error groups, investigators (Gilmartin and Hogan, 1985b, McBrien and Millodot, 1986b, Gilmartin and Bullimore, 1987, Woung et al., 1993, Ciuffreda and Wallis, 1998, Ciuffreda et al., 2000) have proposed that an imbalance of the autonomic input to the ciliary muscle, particularly a sympathetic deficit, may give rise to anomalous accommodation responses that results in or exacerbates myopia development. It has been suggested that a sympathetic deficit may result in increased susceptibility to nearwork-induced accommodative adaptation (Gilmartin and Bullimore, 1987, McBrien and Millodot, 1988, Gilmartin and Bullimore, 1991, Gilmartin et al., 1992), and an increased likelihood that retinal defocus associated with accommodative adaptation triggers the onset or progression of myopia (see sections 1.4.2 and 1.4.4 for details).

Based on the dual innervation theory of accommodation (Toates, 1972), if a sympathomimetic agent is applied to increase the input from the sympathetic system, then the parasympathetic input should increase to maintain the net accommodation response, resulting in an increase in the AC/A ratio. Conversely, if a sympatholytic agent is applied to decrease the sympathetic input, parasympathetic input should also decrease, and this would decrease the AC/A ratio. Stephens (1985) showed that a non-selective adrenergic agonist (hydroxyamphetamine hydrobromide 1%) produced a significant increase in AC/A ratios whereas a \( \alpha \)-adrenergic agonist (phenylephrine HCL 10%) had no significant effect. By subtracting the effects of each agent, Stephens (1985) concluded that \( \beta \)-adrenergic activity was responsible for the changes in AC/A ratio. This hypothesis was supported by findings of Rosenfield and Gilmartin (1987c) that timolol, a \( \beta \)-adrenergic antagonist, produced a significant decrease in AC/A ratios. In a subsequent study, Rosenfield and Gilmartin (1987a) found that timolol produced a reduction in AC in emmetropic but not myopic adults. They suggested that the reduction in AC in emmetropic subjects resulted from timolol reducing the sympathetic input to the ciliary muscle and that the lack of
effect in myopic subjects was suggestive of an absent or reduced sympathetic input to the ciliary muscle.

The purpose of this study was to investigate accommodation and convergence functions of children in Hong Kong, where the prevalence of myopia, at 70-80%, is one of the highest in the world (Lam and Goh, 1991, Yap et al., 1993b, Edwards, 1999, Lam et al., 1999). We hypothesized that if the reason for this involved the accommodation/convergence system that AC/A ratios would also be elevated in Chinese myopic children. In addition if, as suggested by Rosenfield and Gilmartin (1987a), there were reduced sympathetic input to the ciliary muscle in myopia, then timolol would only have effects in emmetropic children. Conversely, if progression rate were the important factor then timolol would reduce AC in stable myopic children, in whom the sympathetic input to the ciliary muscle has presumably returned to normal, but not in progressing myopic children.
Table 5.2. Summary results of AC/A ratios as a function of refractive error

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of subjects</th>
<th>Age (yr)</th>
<th>Target details and distance</th>
<th>Instrumentation and technique</th>
<th>Form of refractive error correction</th>
<th>Stimulus or response AC/A ratio</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Rosenfield and Gilmartin, 1987b)</td>
<td>17 Emm 17 EOMs 17 LOMs</td>
<td>N.A.</td>
<td>N6 number counting task @ 3, 3.9, 4.6 D</td>
<td>V: green Maddox rod &amp; tangent scale A: Canon R-1 infrared optometer</td>
<td>contact lens correction</td>
<td>response AC/A</td>
<td>EOMs have higher AC/A ratios than Emm and LOMs EOMs (10.14 Δ/D) &gt; Emm (8.91 Δ/D) &gt; LOMs (8.67 Δ/D)</td>
</tr>
<tr>
<td>(Jiang, 1995)</td>
<td>33 Emm 11 LOMs</td>
<td>18-27</td>
<td>20/120 Snellen letters @ 2, 0.8, 0.5 m</td>
<td>V: dissociated phoria A: Canon R-1 infrared optometer</td>
<td>no refractive correction</td>
<td>response AC/A</td>
<td>LOMs and Emm-myopes have higher AC/A ratios than Emm-Emm</td>
</tr>
<tr>
<td>(Gwiazda et al., 1999)</td>
<td>68 Emm 33 EOMs</td>
<td>5.8-21.2</td>
<td>3x3 20/100 Snellen letters @ 0.33, 4 m</td>
<td>V: Maddox rod &amp; Risley prism A: Canon R-1 infrared optometer</td>
<td>spectacle correction</td>
<td>response AC/A</td>
<td>Myopes show elevated AC/A ratios compared to Emm +ve lens induced ratio: 6.21 vs 4.92 Δ/D; −ve lens induced ratio: 5.81 vs 4.02 Δ/D</td>
</tr>
<tr>
<td>(Mutti et al., 2000)</td>
<td>726 Emm</td>
<td>6-14</td>
<td>4x4 20/155 grid of letters @ 2, 2.25, 4.37 D</td>
<td>V: Purkinje images I and IV A: Canon R-1 infrared optometer</td>
<td>habitual spectacle or contact lens correction</td>
<td>response AC/A</td>
<td>EOMs have the highest AC/A ratio EOMs (6.39 Δ/D) &gt; Emm (3.94 Δ/D) &gt; Hyp (3.4 Δ/D); a Δ/D unit elevation in the ratio was associated with a 50-60% increase in risk of myopia within 1 year</td>
</tr>
<tr>
<td>(Walline et al., 1999)</td>
<td>184 Hyp 599 Emm 54 myopes</td>
<td>6-14</td>
<td>Distance target: 2 lines above threshold Near target: 20/100 letters @ 40 cm</td>
<td>V: cover test and prism bar</td>
<td>habitual spectacle or contact lens correction</td>
<td>stimulus AC/A</td>
<td>No changes in AC/A ratio with refractive error</td>
</tr>
<tr>
<td>(Walline et al., 1999)</td>
<td>184 Hyp 599 Emm 54 myopes</td>
<td>6-14</td>
<td>Distance target: visual acuity threshold @ 6 m Near target: detailed toy at 40 cm</td>
<td>V: cover test and prism bar</td>
<td>habitual refractive correction</td>
<td>stimulus AC/A</td>
<td>No changes in AC/A ratio with refractive error</td>
</tr>
</tbody>
</table>

Abbreviations: Emm: emmetropes, Emm-myopes: incident myopes, Emm-Emm: emmetropes who remain emmetropic, EOMs: early-onset myopes, LOMs: late-onset myopes, V: vergence, A: accommodation, positive lens-induced ratio: +ve lens, negative lens-induced ratio: −ve lens
AC/A Ratio in HK Children

5.2. Methods

Our experiments involved measuring accommodation and heterophoria both before and after timolol application in emmetropic and myopic children. Response AC/A ratios for both conditions were then calculated.

5.2.1. Subjects

Thirty children aged eight to 12 years (mean±sd = 10.6±1.4 yr) were recruited from the optometry clinic at The Hong Kong Polytechnic University. The following steps were used to determine the subjective refraction: i) non-cycloplegic autorefraction (Shin-Nippon, Japan); ii) subjective monocular refraction with blur-back (+0.50 D to blur the 6/9 line); iii) binocular balance; and iv) final prescription. All subjects had at least 6/6 visual acuity (corrected or uncorrected) in each eye on the Bailey-Lovie acuity chart (Bailey and Lovie, 1976) and all of the subjects were free of ocular disease and oculomotor imbalance. No child had anisometropia or astigmatism greater than 1.5 D. The subjective refraction was used to correct refractive error during measurement and to classify the child into a refractive error group.

Subjects were divided into three groups, based on the refraction results: emmetropes (spherical equivalent refractive error (SERE) (i.e. spherical component + half of the cylindrical component) between −0.25 D and +0.50 D), stable myopes and progressing myopes (SERE ≥ −0.75 D). Information on myopia progression rate was obtained from past clinic records or the subject’s optometrist. Myopes were considered to be progressing if their SERE had decreased by −0.50 D or more over the past two years. The study was conducted in accordance with the requirements of both the Queensland University of Technology Human Research Ethics Committee and The Hong Kong Polytechnic University Human Subjects Ethics Sub-Committee. All children were given a full explanation of the experimental procedures and verbal
agreement from the children and written informed consent of the parents was obtained before commencement of the study.

5.2.2. Accommodation and vergence measurements

Trial frames and lenses were used to correct the child’s refractive error as determined by subjective refraction. The frame was fitted with a pantoscopic tilt of 15 degrees to reduce reflections from the anterior surface of the lens to prevent interference with the operation of the autorefractor. Vergence measures were taken using distant and near Howell-Dwyer cards (Cyclopean Designs, Victoria, Australia) positioned at 3 and 0.33 m respectively. The sizes of the numbers on the distant and near cards were equivalent to 6/12 and N6 respectively. Normal room lighting was maintained to provide target luminance of approximately 320 cd/m² at each target distance.

Children viewed the distant Howell-Dwyer card at 3 m binocularly for 5-10 s and were instructed to keep the numbers on the card as clear as possible and to report if they started to become blurred. A minimum of five accommodation readings of the right eye was then taken. With the child still looking at the target, a 6 Δ base-down loose prism was placed in front of the right eye. The subject was asked whether he or she saw two images one above the other and to report which number in the lower image the arrow of the upper image was pointing to. The magnitude (to the nearest 0.5 Δ) and the direction of the heterophoria (eso or exo) measures were recorded. Two measurements were performed and if they differed by more than 4 Δ, a third reading was taken. The measurement that deviated most from the other two was excluded, and the mean of the two retained measures was used as the heterophoria result. If diplopia was not initially observed, the prism was removed, the subject fused the target and the prism was reintroduced. The procedure was repeated with the child viewing the near target at 0.33 m and then with the child wearing lenses 2 D more positive and then lenses 2 D more negative than their refractive correction.
5.2.3. Apparatus

Accommodation responses were measured using the open-field Shin-Nippon SRW-5000 autorefractor (Japan). The autorefractor is objective and allows unrestricted viewing of targets at any distance through an infrared-reflecting mirror. Accommodation readings measured with the Shin-Nippon autorefractor have been found accurate and repeatable in both adults (Mallen et al., 2001) and emmetropic and myopic children (Chat and Edwards, 2001). A built-in visual display unit was used to monitor the child’s eye position during measurements. Invalid autorefractor readings which are characterized by large cylindrical components or error displays were disregarded. The vertex distance of the autorefractor was set to 12 mm. Sphere and cylinder powers were recorded to an accuracy of 0.125 D and the SERE was used.

5.2.4. Drug treatments

Testing was performed twice: i) after binocular topical saline application, and ii) 30 minutes after binocular timolol maleate 0.5% (Timoptol, Merck, Sharp & Dohme) application. In order to complete all testing in one visit the drug trials were neither double-blind nor randomized. As the accommodation measurements were objective, this should have no bearing on the results obtained.

Prior proxymetacaine hydrochloride 0.5% (Alcaine, Alcon) application was used to inhibit reflex lacrimation and increase corneal permeability (Bartlett and Jaanus, 2001). To standardize drug volumes, drugs were instilled using a precision micropipette (20 µl of drug per eye). Eyelid closure and punctal occlusion were carried out for two minutes to minimize systemic absorption. To measure the ocular hypotensive effects of timolol, pre- and post-instillation IOP was measured using a
non-contact tonometer (Nikon, Japan). Children with a history of current or past cardiac or respiratory conditions were excluded from participation.

5.2.5. Data analysis

None of the measures were significantly different from the normal distribution (Kolmogorov-Smirnov, \( P > 0.05 \)) and parametric tests were used. To determine if differences in heterophoria measures, accommodation responses and AC/A ratios were present between emmetropes and myopes unpaired t-tests were used. One-way analysis of variance was used to assess differences between emmetropes, stable myopes and progressing myopes. Paired t-tests were used to compare saline control and timolol trials. Correlation tests were used to establish if there were statistically significant relationships between variables such as heterophoria and accommodation.

All data are presented as mean±sd unless otherwise indicated.

Negative AC/A ratios or ratios greater than 20 were excluded as they are most likely produced by noise in the measurements (Ciuffreda et al., 1997, Gwiazda et al., 1999). On this basis, AC/A ratios from four emmetropes, and three myopes were excluded from the positive-lens induced AC/A data set and data from three emmetropes were excluded from the negative-lens induced AC/A data set.

