The effect of a cardiac rehabilitation programme on carotid stiffness and haemodynamic properties of patients diagnosed with a transient ischaemic attack: a pilot study

Compiled by Brandon Woolley for the degree of Master of Health Science in Sport and Exercise Science from Massey University, Wellington.

“I certify that all material in this research report which is not my own work has been identified and that no material is included for which a degree has previously been conferred upon me

……………………..”

Dr. James Faulkner
Dr. Sally Lark
Acknowledgements

First of all I wish to acknowledge the invaluable help and direction provided by my supervisors, Dr. James Faulkner and Dr. Sally Lark, who offered up their time and assistance throughout the year, and without which this study would not have been possible. I would also like to thank my fiancée Flo for her love and support and for the many hours she spent proof reading this Thesis. I wish to acknowledge my parents Phil and Joy and thank them for their constant encouragement, which drove me forward in my studies. I would also like to thank Rebecca Grigg, Simon Chatterton and Ryan Tara for their assistance both with testing and running the exercise intervention. Lastly, I wish to thank the participants who volunteered to take part in this investigation and who, with great enthusiasm and interest, dedicated their time to completing this study. Without their commitment this study would not have been possible.
# Table of contents

Acknowledgements........................................................................................................2
List of abbreviations ........................................................................................................6
List of tables .......................................................................................................................7
List of figures .....................................................................................................................8
Abstract ...........................................................................................................................10
1. Introduction ...................................................................................................................12
2. Literature review ..........................................................................................................15
  2.1. Stroke .......................................................................................................................15
    2.1.1. Epidemiology ......................................................................................................15
    2.1.2. Pathophysiology of transient ischaemic attack ...............................................16
    2.1.3. Physical activity and risk factor reduction .......................................................18
  2.2. Arterial stiffness ........................................................................................................19
    2.2.1. Arterial functions ...............................................................................................19
    2.2.2. Mechanisms of arterial stiffness ......................................................................20
    2.2.3. Endothelial function .........................................................................................21
    2.2.4. Arterial structure and function, and stroke risk ................................................22
    2.2.5. Effects of arterial stiffening .............................................................................25
    2.2.6. Pharmacological interventions for reducing arterial stiffness .......................30
  2.3. The effect of exercise on arterial stiffness ...............................................................31
    2.3.1. Aerobic (endurance) exercise ..........................................................................32
    2.3.2. Resistance exercise ..........................................................................................34
  2.4. Arterial haemodynamic properties ..........................................................................35
  2.5. Effects of exercise on arterial haemodynamic properties .........................................39
  2.6. Focus of the present study .......................................................................................40
3. Methods .........................................................................................................................43
  3.1. Participants ...............................................................................................................43
  3.2. Procedures ...............................................................................................................44
  3.3. Measures undertaken at BL and PI assessments ....................................................44
    3.3.1. Coronary artery disease risk stratification .......................................................44
    3.3.2. Carotid artery stiffness .....................................................................................45
    3.3.3. Blood flow velocity ..........................................................................................46
    3.3.4. Treadmill exercise stress test ..........................................................................47
Table of contents

Arterial stiffness and haemodynamic properties in TIA

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4. Randomisation</td>
<td>48</td>
</tr>
<tr>
<td>3.5. Exercise intervention</td>
<td>48</td>
</tr>
<tr>
<td>3.6. Data analysis</td>
<td>49</td>
</tr>
<tr>
<td>3.6.1. Arterial diameter measurement</td>
<td>49</td>
</tr>
<tr>
<td>3.6.2. Arterial stiffness calculations</td>
<td>50</td>
</tr>
<tr>
<td>3.6.3. Blood flow velocity analysis</td>
<td>51</td>
</tr>
<tr>
<td>3.6.4. Blood flow</td>
<td>52</td>
</tr>
<tr>
<td>3.6.5. Shear rate</td>
<td>52</td>
</tr>
<tr>
<td>3.6.6. Conductance</td>
<td>53</td>
</tr>
<tr>
<td>3.7. Statistical analysis</td>
<td>53</td>
</tr>
<tr>
<td>4. Results</td>
<td>54</td>
</tr>
<tr>
<td>4.1. Recruitment</td>
<td>54</td>
</tr>
<tr>
<td>4.2. Participant characteristics at BL</td>
<td>54</td>
</tr>
<tr>
<td>4.3. Arterial stiffness</td>
<td>55</td>
</tr>
<tr>
<td>4.3.1. Arterial compliance</td>
<td>55</td>
</tr>
<tr>
<td>4.3.2. Arterial distensibility</td>
<td>55</td>
</tr>
<tr>
<td>4.3.3. Stiffness index β</td>
<td>55</td>
</tr>
<tr>
<td>4.3.4. Lumen diameter</td>
<td>56</td>
</tr>
<tr>
<td>4.3.5. Systolic blood pressure</td>
<td>57</td>
</tr>
<tr>
<td>4.3.6. Diastolic blood pressure</td>
<td>57</td>
</tr>
<tr>
<td>4.3.7. Pulse pressure</td>
<td>57</td>
</tr>
<tr>
<td>4.4. Arterial haemodynamic properties</td>
<td>57</td>
</tr>
<tr>
<td>4.5. Coronary artery disease risk stratification</td>
<td>58</td>
</tr>
<tr>
<td>4.6. Cardiorespiratory fitness</td>
<td>59</td>
</tr>
<tr>
<td>5. Discussion</td>
<td>60</td>
</tr>
<tr>
<td>5.1. Arterial stiffness</td>
<td>60</td>
</tr>
<tr>
<td>5.2. Coronary artery disease risk stratification</td>
<td>64</td>
</tr>
<tr>
<td>5.3. Arterial haemodynamic properties</td>
<td>65</td>
</tr>
<tr>
<td>5.4. Clinical implications</td>
<td>68</td>
</tr>
<tr>
<td>5.5. Study limitations</td>
<td>68</td>
</tr>
<tr>
<td>5.6. Future research</td>
<td>70</td>
</tr>
<tr>
<td>6. Conclusion</td>
<td>72</td>
</tr>
<tr>
<td>7. References</td>
<td>73</td>
</tr>
</tbody>
</table>
## Table of contents