Lens effectivity was taken into account in all measurements. The ocular accommodation demand (D) was calculated using the formula: \(- \frac{L}{(1-d*Rx){1-d*(L+Rx)}}\) where \( L \) = accommodation stimulus (D) at the spectacle plane; \( d \) = vertex distance (m); \( Rx \) = spectacle correction (D) (Bennett and Rabbetts, 1989, Rosenfield, 1997). The ocular accommodation response (D) was calculated as: \( L_{1}/1+d*L_{1} \), where \( L_{1} \) = spectacle accommodation response (D) (Rosenfield, 1997). Exophoria was scored as a negative number and esophoria as a positive number. Distance-induced AC/A was calculated using the formula: (distance heterophoria (\( \Delta \)) – near
heterophoria (Δ)/(ocular accommodation response at distance (D) – ocular accommodation response at near (D)). Positive lens- and negative lens-induced AC/A ratios were calculated as: (near heterophoria (Δ) – near heterophoria (Δ) with lens)/(ocular accommodation at near (D) – ocular accommodation with lens (D)).

5.3. Results

5.3.1. Subject details

The same group of subjects as those in Chapter 4 were used and their details have been presented in Tables 4.3 and 4.4.

5.3.2. Accommodation

There was a small lead of accommodation while fixating at the distance target for emmetropes (0.22±0.26 D) and myopes (0.19±0.27 D) (t28 = 0.236, P = 0.815; Figure 5.1A). The lead of accommodation between emmetropes (0.22±0.26 D), stable myopes (0.35±0.38 D) and progressing myopes (0.15±0.23 D) was similar (F2, 27 = 1.238, P = 0.305; Figure 5.1B). At near, subjects tended to under-accommodate. The measured lag of accommodation to the 3.3 D stimulus was similar in emmetropic and myopic subjects (0.63±0.31 D cf. 0.45±0.37 D; t28 = 1.247, P = 0.222; Figure 5.1A). Similarly, there were no statistically significant differences in the accommodative lag of emmetropes (0.63±0.31 D), stable myopes (0.25±0.62 D) and progressing myopes (0.50±0.27 D) (F2, 27 = 1.806, P = 0.183; Fig 5.1B).

The additional +2 D lens almost eliminated the lag of accommodation (0.02±0.47 D on average for all subjects) while the −2 D lens produced a greater lag of accommodation (1.11±0.70 D cf. 0.50±0.36 D with no additional lens).
Accommodation responses to the +2 D lens were similar between emmetropes (–0.02±0.46 D) and myopes (0.04±0.49 D) ($t_{28} = -0.284, P = 0.778$; Figure 5.1A), and between emmetropes (–0.02±0.46 D), stable myopes (–0.16±0.5 D) and progressing myopes (0.09±0.48 D)($F_{2,27} = 0.584, P = 0.565$; Fig 5.1B).

The −2 D lens stimulated a significantly greater lag of accommodation in the emmetropic subjects (1.64±0.72 D) compared with the myopic subjects (0.92±0.60 D) ($t_{28} = 2.776, P = 0.01$; Figure 5.1A). The difference in the −2 D lens-induced lag of accommodation of emmetropes (1.64±0.72 D), stable myopes (1.18±0.61 D) and progressing myopes (0.85±0.60 D) was statistically significant ($F_{2,27} = 4.408 P = 0.022$; Figure 5.1B). Emmetropic subjects demonstrated a statistically significant greater lag of accommodation when compared with the progressing myopes (Bonferroni, $P = 0.019$).
Figure 5.1. Mean accommodation responses for A: emmetropes and myopes, B: emmetropes, stable myopes and progressing myopes for the four conditions. There was a lead of accommodation at distance, and lag of accommodation at near, with no significant differences between the groups. The additional +2 D lens improved the accommodation response while the −2 D lens stimulated a greater lag of accommodation. Emmetropes demonstrated a greater lag of accommodation with the −2 D lens compared to myopes, particularly the progressing myopes. Asterisks represent statistically significant differences at * $P < 0.05$, ** $P < 0.01$, level, one-way analysis of variance. Error bars show one standard deviation.
5.3.3. Heterophoria measures

Figure 5.2 shows the distribution of distance and near heterophorias for all subjects. At distance, the majority of emmetropic children were close to orthophoria ($-0.13\pm0.95$ $\Delta$). While myopic children exhibited more exophoria ($-0.76\pm1.1$ $\Delta$) compared to emmetropes, the difference was not statistically significant ($t_{28} = 1.456$, $P = 0.156$; Figure 5.3A). Progressing myopes were more exophoric on average ($-0.92\pm1.03$ $\Delta$) than the stable myopes ($-0.20\pm1.26$ $\Delta$) but again the difference did not reach a statistically significant level ($t_{28} = 1.315$, $P = 0.203$; Fig 5.3B). At near, the mean heterophoria for myopes ($-1.04\pm1.95$ $\Delta$) was not significantly different from that of the emmetropic subjects ($-0.71\pm2.41$ $\Delta$)($t_{28} = 0.371$, $P = 0.714$; Fig 5.3A). In addition, there were no significant differences in near heterophoria between emmetropes ($-0.71\pm2.41$ $\Delta$), stable myopes ($-1\pm3.32$ $\Delta$) or progressing myopes ($-1.06\pm1.52$ $\Delta$)($F_{2, 27} = 0.068$, $P = 0.935$; Figure 5.3B).

Subjects became more exophoric with the +2 D lens ($-2.63\pm2.4$ $\Delta$ cf. $-0.97\pm2.03$ $\Delta$ with no lens). Near heterophoria with the +2 D lens was similar in emmetropes ($-2.29\pm2.36$ $\Delta$) and myopes ($-2.74\pm2.45$ $\Delta$)($t_{28} = 0.432$, $P = 0.669$; Figure 5.3A), and stable ($-2.8\pm3.11$ $\Delta$) and progressing myopes ($-2.72\pm2.35$ $\Delta$)($F_{2, 27} = 0.092$, $P = 0.913$; Figure 5.3B). Subjects became more esophoric in the $-2$ D condition ($0.53\pm2.93$ $\Delta$ cf. $-0.97\pm2.03$ $\Delta$ with no lens), however there were no statistically significant differences in heterophoria position between emmetropes ($0.21\pm2.32$ $\Delta$) and myopes ($0.63\pm3.13$ $\Delta$)($t_{28} = -0.324$, $P = 0.748$; Figure 5.3A), or between emmetropes ($0.21\pm2.32$ $\Delta$), stable myopes ($1\pm1.24$ $\Delta$) and progressing myopes ($0.53\pm2.48$ $\Delta$)($F_{2, 27} = 0.099$, $P = 0.906$; Figure 5.3B).
Figure 5.2. Frequency distribution of A: distance phorias and B: near phorias for all 30 children. At distance, the majority of children were exophoric or orthophoric. There was a wider spread for near heterophoria positions. Children were on average more exophoric at near compared to their distance heterophoria position.
Figure 5.3. Mean heterophorias for A: emmetropes and myopes, B: emmetropes, stable myopes and progressing myopes for the four conditions. Children were exophoric on average at both distance and near. They were more exophoric with the additional +2 D lens and more esophoric with the −2 D lens. There were no significant differences in heterophoria positions between the groups. Error bars show one standard deviation.
5.3.4. Accommodation and heterophoria

There was a significant correlation between distance and near heterophoria positions ($r = 0.474, P = 0.008$; Figure 5.4), i.e. increased near esophoria was associated with increased distance esophoria and vice versa. When all subjects were considered there was no statistically significant correlation between the near accommodation response and near heterophoria ($r = 0.312, P = 0.094$) or distance heterophoria ($r = -0.158, P = 0.397$). A statistically significant correlation between near accommodation and near heterophoria was found for myopic subjects ($r = -0.467, P = 0.025$; Figure 5.5), i.e. reduced accommodation responses were associated with increased esophoria, and greater accommodation responses with increased exophoria. The correlation between distance phoria and the near accommodation response was not statistically significant ($r = -0.308, P = 0.153$).
Figure 5.4. The relationship between distance and near heterophoria. Increased esophoria at near was associated with esophoria at distance; increased exophoria at near was associated with exophoria at distance.

Figure 5.5. The relationship between accommodation response and heterophoria at 33 cm for myopic children. Increased esophoria (decreasing exophoria) was associated with reduced accommodation responses.
5.3.5. AC/A ratios

Myopes tended to demonstrate higher AC/A ratios than the emmetropes, for both lens-induced and distance-induced conditions (+ve lens: $2.69\pm1.81 \Delta/D$ cf. $1.84\pm1.17 \Delta/D$; −ve lens: $3.24\pm4.19 \Delta/D$ cf. $2.46\pm3.38 \Delta/D$; distance: $5.75\pm0.51 \Delta/D$ cf. $5.45\pm0.63 \Delta/D$; Figure 5.6 A). However the differences were not statistically significant (+ve lens: $t_{21} = –1.06, P = 0.301$; −ve lens: $t_{25} = –0.449, P = 0.657$; distance: $t_{28} = –1.288, P = 0.208$). There was a trend for higher lens- and distance-induced AC/A ratios in the progressing myopes but the differences between the groups did not reach significant levels (+ve lens: $F_{2, 20} = 0.595, P = 0.561$; −ve lens: $F_{2, 24} = 0.577, P = 0.569$; distance: $F_{2, 27} = 1.416, P = 0.26$; Figure 5.6B). Age of the subjects had no significant correlation with either distance- or lens-induced AC/A ratios (+ve lens: $r = 0.17, P = 0.368$; −ve lens: $r = 0.026, P = 0.906$; distance: $r = –0.038, P = 0.846$). Degree of myopia was not a significant factor in determining AC/A ratios (+ve lens: $r = –0.255, P = 0.173$; −ve lens: $r = –0.26, P = 0.232$; distance: $r = –0.193, P = 0.325$).
Figure 5.6. Distance- and lens-induced AC/A ratios (mean±sd) of A: emmetropes and myopes, B: emmetropes, stable myopes and progressing myopes. There were no significant differences in AC/A ratios between the groups.
5.3.6. Beta-antagonism

Timolol produced a significant reduction in intraocular pressures by an average of 3.0±2.0 mmHg ($t_{28} = 8.263, P < 0.001$). Timolol did not produce any statistically significant changes in AC/A ratios for either lens- or distance-induced conditions (+ve lens: $t_{21} = 0.337, P = 0.739$; −ve lens: $t_{25} = –0.801, P = 0.43$; distance: $t_{28} = –0.183, P = 0.856$; Figure 5.7). Timolol-induced differences in AC/A ratios of emmetropes or myopes were similar, for either the distance-induced ($t_{28} = –0.183, P = 0.856$) or lens-induced AC/A data (+ve lens: $t_{21} = 0.266, P = 0.793$; −ve lens: $t_{25} = 0.141, P = 0.889$). When myopia was classified as stable or progressing, there was still no effect (+ve lens: $F_{2, 20} = 0.367, P = 0.698$; −ve lens: $F_{2, 24} = 0.161, P = 0.852$; distance: $F_{2, 27} = 0.05, P = 0.951$).

Figure 5.7. Mean AC/A ratios for the distance and lens-induced conditions of both saline control and timolol trials. Timolol instillation did not produce any significant differences in AC/A ratios.
As the AC/A ratio is the ratio between accommodative convergence (numerator) and accommodation (denominator), analysis was also performed on the change in AC and accommodation induced by timolol. The effect of timolol on AC was not significantly different in emmetropes and myopes (+ve lens: $t_{28} = -0.278$, $P = 0.783$; −ve lens: $t_{28} = 1.086$, $P = 0.286$). However, changes in AC due to timolol in the negative-lens induced AC/A data set were significantly different between emmetropes ($0.69 \pm 2.71 \Delta$), stable ($-3 \pm 1.14 \Delta$) and progressing myopes ($0.16 \pm 1.84 \Delta$)($F_{2, 27} = 3.766$, $P = 0.036$). Post-hoc analysis (Bonferroni) revealed that timolol induced a significantly more exophoric shift in AC in the stable myopes compared with the emmetropes ($P = 0.048$; Figure 5.8), and a marginally significant exophoric shift compared with the progressing myopes ($P = 0.058$; Figure 5.8). Timolol did not produce any significant changes in accommodation; the lags of accommodation following timolol instillation were similar in emmetropes, stable myopes and progressing myopes ($F_{2, 27} = 0.392$, $P = 0.679$). Accommodation responses to the additional ±2 D lenses following timolol instillation were not significantly different between the groups (+ve lens: $F_{2, 27} = 0.901$, $P = 0.418$; −ve lens: $F_{2, 27} = 0.517$, $P = 0.602$).
Figure 5.8. Timolol-induced changes (mean±sd) in A: accommodation convergence, B: accommodation, and C: AC/A ratios in the negative lens-induced condition. Timolol reduced AC in the stable myopes but not in the emmetropes or progressing myopes. Timolol produced no significant changes in accommodation or AC/A ratios.
5.4. Discussion

Response AC/A ratios in Hong Kong Chinese children were lower than those reported previously in Caucasian children (Gwiazda et al., 1999) and there was no statistically significant difference between refractive error groups. This result does not appear to support our hypothesis that elevated AC/A ratios are involved in the high prevalence of myopia in Hong Kong. While there were no statistically significant differences in near heterophoria, lag of accommodation or AC/A ratios between the emmetropic, stable and progressing myopic children, the results of the timolol trial suggest that differences in the sympathetic input to accommodation and convergence may exist between stable and progressing myopes. This study provided only a cross-sectional view of the relationship between myopia and the oculomotor system and the findings were based on relatively small group sizes, particularly for stable myopes (See Appendix 7 for power analysis). These factors should be considered when assessing the outcome and clinical significance of our study. We discuss our data in terms of the roles of accommodation, convergence and the sympathetic input in myopia development.

5.4.1. Esophoria, lags of accommodation and myopic progression

Traditionally, the tendency for myopic children to be esophoric at near is thought to occur secondary to excessive accommodative effort at near, which in turn induces excessive accommodative convergence (Goss and Rosenfield, 1998). However, this is at odds with the fact that myopes corrected with spectacle lenses have a reduced accommodation demand compared to emmetropic children. Caucasian children who become myopic, or myopes who progress faster, have a more esophoric heterophoria position compared to emmetropic children (Goss, 1986, Goss, 1990, Goss and Grosvenor, 1990, Goss, 1991, Drobe and de Saint-André, 1995, Goss and Jackson, 1996a, Gwiazda et al., 2001, Brown et al., 2002). However, we did not find Hong
Kong myopic children to be more esophoric at near than the emmetropic children. In addition, this sample of Hong Kong progressing myopic children was not more esophoric and they did not show a significantly greater lag of accommodation compared with the stable myopes. However the test lacked statistical power. A larger group size of the stable myopes may have helped in detecting a difference in accommodation and convergence characteristics. It is not known why the emmetropes demonstrated a greater lag of accommodation with the additional –2 D lens compared to the myopes. The emmetropic children may be less experienced with the optometric testing/experimental protocol or the effect of wearing a minus lens compared to the myopic children.

However, we found a significant correlation between the lag of accommodation and increased esophoria in the myopic group of children ($r = -0.467$, $P = 0.025$). This is consistent with two previous studies that also demonstrated a significant correlation between accommodation response and near heterophoria in myopes, that of Goss and Rainey (1999) which used binocular viewing conditions, and the study of Gwiazda et al. (1996) that used monococular viewing conditions. Thus the increased esophoria appears to be associated with reduced accommodation and not excessive accommodation. This may suggest that myopes with increased esophoria must relax accommodation to reduce accommodative convergence to maintain single clear vision, though why this does not occur in emmetropic children is unclear.

The hyperopic defocus resulting from the lag of accommodation in esophoric myopic children may be the trigger for further myopia progression and near additions, provided as bifocals or as progressive addition lenses have been used to try to retard myopia progression (Goss, 1986, Fulk and Cyert, 1996, Leung and Brown, 1999, Edwards, 2000); the efficacy of this treatment, however, is uncertain. The association between lag of accommodation and esophoria may also be the reason why bifocal and progressive lenses appear to be more effective in myopes with near esophoria
(Goss and Grosvenor, 1990, Goss and Uyesugi, 1995, Fulk et al., 1998, Fulk et al., 2000, Fulk et al., 2002), at least in Caucasian myopic children. In a randomised masked study (Hong Kong Progressive Lens Myopia Control Study), Edwards et al. (2002) did not find that progressive lenses were effective in retarding myopia progression in Hong Kong myopic children. But this group included very few esophores. As we did not find that Hong Kong myopic children were more esophoric or exhibited greater lags of accommodation compared with the emmetropic children, this might in part explain the lack of effect in the Hong Kong Progressive Lens Myopia Control Study.

We found that positive lenses eliminated the lag of accommodation at near and improved the accommodative accuracy in the Hong Kong children, and this is consistent with the premise underlying the use of bifocal and progressive lenses to slow myopia progression. However, Rosenfield (2001) investigated the effect of positive lenses on the accuracy of the accommodation response at near and found that additions may in fact produce a lead of accommodation and subsequently increase the amount of retinal defocus in individuals who initially demonstrate minimal accommodative error during nearwork. Press (2000) speculated that the arbitrary power of the bifocal or progressive lenses additions may have contributed to the variations of the reported efficacy of bifocal/progressive lens studies. It was then suggested that appropriate power of the addition lens may need to be determined on an individual basis, to minimize the amount of retinal defocus associated with nearwork (Hung and Ciuffreda, 2000a, Rosenfield and Carrel, 2001).

5.4.2. Elevated AC/A ratios and myopic progression

Response AC/A ratios of the Hong Kong children are in comparison lower than those measured by Rosenfield et al. (1987b), Gwiazda et al. (1999) and Mutti et al. (2000). Differences in the ratios may be due to difference in experimental techniques and
designs: Rosenfield et al (1987b) and Gwiazda et al. (1999) used Maddox rod, while we used the Howell-Dwyer card (modified Thorton method) for measuring heterophoria positions. Distance-induced AC/A ratios were on average higher than either of the lens-induced ratios. Gwiazda et al. (1999) also found higher AC/A for the distance-induced method and suggested that this may be explained by the proximity cues available.

We did not find response AC/A ratios, either distance- or lens-induced, to vary significantly with refractive error or myopia progression rate. This is contrary to studies that report elevated AC/A ratios in myopic subjects (Jiang, 1995, Gwiazda et al., 1999, Mutti et al., 2000). Mutti et al. (2000) investigated the relationship between refractive error and AC/A ratio in children aged six and 15 years and concluded that an elevated response AC/A ratio was a risk factor for myopia onset, although only 13 out of 727 children in the sample were incident myopes during the study period. Similarly, Jiang (1995) found elevated AC/A ratios in six out of 31 emmetropic young adults who later became myopic. Our data do not support the notion that elevated AC/A ratios are associated with higher myopic progression rate in Hong Kong Chinese children.

As the myopic subjects were significantly older than the emmetropes, and most of the young myopes had progressing myopia while the older myopes were more stable, could this have affected our findings? Several studies have found age-related changes in AC/A ratios; Gwiazda et al. (1999) and Brown et al. (2002) found that AC/A decreased with increasing age whereas Mutti et al. (2000) found that AC/A ratio increased with increasing age. However in our study, AC/A ratios after adjusting for refractive error did not vary significantly as a function of age.
5.4.3. Sympathetic input

Timolol did not significantly alter accommodation responses or AC/A ratios, while timolol reduced AC in stable myopes but not in emmetropes or progressing myopes. This effect of timolol is consistent with the findings of Rosenfield and Gilmartin (1987c) in a group of emmetropic young adults, and demonstrates a sympathetic involvement in the near task. Rosenfield and Gilmartin (1987a) proposed that the reduced AC was the result of reduced sympathetic input, which means a lower parasympathetic input was required to obtain the same net accommodation response. The reduced parasympathetic input was then reflected in the reduction in AC.

Our results support the hypothesis, that timolol would have an effect on AC in stable myopes who presumably have a more adequate, robust sympathetic input to the ciliary muscle, but have little effect on AC of progressing myopes with a sympathetic deficit. This suggests that the neural control of the accommodation and convergence systems may be different between stable and progressing myopia. The finding that emmetropes displayed similar responses to timolol application as the progressing myopes suggests that refractive errors in these emmetropic children may be shifting towards myopia, an unsurprising outcome as about 70% of Hong Kong children are myopic by the age of 17 years (Lam and Goh, 1991).
5.5. Conclusion

We did not find that progressing myopic children were more esophoric or exhibited a greater lag of accommodation at near than their stable counterparts. We report no significant differences in AC/A ratios between the emmetropic, stable and progressing myopic children. Differential effects of timolol on AC may suggest differences in the neural control of accommodation and convergence systems between stable and progressing myopia. While it cannot be concluded from our study that elevated response AC/A ratios are predictive of further myopic progression, longitudinal studies involving a larger sample size and looking into differences in accommodation/convergence characteristics in Hong Kong myopic children are warranted. Studies investigating the neural control of accommodation and convergence systems in stable and progressing myopic children would also be useful.

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CHAPTER 6
CONCLUSIONS

6.1. Summary and implications of results

In this thesis, the hypothesis that an anomaly of the autonomic accommodation control system is responsible for myopia development and progression was raised, and the effect of altering the sympathetic control of the ciliary muscle on tonic accommodation (TA) and nearwork-induced accommodative adaptation, and response AC/A ratios was investigated. The results suggest that the classification system used to separate myopic individuals is important in differentiating accommodation responses and characteristics of the ciliary muscle autonomic inputs that produce the accommodation responses. Findings of previous research into the relationship between accommodation and refractive error have been equivocal; some studies have found clear-cut differences in accommodation responses while others have not been able to replicate the results. In this thesis, classifying myopes according to myopia stability allowed differences of the accommodation responses to be observed, in either the young adult population or the Hong Kong children. This is in agreement with the findings of Gwiazda et al. (1993b) and Abbott et al. (1998) and suggests that intrinsic differences in the accommodation system may provide an explanation as to why some myopes tend to progress, regardless of age.

The association between nearwork effects and the increased prevalence and severity of myopia appears to be different amongst ethnic groups, with the prevalence of myopia reaching ~80% in some Asian countries (Rose et al., 2001). It is possible that Asians are genetically susceptible to myopia development, however, the rate at which the prevalence of myopia is increasing in Asia is not consistent with a purely genetic explanation. We found that separating myopes according to myopia progression rate and also ethnic background allowed distinct characteristics in the
accommodation system to emerge, such as in the resting levels of accommodation, susceptibility to nearwork-induced accommodative adaptation, with the greatest difference observed between Caucasian stable myopes and Asian progressing myopes. The theory of a combination of ethnic background conferring high susceptibility and extreme environmental and educational pressures for the increase in myopia over the past decades appears to be highly plausible (Rose et al., 2001).

Of the accommodation responses investigated, nearwork-induced accommodative adaptation was a feature of progressing myopia, with myopes with an Asian background showing the greatest susceptibility. Although susceptibility to nearwork-induced accommodative adaptation was manifest under open-loop conditions, it may also translate to closed-loop conditions that simulate normal viewing environment, as demonstrated by several recent studies that showed differential refractive susceptibility to sustained nearwork under closed-loop conditions (Ciuffreda et al., 2000, Ciuffreda and Lee, 2002, Vera-Diaz et al., 2002).

Based on animal studies that have found retinal image blur as an important cue for regulating ocular growth (Wildsoet, 1997, Norton, 1999), computer models have simulated the possibility of retinal defocus associated with nearwork-induced transient myopia (NITM) as a trigger for myopia development (Flitcroft, 1998, Hung and Ciuffreda, 1999b, Hung and Ciuffreda, 1999a). However, if the eye is able to distinguish the sign of retinal defocus as suggested by the animal studies, then one may argue the role of nearwork-induced accommodative adaptation as a precursor for myopia development and progression, as the myopic retinal defocus correlated with NITM would paradoxically induce hyperopic ocular growth.
A more recent model by Hung and Ciuffreda (2000b) has added a directional aspect that is more consistent with the animal data but concluded that the blur detection mechanism does not depend on the sign of defocus, but rather on the change in blur magnitude. In addition, Chung et al. (2002) proposed that the emmetropization mechanism in myopia may be defective in detecting the sign of defocus and investigated the effect of undercorrection (which induces hyperopic defocus in the distance) on the rate of myopia progression. Undercorrecting myopic children by +0.75 D while the control subjects were fully corrected for distance produced more rapid myopia progression and this result suggests that myopia development may be caused by a malfunction of the sign detection mechanism in emmetropization and myopia may just be an inappropriate response to the blur signal. Thus the presence of blurred vision at any distance may stimulate myopia progression regardless of the sign of defocus, in eyes that are susceptible (Chung et al., 2002).