**Arterial stiffness and haemodynamic properties in TIA**

### Appendices

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix A</td>
<td>Information sheet</td>
<td>88</td>
</tr>
<tr>
<td>Appendix B</td>
<td>Invitation letter</td>
<td>92</td>
</tr>
<tr>
<td>Appendix C</td>
<td>Informed consent</td>
<td>94</td>
</tr>
<tr>
<td>Appendix D</td>
<td>Letter of ethical approval</td>
<td>96</td>
</tr>
<tr>
<td>Appendix E</td>
<td>Coronary artery disease risk stratification</td>
<td>99</td>
</tr>
<tr>
<td>Appendix F</td>
<td>Health history questionnaire</td>
<td>100</td>
</tr>
</tbody>
</table>
List of abbreviations

ANOVA – Analysis of variance
ACE – Angiotensin-converting-enzyme inhibitors
AII – Angiotensin II
ARB – Angiotensin receptor blockers
AT₁ – Angiotensin type-1
BF – Blood flow
BFV – Blood flow velocity
BFV\(_\text{mean} \) – Mean blood flow velocity
BFV\(_\text{max} \) – Maximum blood flow velocity
BL – Baseline
BMI – Body mass index
BP – Blood pressure
BRS – Baroreflex sensitivity
Ca\(^{2+} \) – Calcium
CAD – Coronary artery disease
CC – Compliance coefficient
CCA – Common carotid artery
CON – Control
CR – Cardiac rehabilitation
DBP – Diastolic blood pressure
DC – Distensibility coefficient
ECG - Electrocardiogram
eNOS – Endothelial nitric oxide synthase
EX – Exercise
FBG – Fasting blood glucose
HDL – High-density-lipoproteins
HIIE – High-intensity intermittent exercise
HR – Heart rate
HR\(_\text{max} \) – Maximum heart rate
IMT – Intima-media thickness
LDL – Low-density-lipoproteins
LTPA – Leisure-time physical activity
NO – Nitric oxide
PI – Post-intervention
PP – Pulse pressure
PW – Pulse wave
PWV – Pulse wave velocity
Q – Cardiac output
RAAS – Renin-angiotensin-aldosterone system
RPE – Ratings of perceived exertion
SAC – Systemic arterial compliance
SBP – Systolic blood pressure
Stiff\(_\text{INX} \) – Stiffness index \( \beta \)
SV – Stroke volume
TC – Total cholesterol
TIA – Transient ischaemic attack
\( \dot{V}O_2\text{max} \) – Maximal oxygen uptake
\( \dot{V}O_2\text{peak} \) – Peak oxygen uptake
List of tables

Table 4.1: Baseline characteristics of both exercise (EX) and control (CON) conditions displayed as mean ± SD……………………………………………………………………...54

Table 4.2: Properties of arterial stiffness including compliance coefficient (CC), distensibility coefficient (DC) and stiffness index $\beta$ (StiffINX) at baseline (BL) and post-intervention (PI) between Control (CON) and Exercise (EX) conditions. Values displayed as mean ± SD. Effect sizes ($\eta^2_p$) reported as small (0.0099), medium (0.0588) and large (0.1379)………………………………………………………………………………56

Table 4.3: Arterial haemodynamic properties including mean blood flow velocity ($BFV_{\text{mean}}$), maximum blood flow velocity ($BFV_{\text{max}}$), blood flow (BF), shear rate and conductance at baseline (BL) and post-intervention (PI) between exercise (EX) and control (CON) conditions. Values displayed as mean ± SD. Effect sizes ($\eta^2_p$) reported as small (0.0099), medium (0.0588) and large (0.1379)…………………………………………………………58

Table 4.4: Coronary artery disease risk stratification measures including total cholesterol (TC), high-density lipoproteins (HDL), TC:HDL ratio, fasting blood glucose (FBG) and hip and waist circumference between baseline (BL) and post-intervention (PI) assessments in exercise (EX) and control (CON) conditions. Values displayed as mean ± SD.................58
List of figures