Given that the increased susceptibility to nearwork-induced accommodative adaptation was found to be a feature of progressing myopia, one question to pose is what may be the possible underlying mechanism which could account for the increased susceptibility. As the sympathetic control of accommodation is related to how an individual adapts to sustained near tasks, an anomaly of the sympathetic system has been suggested as a possible mechanism for increased nearwork-induced accommodative adaptation and myopia development; an individual who has a deficit in sympathetic inhibition may therefore be more susceptible to myopia development induced by nearwork (Gilmartin et al., 2002). Although the contribution of the sympathetic input to accommodation is smaller relative to the parasympathetic input, its function is important in minimizing nearwork-induced accommodative adaptation and thereby reducing post-task transient accommodative changes in the distance (Gilmartin and Hogan, 1985c).
A recent study by Gilmartin et al. (2002) suggested that only 30 to 40% of individuals are likely to have access to a sympathetic inhibitory facility during sustained nearwork and this is independent of refractive status. In our study, 14 young adult subjects out of 45 demonstrated accommodative regression patterns that were suggestive of an adequate sympathetic facility during nearwork. This prevalence value (31%) is similar to that found by Gilmartin et al. (2002) (30-40%).

We also found that classifying myopes according to stability of their myopia and ethnic background allowed differences between the characteristics of the autonomic inputs to accommodation to be distinguished. While progressing myopes were found to show greater accommodative adaptation effects and a slower decay to base-line TA level and this was suggested to result from a possible parasympathetic dominance and a relative sympathetic deficit to the ciliary muscle, stable myopes displayed minimal accommodative adaptation following nearwork.

The response profiles to β-antagonism with timolol also differed between stable and progressing myopia. These results provide further evidence of differing sympathetic inputs to the ciliary muscle between stable and progressing myopia: stable myopes may have sympathetic dominance or a more balanced autonomic innervation while progressing myopes may have parasympathetic dominance and a relative deficit in the sympathetic input to the ciliary muscle. A surprising result was that Asian stable myopes, both the young adults and the Hong Kong children, demonstrated counter-adaptive changes in their accommodation following sustained nearwork. Response profiles to timolol application were also similar between the young adult Asian stable myopes and the Hong Kong stable myopic children, i.e. timolol produced enhanced nearwork-induced adaptation effects in both groups. Thus, understanding the accommodation changes induced by nearwork in the stable myopes, particularly in this ethnically susceptible population, may help devise methods to reduce accommodative adaptation as means to retard myopia progression. Possibilities may include using positive lenses to reduce the accommodation stimulus during nearwork.
or to stimulate the sympathetic facility as we demonstrated in Chapter 3 using topical 
β-agonist application.

Characteristics of the convergence system and the interaction between 
accommodation and convergence were also investigated in Hong Kong children as 
possible precursors to myopia development and progression, but no significant 
differences in response AC/A ratios between the emmetropic, stable and progressing 
myopic children were found. In addition, progressing myopic children were not more 
esophoric at near than their stable counterparts. This points to the likelihood that the 
accommodation system may play a larger role in myopia development while the 
convergence system may be of a secondary importance through its interaction with 
the accommodation system.

Consistent with the differential effects of timolol on accommodation between stable 
and progressing myopia, the effect of timolol on accommodative convergence was 
different between the two groups. Timolol reduced accommodative convergence in 
stable myopes who presumably have a more robust sympathetic input to the ciliary 
muscle, but had little effect in progressing myopes possibly resulting from a relative 
sympathetic deficit. The results thus provide information on the differences in the 
sympathetic control of accommodation and convergence systems between stable and 
progressing myopia.

6.2. A relative sympathetic deficit – neurotransmitters and receptors revisited

In the light of the differences in accommodation responses and response profiles to 
β-antagonism with timolol observed in individuals with different myopia stability 
and ethnic background, an important question is, are these differences due to 
differences in the underlying autonomic inputs to the ciliary muscle which could be a

198
 precursor to myopia and the causative axial elongation? Woung et al. (1993) found increased accommodative adaptation for the late-onset myopes compared to emmetropes and early-onset myopic subjects and speculated that a peripheral myoneural transmission anomaly may potentially be the underlying mechanism. It was suggested that the anomaly of the ciliary muscle innervation may be due to a reduced amount of acetylcholinesterase. With a reduced amount of acetylcholinesterase, acetylcholine persists longer at the neuroeffector junction, sustaining the stimulation of accommodation and inducing the myopic shift of TA (hence the increased accommodative adaptation effects) following nearwork.

Under normal circumstances, the number of interactions between the neurotransmitters and the post-synaptic receptors is sufficiently large to trigger an action potential, then a series of biochemical events will be induced that result in contraction/or relaxation of the ciliary muscle (Rang and Dale, 1995). In addition, only a small fraction of receptors are activated by the neurotransmitters at any one time and the number of successful interactions between the neurotransmitters and the receptors is a matter of probability. Any factor that reduces the probability of interactions may cause impaired neuromuscular transmission.

If it is hypothesized that the sympathetic input to the ciliary muscle is anomalous and thus responsible for producing anomalous accommodation responses, there may be two possibilities that cause impaired neurotransmission of the ciliary muscle (Figure 6.1):

1) the post-synaptic receptors sites may be anomalous (i.e. a reduced number of active post-synaptic receptors available),

2) the neurotransmission of the innervation system may be anomalous (i.e. there is a reduced number of neurotransmitters, or there is an impaired re-uptake of neurotransmitters by enzymes).
A: Neuro-effector junction of a normal innervation system

B: Two anomalous innervation systems

Figure 6.1. Schematic diagrams of pharmacological events at the neuro-effector junction of A: a normal innervation system and B: two anomalous innervation systems with different underlying factors resulting in reduced responses.
Studies cited throughout the thesis have used pharmacological modifications of accommodation responses with autonomic agents to alter the peripheral innervation and deduce the underlying characteristics of the autonomic inputs to the ciliary muscle. If one was to deduce the underlying characteristics of autonomic inputs to accommodation by the presumed effect of autonomic agents on the accommodation system, it is important to make assumptions with regard to what the possible underlying factor of an anomalous innervation system might be. For example, the effect of an agonist on an anomalous innervation system caused by a lack of neurotransmitters would be different from that on an anomalous innervation system caused by a low number of active post-synaptic receptor sites. Table 6.1 and Figure 6.2 summarise the predicted effects of an agonist and an antagonist on anomalous innervation systems with the two proposed underlying factors compared to that of the normal innervation system.

Table 6.1. The proposed effect of pharmacological agents on an anomalous innervation system cf. a normal innervation system

<table>
<thead>
<tr>
<th>Predicted effects of pharmacological agents on an anomalous innervation system cf. a normal system</th>
<th>Underlying factor for anomalous innervation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↓ Post-synaptic receptor sites</td>
</tr>
<tr>
<td></td>
<td>↓ Neurotransmitters</td>
</tr>
<tr>
<td>An agonist</td>
<td>Reduced response (i.e. the agonist can only activate the limited number of receptor sites present in the anomalous system)</td>
</tr>
<tr>
<td>An antagonist</td>
<td>Reduced response (i.e. easier to produce the blocking effect if only a limited number of receptors are present)</td>
</tr>
</tbody>
</table>
A: Physiologically stimulated state

A normal, functional innervation system with adequate number of active receptors and neurotransmitters

An anomalous innervation system due to anomalous neurotransmission (i.e. low neurotransmitter availability)

An anomalous innervation system due to anomalous receptor sites (i.e. low receptor numbers)

B: Pharmacologically stimulated state - (instillation of agonists which mimic the action of the neurotransmitters)

A normal, functional innervation system

Little stimulating effect as there is only a limited number of receptors to be stimulated. Thus the response generated would be reduced cf. that of the normal system

Similar stimulating effect compared to the normal innervation system as the agonist supplements the natural neurotransmitters. The effect may also be enhanced due to a possible up-regulation of the post-synaptic receptors (i.e. denervation supersensitivity)

C: Pharmacologically inhibited state – (instillation of antagonists which compete with the natural neurotransmitters)

A normal, functional innervation system

Little inhibiting effect as there is only a limited number of receptors to be blocked. Thus the response generated would be reduced cf. that of the normal system

Enhanced blocking effect (i.e. less natural neurotransmitters to compete with at the receptor sites)

Figure 6.2. A schematic representation of the proposed effects of pharmacological agents on an anomalous innervation system cf. a normal innervation system.
6.3. Hypotheses of autonomic imbalance

Based on the assumption of the effect of autonomic agents on anomalous innervation systems (Figure 6.2) and the summary of results (Table 2.6), Table 6.1 lists the possible autonomic imbalance and the underlying mechanism that may account for the differences in accommodation responses.

Table 6.1. Suggested autonomic imbalance model with possible underlying mechanisms of stable and progressing myopia with Asian or Caucasian background. This is based on the assumption of normal autonomic input in non-myopes.

<table>
<thead>
<tr>
<th></th>
<th>Caucasian stable myopia</th>
<th>Asian stable myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main findings</strong></td>
<td>Minimal adaptation effects</td>
<td>Counter-adaptation effects</td>
</tr>
<tr>
<td></td>
<td>Fast regression profile</td>
<td>Fast regression profile</td>
</tr>
<tr>
<td></td>
<td>No significant change in adaptation effects with timolol</td>
<td>Enhanced accommodative adaptation with timolol</td>
</tr>
<tr>
<td><strong>Possible autonomic characteristics</strong></td>
<td>Autonomic balance</td>
<td>Sympathetic dominance</td>
</tr>
<tr>
<td><strong>Possible underlying mechanism</strong></td>
<td>Anomalous neurotransmission – antagonist producing an enhanced blocking effect as there are fewer natural neurotransmitters to compete with at the receptor sites</td>
<td></td>
</tr>
</tbody>
</table>
### Conclusions

<table>
<thead>
<tr>
<th>Main findings</th>
<th>Caucasian progressing myopia</th>
<th>Asian progressing myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate accommodative adaptation effects</strong></td>
<td>Retarded regression profile</td>
<td>Retarded regression profile</td>
</tr>
<tr>
<td><strong>Significant accommodative adaptation effects</strong></td>
<td>Some blocking effect of timolol initially but overall no significant change in adaptation effects with timolol</td>
<td>No significant change in adaptation effects with timolol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible autonomic characteristics</th>
<th>Parasympathetic dominance and relative sympathetic deficit</th>
<th>Parasympathetic dominance and relative sympathetic deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anomalous receptor sites or anomalous neurotransmission</strong></td>
<td>Anomalous receptor sites – antagonist producing little inhibiting effect as there may only be a small number of active receptors to be blocked. Thus the response generated is reduced compared to that of the normal innervation system</td>
<td>Anomalous receptor sites – antagonist producing little inhibiting effect as there may only be a small number of active receptors to be blocked. Thus the response generated is reduced compared to that of the normal innervation system</td>
</tr>
</tbody>
</table>

The autonomic characteristic suggested for each refractive error group may be genetically predetermined and this could lead to a differential sensitivity to the visual environment. If the autonomic accommodation control of an individual is of a profile that is susceptible to the development of myopia, then prolonged nearwork may trigger the onset of myopia. However, the genetically predetermined autonomic profile may be subject to change over time. In the case of an autonomic anomaly, neurotransmitters are known to down-regulate or up-regulate their own receptors in target tissues to modify the responsiveness of the target tissue and the associated physiological response (Costanzo, 2002). Therefore it is possible that the autonomic balance may be restored, resulting in improved accommodation responses and myopia stabilization, despite no changes in the environmental conditions (i.e. the same nearwork demands).
6.4. Computer modelling of accommodation

Computer models of human refractive error development have long been constructed to predict the extent of contributions from the accommodation and vergence systems, particularly to model the development of myopia. One model of particular relevance to this thesis was that of tonic accommodation after sustained near focus developed by Hung and Ciuffreda (1991), which simulated the characteristics of the nearwork-induced changes in tonic accommodation found experimentally by Fisher et al. (1987a). Fisher et al. (1987a) found that immediately following nearwork, TA decayed rapidly but remained above the pre-task base-line level even after 20 minutes in the dark. The negative feedback model hence incorporated two parallel dynamic components, transient and adaptive, to account for the initial rapid decrease and the non-decayed adaptation effects in TA following nearwork.

The two dynamic components in the feedback loop are represented by the transfer functions of $\frac{K}{1 + \tau s}$, where $K$ is the accommodative gain controlling the magnitude of the accommodative output, and $\tau$ is the time constant of the decay process. It has been suggested that the adaptive gain represents a neuro-oculomotor feedback process that controls the effect of sustained stimulation of the accommodation system during nearwork and may have a role in modifying the time constant of the regression profile of accommodative adaptation (Hung and Ciuffreda, 1999a), i.e. the larger the adaptive gain, the slower the decay of adaptation effects. Fisher et al. (1987a) found a greater tendency to increased accommodative adaptation for the high myopes compared to other refractive error groups and by manipulating the adaptive gains and the time constants of the two components of the computer model, experimental results of the differences in the accommodation responses of the different refractive error groups were able to be simulated accurately. Reflecting back to the results in this thesis suggests that the Asian progressing myopes with an increased susceptibility to accommodative adaptation
may have the highest adaptive gain. \(\beta\)-antagonism with timolol may have the largest effect on the adaptive gain in Asian stable myopes.

Results of this thesis may lead to further work on computer modelling, to simulate accurately the experimental results of this thesis and to model the accommodation system, particularly the characteristics of the adaptation and decay processes of groups with different refractive error, myopia stability and ethnic backgrounds (Figure 6.3). Furthermore, as it has been suggested that regression of nearwork-induced accommodative adaptation may have significant neural, pharmacological, mechanical contributions (Hung and Ciuffreda, 1991), models that incorporate additional components to take into account the role of autonomic inputs to accommodation may be able to simulate the effect of autonomic agents on the adaptive gain or the time constants of the adaptive component. Differences in the decay response characteristics could thus be reflected in the variation of the adaptive gain parameter with the emphasis of the model on the modification of the adaptive gains by the use of autonomic agents. This may be helpful in investigating model parameters that could be modified to account for the differences in the accommodation responses and drug response profiles and lead to a better understanding of the underlying myopigenic mechanisms of autonomic imbalance as potential indicators of myopia development and progression.
Figure 6.3. The adaptive accommodation model adapted from Figure 1 of Hung and Ciuffreda (1991), the model of tonic accommodation after sustained near focus. The model is composed of two parallel components, reflex and adaptive, in the forward negative loop to simulate the initial rapid drop and the non-decayed adaptation effects in TA following nearwork. The depth of focus of the accommodation system was set to zero. Results of this thesis may lead to further work on this model by taking into account the autonomic inputs to accommodation and the effect of classifying myopic individuals according to myopia stability and ethnic background.

Abbreviations:
AS = accommodation stimulus, AR = accommodation response, TA = tonic accommodation, K = accommodative gain controlling the magnitude of the accommodative output, τ = the time constant of the decay process.
6.5. Future experiments

While characteristics of the accommodation and convergence system of myopic individuals were obtained in this thesis, it cannot be concluded that anomalous accommodation and convergence responses such as increased accommodative adaptation, or elevated response AC/A ratios, are predictive of further myopia progression. Longitudinal studies are important in establishing whether anomalous accommodation such as susceptibility to nearwork-induced accommodative adaptation and different response profiles to \( \beta \)-antagonism with timolol hold a cause or effect relationship with myopia development and progression. Our results support the hypothesis that sympathetic input to the ciliary muscle differs in myopes with different myopia progression rate and ethnic background. Longitudinal studies (Gilmartin et al., 2002) are currently underway to determine the percentage of individuals who have an active sympathetic facility during nearwork and to confirm or otherwise the notion that sympathetic deficit is aetiologically significant in the development and progression of myopia. Such an investigation of the profile of autonomic inputs to accommodation during sustained nearwork in a genetically susceptible population such as the Hong Kong Chinese could also provide the reason for the dramatically increased prevalence of myopia in Asian countries.

Further experiments into autonomic imbalance and myopia may include studies on pupil sizes. Autonomic nervous system abnormalities have been associated with a reduction in pupil size and reduced pupillary size fluctuation (Hreidarsson and Gundersen, 1989). Woug et al. (1998) found smaller pupils in early-onset myopes than in emmetropes and suggested that this may be of aetiological significance to myopia development. Smaller pupils have also been observed following nearwork (Tsuchiya et al., 1989) and this reduced pupil size may be consistent with the sympathetic deficit hypothesis suggested in this thesis.
APPENDIX 1

QUESTIONNAIRES

The following questionnaires, which were used in this thesis, were not validated research questionnaires but were designed to gather information on potential subject’s including: family and past ocular history, ethnic background and suitability for the instillation of β-adrenergic agents.

Questionnaire used in Chapter 2

Please circle your answer and/or write you answer in the space provided as appropriate.

♦ Date of birth  /  /  Age (yrs) ……………

♦ Please circle  Female (1)  /  Male (2)

♦ What is your ethnic background?  Caucasian (1) / Asian (2) / Other (3) ……………

♦ If you are short-sighted, how old were you when you were first diagnosed to be short-sighted?

Myopia onset: Age (yrs) ……………

<10 (1)  /  10-15 (2) /  15-20 (3) /  > 20 (4) years

♦ If you are short-sighted, has your prescription remained relatively stable?

Yes (1)  /  No (2)

♦ If not, how often have you had to update your glasses in the past two years?

Every 6 months (1)  /  once a year (2)  /  once every 2 years (3)  /  glasses older than 2 years (4)
♦ Please tick the appropriate box if you have or have had the following conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emphysema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal detachment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iritis/keratitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe heart block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyrodism</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Questionnaire used in Chapters 4 and 5

Please answer the following questions

1. Date of birth of your child  Age: ______
   ___/___/____

2. Only answer Question 3 if your child is short-sighted.

   a) If your child is short-sighted, how old was he/or she when first diagnosed to be short-sighted?  Age: ______

   b) How old was your child when he/or she got his/or her first pair of glasses?
      Age ______

   c) How often has your child had to update the prescription of the glasses?
      Please circle
3. How often does your child read for pleasure (outside of school)?
   Never / Rarely / Sometimes / Often

4. How many hours per week outside of school does your child ….
   Study or read for school homework? ______ h per week
   Read for pleasure? ______ h per week
   Watch television? ______ h per week
   Play video/computer games? ______ h per week
   Engage in outdoor/sports activities? ______ h per week
   Engage in other activities requiring looking at objects within arm’s reach (eg reading music, painting) ______ h per week

5. Are you short-sighted?? Yes / No
   If yes, how old were you when you were first diagnosed with short-sightedness??
   Age ______

6. Is your spouse also short-sighted?? Yes / No

7. Is there a positive history of active cardiac and/or respiratory conditions (eg asthma) in your child?
   Please circle Yes / No
APPENDIX 2
EFFECT OF MONOCULAR VS BINOCULAR INSTILLATION ON TONIC ACCOMMODATION

Studies investigating the effect of adrenergic agents on accommodation, such as those with timolol application have varied in terms of the dosage used and the number of eyes treated (Table A2.1). Here we present how the drug dosage used in this thesis was determined and compare the effect of applying drugs monocularly and binocularly.

Table A2.1. Summary on dosage information of previous studies

<table>
<thead>
<tr>
<th>Studies (yr)</th>
<th>Dosage information</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhD thesis</td>
<td>1 drop RE / 20 µL 0.5% timolol (adults)</td>
</tr>
<tr>
<td></td>
<td>2 drops RE / 20 µL 0.25% betaxolol S (adults)</td>
</tr>
<tr>
<td></td>
<td>1 drop RE and LE / 20 µL 0.5% timolol (children)</td>
</tr>
<tr>
<td>(Gilmartin et al., 2002)</td>
<td>1 drop RE and LE / 30 µL 0.5% timolol</td>
</tr>
<tr>
<td></td>
<td>2 drops RE and LE / 30 µL 0.5% betaxolol (60 µL)</td>
</tr>
<tr>
<td>(Winn et al., 2002)</td>
<td>1 drop RE and LE / 30 µL 0.5% timolol</td>
</tr>
<tr>
<td></td>
<td>2 drops RE and LE / 30 µL 0.5% betaxolol (60 µL)</td>
</tr>
<tr>
<td>(Otsuka et al., 1998)</td>
<td>2 drops RE and LE / 50 µL 0.5% timolol (100 µL)</td>
</tr>
<tr>
<td></td>
<td>2 drops RE and LE / 50 µL 0.5% betaxolol (100 µL)</td>
</tr>
<tr>
<td>(Gilmartin and Winfield, 1995)</td>
<td>1 drop RE and LE / 30 µL 0.5% timolol</td>
</tr>
<tr>
<td></td>
<td>2 drops RE and LE / 30 µL 0.5% betaxolol (60 µL)</td>
</tr>
<tr>
<td>(Gilmartin and Bullimore, 1987)</td>
<td>2 drops RE and LE / 25 µL 0.5% timolol (50 µL)</td>
</tr>
<tr>
<td>(Gilmartin and Hogan, 1985b)</td>
<td>2 drops RE and LE / 25 µL 3% isoprenaline (50 µL)</td>
</tr>
<tr>
<td>(Gilmartin et al., 1984)</td>
<td>2 drops RE and LE / 25 µL 0.5% timolol (50 µL)</td>
</tr>
</tbody>
</table>
Drug volume

Due to the possible systemic effects of β-adrenergic antagonists ocular instillation (Rait, 1999), it is desirable to use the lowest possible dose required to achieve the wanted effect. The volume of a single-dose minim was measured (320 µL) and divided by the number of eye drops from a minim (17 drops) and the volume of one drop was calculated to be 18.82 µL. There is evidence that increasing the drop size above 20 µL does not lead to greater ocular absorption (Maurice and Mishima, 1984) and an eye drop volume exceeding the capacity of the conjunctival cul-de-sac will be rapidly removed by the drainage system and via excessive blinking. This will result in a less accurate measure of the effective dose. For these reasons, a 20 µL drug volume was used.

Monocular vs binocular application

As the accommodation responses (Chapters 2 and 3) were measured monocularly and the drug agent was also applied monocularly, a study was conducted to compare the effect of monocular vs binocular instillation of timolol. We found no significant differences in TA measured following monocular or binocular timolol instillation, i.e. there was no significant difference between the two instillation regimes ($t_4 = -0.024$, $P = 0.982$; Table A2.2). Therefore the fact that timolol was applied monocularly in this thesis should not have attributed to the differences in the results obtained from those of the study by Gilmartin et al. (1995).
### Table A2.2. Effect of monocular vs binocular instillation of timolol on tonic accommodation

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Monocular</th>
<th></th>
<th>Binocular</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-instillation</td>
<td>Post-instillation</td>
<td>Difference</td>
<td>Pre-instillation</td>
<td>Post-instillation</td>
</tr>
<tr>
<td>TB</td>
<td>0.53</td>
<td>1.34</td>
<td>−0.19</td>
<td>0.61</td>
<td>0.46</td>
</tr>
<tr>
<td>AS</td>
<td>0.63</td>
<td>0.25</td>
<td>−0.37</td>
<td>0.11</td>
<td>0.08</td>
</tr>
<tr>
<td>EM</td>
<td>0.36</td>
<td>0.13</td>
<td>−0.24</td>
<td>0.12</td>
<td>0.19</td>
</tr>
<tr>
<td>SC</td>
<td>0.67</td>
<td>2.34</td>
<td>1.67</td>
<td>0.73</td>
<td>1.01</td>
</tr>
<tr>
<td>JH</td>
<td>2.24</td>
<td>1.58</td>
<td>−0.66</td>
<td>1.11</td>
<td>1.19</td>
</tr>
<tr>
<td>Average</td>
<td>1.09</td>
<td>1.13</td>
<td><strong>0.04</strong></td>
<td>0.54</td>
<td>0.59</td>
</tr>
</tbody>
</table>
APPENDIX 3

BEHAVIOURAL MANIPULATION OF THE AUTONOMIC INNERVATION IN ACCOMMODATION

A3.0. Summary

While most studies have utilized pharmacological modification to investigate the role of the autonomic nervous system in accommodation control, it has been suggested that behavioural manipulations may provide a novel way to explore the relative roles of the parasympathetic and sympathetic inputs in accommodation (Tyrrell and Thayer, 1995). Behavioural manipulation methods, such as cold face stress (Miller and Takahama, 1988, Khurana and Setty, 1996) and handgrips (Palatini et al., 1989, Tyrrell and Thayer, 1995) have been found to reliably activate the sympathetic system. The purpose of this experiment was to investigate the effect of hemispheric activation of autonomic activity using a behavioural technique, forced unilateral nostril breathing (FUNB), on tonic accommodation (TA), the resting state of the accommodation system. TA measurements were made using the Shin-Nippon autorefractor before and after 20 minutes of FUNB. The effect of FUNB on intraocular pressures and blood pressures were also monitored with a non-contact tonometer and an automated blood pressure monitor respectively. We found that both right and left FUNB had no significant effect on TA and there were no differential accommodation effects when subjects were separated based on their refractive error or myopia progression rate. Right FUNB produced a statistically significant decrease in IOP while left FUNB had no significant effect. The effect of FUNB may not be localised enough to induce any changes to the autonomic inputs of the ciliary muscle and accommodation.
A3.1. Introduction

Based on the dual innervation theory of accommodation control, behavioural manipulations that activate the parasympathetic system should increase accommodation, and manipulations that activate the sympathetic system should lead to a relaxation of accommodation. Consistent with this, Miller and Takahama (1988) found that manipulations, which are known to result in sympathetic activation such as cold face stress (i.e. placing a plastic bag of ice water against the forehead), produced lower tonic accommodation (TA) levels. Lower TA levels have also been observed following tasks that increase psychological stress (i.e. sympathetic activation) presumably due to the association between autonomic activity and emotional state (Miller and Takahama, 1987). Alternatively, relaxation techniques or exposure to natural sounds that result in parasympathetic activation produce higher TA levels (Miller and Takahama, 1987). However results that are inconsistent with the dual innervation theory have also been reported. Tyrrell and Thayer (1995) found TA levels to be greater during sympathetic dominance (shock avoidance/hand grip task); and Ritter and Huhn-Beck (1993) similarly found that stimulation of the sympathetic nervous system (produced by running) produced higher TA levels.