**Figure 2.1:** Illustration of the mechanisms by which central and local arterial stiffness lead to the occurrence of stroke…………………………………………………………………………………………………………………24

**Figure 2.2:** An illustration representing the circular nature of the relationship between stiffness of large elastic arteries, exercise capacity and cardiovascular risk (Kingwell, 2002; pg. 215). Accordingly, arterial stiffening augments pulse pressure, which leads to a decrease in diastolic blood pressure and a decrease in coronary perfusion. Myocardial performance is negatively affected, which results in a reduced exercise capacity and thus physical fitness. Ultimately, a lower physical fitness leads to progressive vascular stiffening. Kingwell, B. A. (2002). Large artery stiffness: implications for exercise capacity and cardiovascular risk. *Clinical and Experimental Pharmacology & Physiology, 29*(3), 214-217…………………………………………………………………………………29

**Figure 2.3:** Endothelium-dependent dilation (Stoner & Sabatier, 2012; pg. 410). As blood flows parallel to the vessel wall, it creates a shearing stress at the surface of the endothelium. The average velocity of the red blood cells will increase from the lowest velocity at the periphery to the greatest velocity towards the centre of the lumen where the resulting gradient of velocities produces a parabolic-like shape (1a & b). Mechano-receptors detect the shear stress-induced deformation of the endothelial cells releasing a signalling cascade that leads to smooth muscle cell relaxation (2 – 5). Stoner, L., & Sabatier, M. J. (2012). Use of Ultrasound for Non-Invasive Assessment of Flow-Mediated Dilation. *Journal of Atherosclerosis and Thrombosis, 19*(5), 407-421……………………………………………………………………………………………………………………………………36

**Figure 3.1:** Local arterial stiffness and haemodynamic assessments. (A) Participants lay supine with their head tilted 45° away from the examined right side. (B) Magnified ultrasound image of the common carotid artery……………………………………………………………………………………………………………………………………45

**Figure 3.2:** Visual representation of the common carotid artery with the Insonation Angle, Steering Angle and Gate size illustrated……………………………………………………………………………………………………………………………………47

**Figure 3.3:** Doppler Spectral Trace over a 4.8 s period………………………………………………………………………………………………………………………………………………47

**Figure 3.4:** Semi-automated edge-detection image-analysis software. (A) B-mode image of the common carotid artery, which corresponds with the (B) histogram. The stars correspond to the vessel walls. The distance between the brightest horizontal segments was recorded. (C) Diameter waveform representing nine cardiac cycles. The yellow markers represent systole while the green markers represent diastole…………………………………………………………………………………………………………………………………………………50

**Figure 3.5:** Analysis of the Doppler Spectral Trace. Representation of time average mean (blue line), maximum (red line) and minimum (green line) for each cardiac cycle over the 4.8 s period…………………………………………………………………………………………………………………………………………………52
Figure 4.1: Mean percent (%) change in compliance coefficient (CC), distensibility coefficient (DC) and stiffness index $\beta$ (StiffINX). Displayed as mean ± SD. *Significant difference between Control and Exercise conditions. .............................................................56
Abstract

Arterial stiffness is associated with cardiovascular risk factors (e.g., hypertension, abnormal blood lipids and lipoproteins, physical inactivity and obesity) and the existence of atherosclerosis, and is identified as an independent risk factor for coronary artery disease and ischaemic stroke. The common carotid artery is the major conduit supplying blood to the brain is of particular interest. Research has demonstrated that interventions, which target the aforementioned risk factors, reduce the risk of occurring vascular events. The aims of this study were to 1) identify whether an 8-week cardiac rehabilitation programme reduces the stiffness of the common carotid artery, as determined by changes in arterial compliance, distensibility and stiffness index $\beta$, in transient ischaemic attack (TIA), and; 2) investigate the relationship between changes to arterial stiffness and haemodynamic properties of the common carotid artery. Eighteen male and female participants (mean ± SD; 65 ± 11 y, 1.72 ± 0.07 m, 85.6 ± 11.5 kg) recruited within a 14 day period following a TIA, volunteered to take part in the present study. Initial risk stratification assessments (i.e., cholesterol, glucose, ECG, etc) were completed prior to assessing arterial stiffness and haemodynamic properties. An ultrasound device was used to obtain arterial measures while participants were rested and in a supine position. Participants were then randomised to either an exercise (EX; 8-week intervention), or to a usual-care control (CON) condition. Identical vascular measures were obtained post-intervention. Results revealed a significant Test by Condition interaction for arterial compliance, distensibility and stiffness index $\beta$, and for compliance and distensibility following the 8-week exercise intervention (all $P < 0.05$). Post-hoc analysis demonstrated a significantly greater change in compliance and distensibility for the EX condition. No significant changes were observed in arterial haemodynamic properties or CAD risk stratification measures. The present study has demonstrated that exercise leads to improved
vascular health, as determined by a decrease in arterial stiffness, thus potentially leading to a reduced risk of an ensuing or recurring cardio- or cerebrovascular event.