It has been suggested that the nasal cycle, the simultaneous congestion-decongestion response in the nasal cavities, is regulated by both the parasympathetic and sympathetic branches of the autonomic nervous system (Keuning, 1968) and may reflect the lateralization of the autonomic nervous system (Werntz et al., 1983). By manipulating the nasal cycle, forced unilateral nostril breathing (FUNB) has been demonstrated to cause selective contralateral hemispheric stimulation of the brain and based on brain lateralization of autonomic activity, FUNB may also manipulate the parasympathetic and sympathetic activities (Backon, 1990). Right nostril breathing would therefore induce left hemisphere stimulation and increase
sympathetic activity whereas left nostril breathing would induce right hemisphere stimulation and increase parasympathetic activity.

Previous studies have found that right FUNB produced a significant reduction in IOP in both normal subjects (Backon et al., 1989) and glaucoma patients (Backon et al., 1990). The reduction in IOP mediated by right FUNB (i.e. sympathetic activation) in normal subjects was as much as 25% (4-6 mmHg)(Backon et al., 1989). Other ocular effects produced by FUNB have included pupillary dilatation/miosis, and changes to the pupil cycle time, although these are unpublished data (Backon et al., 1989).

TA has been suggested to represent the resting position of the accommodation system or a state of equilibrium between the parasympathetic and sympathetic inputs to the ciliary muscle (Gilmartin and Hogan, 1985b, Gilmartin, 1986). The role of TA in myopia development has been extensively investigated, and the finding of lower TA levels in myopia implicated in myopia development and progression (Bullimore and Gilmartin, 1987a, McBrien and Millodot, 1987, Owens et al., 1989, Adams and McBrien, 1993, Gwiazda et al., 1995b, Woung et al., 1998, Zadnik et al., 1999). To our knowledge, the effect of FUNB on TA has not been investigated and FUNB may provide a novel way to explore the relative roles of the parasympathetic and sympathetic inputs in the control of accommodation, particularly in myopic subjects.

We predicted that right FUNB would activate sympathetic activity whereas left FUNB would activate parasympathetic activity and they would produce the effects described in Table A3.1.
Table A3.1. Predicted ocular and systemic effect of right and left FUNB based on brain lateralization of autonomic activity.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Right FUNB</th>
<th>Left FUNB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateralization</td>
<td>Left brain hemisphere stimulation</td>
<td>Right brain hemisphere stimulation</td>
</tr>
<tr>
<td></td>
<td>↑ Sympathetic activity (sympathetic dominance, parasympathetic withdrawal)</td>
<td>↑ Parasympathetic activity (parasympathetic dominance, sympathetic withdrawal)</td>
</tr>
<tr>
<td>Autonomic activity</td>
<td>↓ IOP</td>
<td>↑ IOP</td>
</tr>
<tr>
<td>IOP</td>
<td>↓ TA</td>
<td>↑ TA</td>
</tr>
<tr>
<td>TA</td>
<td>↑ Blood pressure</td>
<td>↓ Blood pressure</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↑ Heart rate</td>
<td>↓ Heart rate</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symbols: ↑ Increase
         ↓ Decrease

A3.2. Methods

A3.2.1. Subjects

Seventeen subjects aged between 18 and 26 years were recruited from the student population at Queensland University of Technology. Monocular visual acuities were 6/6 or better using the Bailey-Lovie acuity chart (Bailey and Lovie, 1976) and all of the subjects were free of ocular disease or oculomotor imbalance. Subjects with known nasal problems such as polyps or a deviated septum were excluded.

Based on non-cycloplegic subjective refraction results, subjects were divided into three groups, non-myopes (n = 4)(spherical equivalent refractive error (SERE) (i.e. spherical component + half of the cylindrical component) between −0.25 D and
Subjects with SERE ≥ −0.75 D of myopia were categorized as being myopes. Myopic subjects were also separated into stable myopes (n = 9), and progressing myopes (n = 4) based on their myopia progression rate. Information on progression rate was obtained from past clinic records or the subject’s optometrist. Myopes were considered to be progressing if their myopia had worsened by −0.50 D or more over the past two years. The study was conducted in accordance with the requirements of the Queensland University of Technology Human Research Ethics Committee. All subjects were given a full explanation of the experimental procedures and informed consent was obtained.

A3.2.2. Tonic accommodation measurements

The subject was directed to the distance target (6/9 letters on a Bailey-Lovie chart at 6 m) and initial base-line far readings were taken at 2-second intervals for one minute (~30 readings). A 3-minute period in the dark was used to allow accommodation to regress to the base-line tonic level. Darkroom accommodation readings (~30 readings) were measured for one minute with the subject being instructed to look straight ahead. The tonic accommodation value was taken as the difference between the average of the darkroom readings and the average of the initial base-line far readings.

A3.2.3. Apparatus

TA was measured using the Shin-Nippon SRW-5000 autorefractor (Topcon, Japan) in a static mode. All myopes were corrected with trial frames and lenses, fitted with a pantoscopic tilt of 15 degrees to prevent reflections from the anterior surface of the lens to prevent interference with the operation of the autorefractor. Measurements were made on the right eye only while left eye was covered with an opaque occluder.
A3.2.4. Intraocular and blood pressures measurements

Intraocular pressures (IOP) were measured using a non-contact tonometer (American Optical, UK). Three consecutive readings were taken to obtain a difference of less than 2 mmHg between the readings. If the difference was greater than 2 mmHg, a fourth reading was taken and an average of the three closest readings was calculated. Heart rate and blood pressures were monitored using a digital automated blood pressure monitor (Omron M4, Japan). It is accurate to within 2% of blood pressure readings and 5% of heart rate readings.

A3.2.5. Procedure

Base-line measurements on accommodation, IOP, blood pressure, and pulse rate were made. Right FUNB was administered for 20 minutes with the left nostril completely blocked by cotton packing. Immediately following this, measurements were repeated in the same order. Left FUNB was performed at a second visit, which on average was scheduled one week later.

A3.2.6. Data analysis

Statistical analysis of the data was conducted using Statistical Packages for Social Sciences (SPSS). No measures differed significantly from the normal distribution (Kolmogorov-Smirnov, $P > 0.05$) and parametric tests (paired t-test) were used. Nonparametric (Wilcoxon signed ranked test) tests were included as the sample size of this study was small.
A3.3. Results

A3.3.1. Subject characteristics

The EOMs had a mean SERE of $-4.59 \pm 1.65$ D which was statistically higher than the LOMs (mean SERE $= -1.75 \pm 1.06$) ($t_{11} = -3.612, P = 0.004$). Base-line IOP of non-myopes, EOMs and LOMs were similar (Table A3.2). There were no significant differences in TA levels between the refractive error groups (Table A3.2), nor were there differences in base-line IOP and TA levels when myopic subjects were separated into stable myopes and progressing myopes (Table A3.3).

Table A3.2. Base-line refractive error, IOP and TA levels of different subject groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-myopes (4)</th>
<th>EOMs (7)</th>
<th>LOMs (6)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractive error (D)</td>
<td>0±0.44</td>
<td>-4.59±1.65</td>
<td>-1.75±1.06</td>
<td>$F_{2, 14} = 18.290, P &lt; 0.001$</td>
</tr>
<tr>
<td>Baseline IOP (Right eye) (mmHg)</td>
<td>13.00±1.58</td>
<td>15.07±2.46</td>
<td>15.25±3.74</td>
<td>$F_{2, 14} = 0.881, P =0.436$</td>
</tr>
<tr>
<td>Baseline IOP (Left eye) (mmHg)</td>
<td>12.88±2.06</td>
<td>14.00±2.20</td>
<td>15.33±3.30</td>
<td>$F_{2, 14} = 1.094, P =0.362$</td>
</tr>
<tr>
<td>Baseline TA (D)</td>
<td>0.54±0.92</td>
<td>1.17±1.00</td>
<td>0.76±0.72</td>
<td>$F_{2, 14} = 0.720, P =0.504$</td>
</tr>
</tbody>
</table>
Table A3.3. Base-line refractive error, IOP and TA levels of subjects when separated based on myopia progression rate.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Refractive error groups</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-myopes (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stable myopes (7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progressing myopes (6)</td>
<td></td>
</tr>
<tr>
<td>Refractive error (D)</td>
<td>0±0.44</td>
<td>F_{2, 14} = 4.770, P = 0.026</td>
</tr>
<tr>
<td>Baseline IOP (Right eye) (mmHg)</td>
<td>13.00±1.58</td>
<td></td>
</tr>
<tr>
<td>Baseline IOP (Left eye) (mmHg)</td>
<td>12.88±2.06</td>
<td></td>
</tr>
<tr>
<td>Baseline TA (D)</td>
<td>0.54±0.92</td>
<td>F_{2, 14} = 0.480, P = 0.629</td>
</tr>
</tbody>
</table>

A3.3.2. Effect of FUNB on TA

Right FUNB had no statistically significant effect on TA (paired t-test, t_{16} = 0.181, P = 0.859; Table A3.4). TA was lowered by an average of −0.25D after left FUNB application (paired t-test, t_{16} = 2.120, P = 0.05; Table A3.4), which was approaching statistical significance. There was a significant negative correlation between the decrease in TA produced by left FUNB and the base-line TA (r = −0.749, P = 0.001; Figure A3.1), i.e. the higher the base-line TA, the greater the decrease in TA. FUNB also lowered TA levels to a greater extent in subjects who had high base-line TA levels (i.e. > 1.5 D; subjects 1-4 in Figure A3.2). However this decrease in TA was opposite to the predicted effect of left FUNB described in Table A3.1.
FUNB had no differential effect on TA between non-myopes, EOMs and LOMs and all refractive error groups had a similar change in TA ($F_{2, 14} = 0.374, P = 0.695$ (right FUNB); $F_{2, 14} = 1.874, P = 0.190$ (left FUNB); Figure A3.3A). The change induced by FUNB in TA between non-myopes, stable myopes and progressing myopes was also similar ($F_{2, 14} = 0.084, P = 0.920$ (right FUNB); $F_{2, 14} = 1.775, P = 0.206$ (left FUNB); Figure A3.3B). However, the results of left FUNB lacked statistically power and differences may be detected if the study was repeated with more subjects.

Table A3.4. Effect of 20 minutes of FUNB on TA (mean±s.d.)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline TA (D)</th>
<th>TA after FUNB (D)</th>
<th>Change in TA (D)</th>
<th>p-value (paired t-test)</th>
<th>p-value (Wilcoxon signed-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right FUNB</td>
<td>0.88±0.87</td>
<td>0.85±0.81</td>
<td>−0.03</td>
<td>0.859</td>
<td>0.758</td>
</tr>
<tr>
<td>Left FUNB</td>
<td>0.85±0.90</td>
<td>0.60±0.63</td>
<td>−0.25</td>
<td><strong>0.05</strong></td>
<td>0.084</td>
</tr>
</tbody>
</table>
Figure A3.1. A scattergram of the relationship between base-line TA and change in TA produced by left FUNB. There appeared to be a negative correlation, i.e. the higher the base-line TA, the greater the decrease induced by left FUNB.

Figure A3.2. Tonic accommodation before and after left FUNB and the change in TA (ranked by pre-LFUNB TA level) in 17 subjects. The left FUNB appeared to have a greater effect on subjects with a base-line TA levels of greater than 1.5 D.
Figure A3.3. TA before and after right and left FUNB of A: non-myopes, EOMs and LOMs, B: non-myopes, stable myopes and progressing myopes. There were no statistically significant differences in base-line TA between groups nor were there differences in the effect of right and left FUNB. Error bars represent one standard deviation.
A3.3.3. Effect of FUNB on IOP

Sympathetic activation via right FUNB produced a mean decrease of 9.6% in IOP (right eye), which was statistically significant (paired t-test, $t_{16} = 2.962$, $P = 0.009$; Wilcoxon signed ranked test, $Z = -2.333$, $P = 0.02$; Table A3.5). There was a mean decrease of 6.7% in IOP in the left eye (paired t-test, $t_{16} = 1.594$, $p = 0.12$; Wilcoxon signed ranked test, $Z = -2.022$, $P = 0.043$). IOP in 14 out of 17 cases was changed in the predicted direction (i.e. an IOP reduction with right FUNB, Table A3.1). One subject showed no changes in IOP while two subjects had an increase in IOP. A binomial test with a probability of 0.33 (IOP could either increase, decrease or not change) showed that there was a significant trend towards lower IOP following right FUNB ($P < 0.002$).

The effect of parasympathetic activation via left FUNB on IOP showed a trend toward higher IOP (mean increase of 5.7% and 2.5% in the right and left eye respectively) although the changes were not statistically significant (Table A3.5). The binomial test showed that the probability that IOP in 10/16 observations would change in the predicted direction (i.e. an IOP increase with left FUNB application) was significant ($P = 0.015$). There are no significant interocular differences in baseline IOP (paired t-test, $t_{16} = 0.982$, $P = 0.341$ for right FUNB; $t_{16} = 0.445$, $P = 0.662$ for left FUNB). Also, FUNB produced no significant effect on heart rate and blood pressure, either systolic and diastolic (Tables A3.6 and A3.7).
### Table A3.5. Mean changes in IOP following right and left FUNB

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Eye</th>
<th>Pre-FUNB IOP (mmHg)</th>
<th>Post-FUNB IOP (mmHg)</th>
<th>Change in IOP (mmHg)</th>
<th>Mean change in IOP (%)</th>
<th>Paired t-test</th>
<th>Wilcoxon signed-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right FUNB</td>
<td>R</td>
<td>14.65±2.83</td>
<td>13.31±3.23</td>
<td>−1.34±1.86</td>
<td>−9.59</td>
<td>0.009</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>14.21±2.63</td>
<td>13.36±2.87</td>
<td>−0.84±2.18</td>
<td>−6.19</td>
<td>0.13</td>
<td>0.04</td>
</tr>
<tr>
<td>Left FUNB</td>
<td>R</td>
<td>14.19±2.74</td>
<td>15.26±3.58</td>
<td>+1.07±2.87</td>
<td>+5.67</td>
<td>0.14</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>13.89±3.03</td>
<td>14.36±3.50</td>
<td>+0.47±2.35</td>
<td>+2.51</td>
<td>0.13</td>
<td>0.39</td>
</tr>
</tbody>
</table>

### Table A3.6. Effect of 20 minutes of FUNB on heart rate (mean+s.d.)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Base-line Heart rate (beats/minute)</th>
<th>Heart rate after FUNB (beats/minute)</th>
<th>p-value (paired t-test)</th>
<th>p-value (Wilcoxon signed-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right FUNB</td>
<td>69.94±13.9</td>
<td>70.181±4.77</td>
<td>0.941</td>
<td>0.221</td>
</tr>
<tr>
<td>Left FUNB</td>
<td>74.53±9.52</td>
<td>73.82±14.57</td>
<td>0.734</td>
<td>0.711</td>
</tr>
</tbody>
</table>
Table A3.7. Effect of 20 minutes of FUNB on blood pressure (mean±s.d.)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Base-line systolic pressure (mmHg)</th>
<th>Systolic pressure after FUNB (mmHg)</th>
<th>p-value (paired t-test)</th>
<th>p-value (Wilcoxon signed-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right FUNB</td>
<td>111.94±19.37</td>
<td>107.35±19.89</td>
<td>0.302</td>
<td>0.132</td>
</tr>
<tr>
<td>Left FUNB</td>
<td>105.88±17.72</td>
<td>109±13.51</td>
<td>0.12</td>
<td>0.088</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Base-line diastolic pressure (mmHg)</th>
<th>Diastolic pressure after FUNB (mmHg)</th>
<th>p-value (paired t-test)</th>
<th>p-value (Wilcoxon signed-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right FUNB</td>
<td>71.65±10.87</td>
<td>67.12±7.46</td>
<td>0.089</td>
<td>0.064</td>
</tr>
<tr>
<td>Left FUNB</td>
<td>63.71±8.34</td>
<td>65.82±5.76</td>
<td>0.218</td>
<td>0.350</td>
</tr>
</tbody>
</table>

A3.3.4. IOP and refractive error

Base-line IOP (right eye) prior to right FUNB application of non-myopes (13.00±1.58 mmHg), EOMs (15.07±2.46 mmHg) and LOMs (15.25±3.74 mmHg) were similar (F2, 14 = 0.881, P = 0.436; Figure A3.4A) and right FUNB were not significantly different between the refractive error groups (F2, 14 = 0.956, P = 0.408; Figure A3.4A). Similarly, there were no statistically significant differences in base-line IOP (right eye) between non-myopes, stable myopes and progressing myopes (F2, 14 = 1.215, P = 0.326; Figure A3.4B) nor were there differential effects of right FUNB between the groups (F2, 14 = 0.160, P = 0.854; Figure A3.4B). Results for left FUNB were similar.
Figure A3.4. IOP before and after right and left FUNB of A: non-myopes, EOMs and LOMs, B: non-myopes, stable myopes and progressing myopes. There were no statistically significant differences in base-line IOP between groups nor were there differential effects of right and left FUNB in different refractive error groups. Error bars represent one standard deviation.
A3.4. Discussion

By activating the sympathetic activity via left hemisphere stimulation, right FUNB produced a significant decrease in IOP by 9.6 %, whereas by activating the parasympathetic activity via right hemisphere stimulation, IOP on average was increased by 5.7 %. The percentage of change in IOP reported here is smaller than a previous study where a reduction of 25 % was reported (Backon et al., 1989). FUNB appears to have a greater influence on IOP compared to that on TA. It is possible that a systemic alteration of autonomic activity by manipulating the nasal cycle may not have been sufficient to induce significant local effects to the autonomic input to the ciliary muscle.

As TA has been suggested to be the result of parasympathetic innervation to the ciliary muscle (Gilmartin and Hogan, 1985b, Gilmartin and Hogan, 1985a), it is reasonable that left FUNB that is associated with the parasympathetic activity appeared to have a greater effect than right FUNB, which activates the sympathetic activity. Decreases in TA produced via left FUNB only occurred in subjects who had base-line TA levels greater than 1.5 D. This suggests that subjects with a parasympathetic dominance or a more robust parasympathetic inputs to the ciliary muscle (i.e. higher TA levels) are more susceptible to left FUNB manipulation. Although the decrease in TA via left FUNB was close to being statistically significant, we cannot conclude that this was a true effect as it was observed in less than half the subjects. Also, the direction of TA change was opposite to the effect predicted based on parasympathetic activation via left FUNB. Refractive error and myopia progression rate were not significant factors in the effect of FUNB produced on TA and IOP. This conclusion must be viewed in light of the small sample size and the unequal number of subjects in each refractive error subgroup, and the inherent variability in the effect of this technique. Power analysis revealed that a sample size
of 85 in each subject group is required to detect a difference of 0.5 D in TA or 2 mmHg in IOP at a significance level of 0.05 (power = 0.90).

Given the present data and inconsistencies in the literature regarding the relationship between TA and autonomic innervation to the ciliary muscle, the interactions between autonomic activity and TA appear to be more complex than the simple balance theory between two opposing forces that dual innervation theory suggests. In addition, the lateralized relationship of autonomic activity is another area of debate. FUNB appears to produce more reliable effects on IOP than on accommodation. In order to unravel the role of the autonomic balance in the control of accommodation in myopia, manipulations that produce predictable accommodation effects are more appropriate.

A3.5. Conclusion

FUNB, a technique that is known to affect autonomic activity, did not produce the predicted effect on tonic accommodation. Manipulations that produce predictable accommodation effects are necessary if they are to be applied to the investigation of accommodation and myopia.
APPENDIX 4
PILOT STUDIES OF DRUG DOSAGE AND CONCENTRATION:
TROPICAMIDE AND PILOCARPINE

A4.0. Summary

Variations of the parasympathetic inputs to the ciliary muscle are predominantly responsible for the variations in tonic accommodation levels with sympathetic inputs playing a smaller role. This prompted us to study the effects of two agents, tropicamide and pilocarpine, on the relative balance between parasympathetic and sympathetic control of accommodation.

As a parasympatholytic agent, tropicamide inhibits the parasympathetic inputs to the ciliary muscle and hence the accommodation system. Gilmartin and Hogan (1985a) found that 0.5% tropicamide application produced a reduction in tonic accommodation from 1.67 to 0.02 D. As it is likely that tropicamide will eliminate most of the accommodation responses, a pilot study of the dose-response and time-response was conducted to determine the lowest possible concentration of tropicamide which, when applied, would reduce accommodation but leave a residual amplitude sufficient to be measured or modified by other autonomic agents (at least 5 D of accommodation remaining).

Application of pilocarpine, a parasympathomimetic agent, may pose a potential problem as this drug constricts the pupil, which can interfere with accommodation measurements. The minimum pupil size for efficient operation of the autorefractor is 2.9 mm and even in low concentration (0.125%), pilocarpine has been reported to constrict the normal pupil by 2.4 mm (Bartlett et al., 1995). It was thus important to determine the minimum concentration of pilocarpine that could be used to maintain
the pupil size at a sufficiently large diameter for the operation of the autorefractor while still having an effect on parasympathetic stimulation.

A4.1. Method

A4.1.1. Subjects

Thirteen subjects aged 18-27 years participated in the pilot study. Monocular visual acuities were 6/6 or better on the Bailey-Lovie acuity chart and all of the subjects were free of ocular disease or oculomotor imbalance. Subjects were excluded if they had any of the contraindications to the instillation of tropicamide and pilocarpine (i.e., glaucoma). Two subjects were used to determine the dose-response effects of tropicamide, eight subjects for the time-response effect of 0.125% tropicamide while three subjects were used for the time-response effect of 0.125% pilocarpine.

A4.1.2. Measurements of accommodation and pupil size

The amplitude of accommodation was measured at 2-minute intervals using the push-up method with a N6 print on a Bailey-Lovie near acuity chart ten minutes following instillation. The pupil size was also measured every 2 minutes using a pupillometer and a Burton lamp 10 minutes post-instillation.

A4.1.3. Apparatus

Trial frames and lenses were used to correct the subject’s refractive error as determined by subjective refraction. The frame was fitted with a pantoscopic tilt of 15 degrees to reduce reflections from the anterior surface of the lens to prevent interference with the operation of the autorefractor. Accommodation was measured using a Canon Autoref R-1 autorefractor. A video system was used to monitor the
subject’s eye position during measurements to ensure proper fixation and alignment. Invalid autorefractor readings characterized by large cylindrical components or error display, due to blinking or fixation losses, were disregarded. Sphere and cylinder powers were recorded to an accuracy of 0.12 D with all powers being referred to the corneal plane and the SERE was used. All measurements were made on the right eye while the left eye was occluded with an eye patch.

A4.1.4. Drug treatments

Drugs were applied to the right eye only using a precision micropipette. Each instillation delivered 20 µl of drug. Eyelid closure and punctal occlusion techniques were carried out for two minutes to minimize systemic absorption. Prior to instillation, benoxinate HCL 0.4% was used to inhibit reflex lacrimation and increase corneal permeability (Bartlett and Jaanus, 2001).

The common dosage of tropicamide applied clinically is 0.5% and the concentration of tropicamide was diluted with saline (i.e. 0.5%, 0.25%, 0.125%) to generate a dose-response curve. Measurements were repeated for different concentration of the agent on separate days. The experimental sessions were separated by at least two days to ensure total wash-out of the drug.

A4.1.5. Iris colour grading scale

It is well known clinically that eyes with dark irides require a higher dosage or concentration of the drug to produce the same effects as eyes with light irides and that drugs such as pilocarpine bind to the iris pigment epithelium. Therefore, the aim of an iris colour grading scale was used to assess the effect of iris colour on drug effectiveness. The subject’s iris colour was graded on a 1-5 scale (1: light blue/grey,

A4.2. Results

Dose-response curve of tropicamide

Figure A4.1. Time course of the effect of three different volumes and concentration combinations of two subjects.

We found that 20 µl of 0.125% tropicamide reduced the accommodation to the level (with a residual amplitude of accommodation of ~6 D) where the remaining accommodation could be measured or modified with other autonomic agents.
Figure A4.2. Time-response curves of 0.125% tropicamide for A: the effect on amplitude of accommodation, and B: the effect on pupil size. Tropicamide did not appear to have a stronger effect on subjects with light iris colours.
Appendix 4

Figure A4.3. Time-response curves of 0.125% pilocarpine for A: the effect on amplitude of accommodation, and B: the effect on pupil size.

Consistent with previous studies, the maximal cycloplegic effect of tropicamide occurred 20-25 minutes after its instillation. The maximal mydriatic effect also occurred at about the same time. The subject’s iris colour or refractive error did not appear to have any significant effect on the time-response curve. There appeared to be more inter-subject variability on the time-response effect of 0.125% pilocarpine. The concentration of 0.125% may have been too weak to induce any parasympathetic activation, as there was an increase in the amplitude of accommodation in only one subject. The effect of 0.125% pilocarpine on pupil miosis was also minimal.
Effect of 0.125% tropicamide and pilocarpine on TA

Figure A4.4. Effect on tonic accommodation of **A:** 0.125% tropicamide, and **B:** 0.125% pilocarpine.

Consistent with the findings of Gilmartin et al. (1985b), 0.125% tropicamide reduced tonic accommodation in seven of the eight subjects while the effect of pilocarpine was more variable. Due to the technical difficulty of measuring accommodation responses with the pilocarpine-induced miosis and the stronger concentration of pilocarpine that may have been necessary to induce parasympathetic activation, we decided to study the effect of adrenergic agents in isolation rather than using combinations of muscarinic and adrenergic agents to study the autonomic control of accommodation.
APPENDIX 5
NEARWORK-INDUCED TRANSIENT MYOPIA:
COMPARISON OF OPEN- AND CLOSED-LOOP MEASURES

A5.0. Summary

Significant differences in the amount of nearwork-induced accommodative adaptation were observed under open-loop conditions between groups classified based on myopia progression rate and ethnic background and it was suggested that accommodative adaptation may play a role in the development and progression of myopia (Chapter 2). Under closed-loop conditions, normal blur-feedback mechanisms operate and the magnitude of nearwork-induced accommodative adaptation observed under such conditions is smaller (see section 1.3.1).

This appendix presents a study investigating nearwork-induced transient myopia (NITM) in different refractive error groups and assessing the effect of β-adrenergic antagonism with timolol. The difference of this experiment from that of Chapter 2 was that all measurements were made under closed-loop conditions (i.e. in the light) and changes in distance refraction were measured rather than changes in tonic accommodation. Forty-five subjects who had accommodative adaptation measured under open-loop conditions also had NITM measured under closed-loop conditions. The same experimental protocol (i.e. sequence of accommodation measurements, drug treatments, and apparatus) was followed. Figure A5.1. shows the accommodation demands and the sequence of measurements.
Figure A5.1. A schematic representation of the experimental protocol. Thirty readings of the refractive state (DRx) were taken for one minute and averaged. Subjects then viewed the target (distant or near) for a 3-minute period. Immediately following task completion, accommodation regression towards the base-line pre-task TA level was measured over a 90-second period (45 readings).

A5.1. Results

A5.1.1. Refractive error and NITM (closed-loop)

Under closed-loop conditions, NITM was induced in all refractive error groups (Table A5.1). Contrary to recently published studies (Ciuffreda and Wallis, 1998, Ciuffreda and Lee, 2002), we did not find susceptibility to NITM to be related to refractive error, i.e. myopes (both EOMs and LOMs) did not show a greater magnitude of NITM compared to non-myopes (F2, 42 = 0.804, P = 0.454; Table A5.1 and Figure A5.2). Classifying myopes according to myopia progression rate did not alter these findings (F2, 42 = 0.0.437, P = 0.649); neither did classifying myopes...
according to both progression rate and ethnic background ($F_{4, 40} = 0.226, P = 0.922$; Table A5.1 and Figure A5.2).

**Table A5.1.** Magnitude of nearwork-induced transient myopia (D) as a function of refractive group (myopia onset, progression rate and ethnic background) averaged over the 90 s post-task period.

<table>
<thead>
<tr>
<th></th>
<th>Non-myopes</th>
<th>EOMs</th>
<th>LOMs</th>
<th>Stable myopes</th>
<th>Progressing myopes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NITM averaged over 90 s (D)</td>
<td>0.29±0.08</td>
<td>0.25±0.25</td>
<td>0.23±0.17</td>
<td>0.28±0.21</td>
<td>0.19±0.20</td>
</tr>
<tr>
<td></td>
<td>Caucasian stable myopes</td>
<td>Caucasian progressing myopes</td>
<td>Asian stable myopes</td>
<td>Asian progressing myopes</td>
<td></td>
</tr>
<tr>
<td>NITM averaged over 90 s (D)</td>
<td>0.31±0.21</td>
<td>0.25±0.21</td>
<td>0.18±0.23</td>
<td>0.13±0.20</td>
<td></td>
</tr>
</tbody>
</table>

A5.1.2. Effect of timolol on NITM (closed-loop)

The magnitude of the timolol-induced changes in NITM was small and no differences were observed between groups with different refractive error, myopia progression rate and ethnic background. Figures A5.3 and A5.4 show the regression profiles of NITM of both the control saline and timolol trials in different subject groups (refractive error and myopia progression).
Figure A5.2. Regression patterns of NITM when subjects were separated based on A: refractive error, B: myopia progression rate, C: myopia progression/ethnic background. NITM was induced in all subject groups but there were no statistically significant differences between the groups.
Regression profiles of NITM of the control betaxolol trial and timolol trial were similar for all groups.
Figure A5.4. Post-task decay of NITM in A: non-myopes, B: stable myopes C: progressing myopes. Timolol did not produce any significant differences in the regression profiles of NITM.
A5.2. Discussion

A5.2.1. Closed-loop vs open-loop accommodative adaptation

When assessing accommodation immediately following nearwork under open-loop conditions, the assumption is that the accommodation system would adopt a position that is different from the normal resting state of accommodation to reflect the within-task accommodative adaptation processes operating during nearwork. Under closed-loop conditions, accommodative adaptation can still occur but the magnitude of nearwork-induced accommodation changes would smaller than those observed under open-loop conditions and this is due to the blur-feedback mechanism that is allowed to operate under such conditions.

The greater susceptibility of myopes, particularly progressing myopes, to NITM that has been previously reported was not reproduced in this study. Several reasons could account for this negative effect. The task duration employed in our study was three minutes, which was shorter compared to the ten minutes task duration used in the studies of Vera-Diaz et al. (2002) and Ciuffreda and Wallis (1998) and four hours used in the study of Ciuffreda and Lee (2002). It is likely that a longer task duration may be required to induce changes in the accommodation system under closed-loop conditions. The type of task may also have been a factor, as cognitive effort such as performing arithmetical tasks was not employed in this study.

A5.2.2. Significance of sympathetic control of accommodation

To our knowledge, this is the first study that investigated the effect of β-adrenergic antagonism on nearwork-induced accommodative adaptation under closed-loop conditions. Timolol application failed to induce any significant changes to NITM and the effect of modifying the sympathetic control of accommodation on the closed-loop
measures of accommodation was mostly likely masked by blur-feedback and the
depth of focus of the eye. This explanation may also be applied to the lack of effect
of β-adrenergic agents on the amplitude of accommodation (Gilmartin et al., 1984).
Although there is strong evidence that sympathetic inputs play an important role in
the control of ocular accommodation, the contribution of the sympathetic system in
normal visual environment is smaller compared to that under open-loop conditions.
APPENDIX 6

AUTOREFRACTOR MEASUREMENTS OF ACCOMMODATION

Correction factor to Canon autorefractor data

When the Canon Autoref R-1 is calibrated the output signal from the autorefractor should read –8.00 D when there is no input (i.e. when the reflecting mirror of the autorefractor is covered). However, the output signal of the autorefractor was less than what it should be and a correction factor should be added to all the accommodation values to account for this slight discrepancy.

Five hundred output readings were taken with the reflecting mirror of the Canon autorefractor covered and the average reading was –7.7985 D. Therefore, a correction of –0.20 D was added to all accommodation measurements using this instrument in Chapter 2.

Canon vs Shin-Nippon autorefractor

Both the open-field Canon vs Shin-Nippon autorefractors were used in the thesis and although accommodation readings from the two instruments have been found comparable (Chat and Edwards, 2001, Mallen et al., 2001), this is a factor which needs to be taken into account when comparing the results obtained using the different autorefractors (Chapter 2 vs Chapters 3, 4 and 5).
The following table presents a comparison of the main features of the Canon and Shin-Nippon autorefractors.

**Table A6.1.** Comparison of the Canon and Shin-Nippon autorefractors (McBrien and Millodot, 1985, Chat and Edwards, 2001, Mallen et al., 2001)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Canon</th>
<th>Shin-Nippon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binocularity</td>
<td>Binocular field of view</td>
<td>Binocular field of view</td>
</tr>
<tr>
<td>Light source</td>
<td>Infrared</td>
<td>Infrared</td>
</tr>
<tr>
<td>Mirror</td>
<td>Semi-silvered</td>
<td>Semi-silvered</td>
</tr>
<tr>
<td>Target imaged at the retina</td>
<td>Infrared square wave grating target</td>
<td>Ring target of infrared</td>
</tr>
<tr>
<td>Image analysis</td>
<td>Reflected light assessed in three meridians 60° apart</td>
<td>Image analysis in multiple meridians</td>
</tr>
<tr>
<td>Refractive error form</td>
<td>Sphero-cylindrical form</td>
<td>Toroidal refractive prescription</td>
</tr>
<tr>
<td>Vertex distance</td>
<td>0 and 12 mm</td>
<td>0, 10, 12, 13.5, 15, 16.5 mm</td>
</tr>
<tr>
<td>Speed of measurement</td>
<td>0.2 s</td>
<td>0.15 s</td>
</tr>
<tr>
<td>Power range</td>
<td>±15.00 sphere</td>
<td>±22.00 sphere</td>
</tr>
<tr>
<td></td>
<td>±7.00 cylinder</td>
<td>±10.00 cylinder</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.12 D</td>
<td>0.125 D</td>
</tr>
<tr>
<td>Minimum pupil size</td>
<td>2.9 mm</td>
<td>2.9 mm</td>
</tr>
</tbody>
</table>
APPENDIX 7
STATISTICS

The initial choice of statistical tests used in this thesis was based on information in the publications of Gilmartin et al. (1995, 2002). Consultation was also sought with a statistician, Dr. Harry Bartlett, the Mathematics and Statistics Consulting unit, School of Mathematical Sciences, QUT. None of the variables measured were significantly different from the normal distribution and parametric tests were used.

Repeated measures analysis of variance

Repeated measures analysis of variance was performed using the general linear model to determine the main effects for each of the independent variables and whether the interaction between the two variables was significant. The assumption was that the populations from which the samples were taken were normally distributed and were of equal variances. There is no non-parametric alternative for this test. For experiments in this thesis, the between-subject variable was subject grouping (i.e. refractive error, myopia progression rate, ethnic background) and the within-subject variables were time, and drug trial. The Bonferroni post-hoc test was used to determine which groups were significantly different from each other.

Sample size

There were a few instances where no significant differences between subject groups were detected and a power analysis was performed using the Instat program to calculate the number of subjects required to detect a statistically significant difference.
Chapter 3: to detect a difference of 0.25 D in the magnitude of accommodative adaptation between the Rx change group and the No Rx change group, a sample size of 118 per subject group was required to show a statistically significant difference at the 0.05 level (power = 0.90).

Chapter 5: to detect a difference of 0.5 \( \Delta/D \) in the AC/A ratio between Hong Kong myopic and emmetropic children, a sample size of 34 per subject group was required to show a statistically significant difference at the 0.05 level (power = 0.90) in distance-induced AC/A ratios, 276 for positive-lens induced and 1477 for negative lens-induced AC/A ratios.


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