Heart Rate Recovery Velocity in Cardiac Disease

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Medicine

Trinity College Dublin,
The University of Dublin
2022
Declaration

I declare that the work in this thesis is entirely my own, except where credit is given in the acknowledgements.

The study was approved by the St James’s Hospital/Tallaght University Hospital Joint Research Ethics Committee, and all participants provided written informed consent. All experimental procedures adhered to the Declaration of Helsinki.

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. I agree to deposit this thesis in the University’s open access institutional repository or allow the Library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement. I consent to the examiner retaining a copy of the thesis beyond the examining period, should they so wish (EU GDPR May 2018).

Signed

Richard Armstrong
Acknowledgements

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Thesis list of Abbreviations

ACEI Angiotensin Converting Enzyme Inhibitor
ACS Acute Coronary Syndrome
ANS Autonomic Nervous System
ARB Angiotensin Receptor Blocker
AS Active Stand
ApEn Approximate Entropy (of heart rate)
AVN Atrioventricular Node
ATRAMI Autonomic Tone and Reflexes After Myocardial Infarction study
BES Biolimus Eluting Stent
BP Blood Pressure
CABG Coronary Artery Bypass Graft surgery
CCB Calcium Channel Blocker
CCS Chronic Coronary Syndrome
CMR Cardiac Magnetic Resonance Imaging
CO Cardiac Output
CRP C Reactive Protein
CTO Chronic Total Occlusion
DBP Diastolic Blood Pressure
DES Drug Eluting Stent
DM Diabetes Mellitus
ESC European Society of Cardiology
EES Everolimus Eluting Stent
FFR Fractional Flow Reserve
FinAP Finger Arterial Pressure
HR Heart Rate
HRR Heart Rate Recovery
HRRt Heart Rate Recovery Time
HRRt10-20 Heart Rate Recovery between 10 and 20 seconds following orthostatic challenge
HRT Heart Rate Turbulence
HRV Heart Rate Variability
HUT Heads Up Tilt Table Test
iFR Instantaneous wave Free Ratio
I SEARCH Survey for Evaluating Microalbuminuria Routinely by Cardiologists in patients with Hypertension
IPAQ International Physical Activity Questionnaire
IQR Inter-quartile Range
LAD Left Anterior Descending coronary artery
Lcx Left Circumflex coronary artery
LMS Left Main Stem coronary artery
MACE Major Adverse Cardiovascular Event
MAP Mean Arterial Pressure
NSTEACS Non-ST segment Elevation Acute Coronary Syndrome
OH Orthostatic Hypotension
PCI Percutaneous Coronary Intervention
PNS Parasympathetic Nervous System
RCA Right Coronary Artery
RCT Randomised Control Trial
rSS Residual Syntax Score
SAN Sino-atrial Node
SBP Systolic Blood Pressure
SNS Sympathetic Nervous System
STEMI ST segment Elevation Myocardial Infarction
SYNTAX Taxus Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries
TILDA The Irish Longitudinal Study on Aging
TLOC Transient Loss of Consciousness
TPR Total Peripheral Resistance
UK United Kingdom
USA United States of America
WCC White Cell Count
ZES Zotarolimus Eluting Stent
Abstract

Introduction
Rate of recovery of heart rate between 10 and 20 seconds following orthostatic challenge (HRR$_{10-20}$) is a risk factor for all-cause mortality. Furthermore, both cardiac rehabilitation and completeness of coronary revascularisation have been shown to improve prognosis of patients with cardiovascular disease. We aim to determine if, by assessing HRR$_{10-20}$ in patients who have undergone complete coronary revascularisation in comparison with those who have had incomplete revascularisation, we can determine which patients are at greatest risk of future cardiovascular events. We will also evaluate HRR$_{10-20}$ before, during and after cardiac rehabilitation to determine if this known risk factor for all-cause mortality is a modifiable risk factor in cardiac disease.

Methods
Between July 2019 until March 2020 cross sectional and longitudinal assessment of the same patient groups were carried out as a case-control study. Patients aged >18 years of age who had percutaneous coronary intervention, coronary artery bypass surgery, transcatheter aortic valve implantation or surgical aortic valve replacement were enrolled at the beginning of phase 2 of cardiac rehabilitation. A cross-sectional comparison was made initially between those who had undergone complete coronary revascularisation and those with incomplete revascularisation. Thereafter, a longitudinal assessment was made comparing those who completed a cardiac rehabilitation programme and those who did not.

Assessment of HRR$_{10-20}$ was performed at the beginning of rehabilitation, at 6-weeks, and again at 12-weeks. During active stand, real time heart rate, blood pressure and ECG recordings were taken via non-invasive digital photoplethysmography (Finometer, Finapres Medical systems, Arnhem, The Netherlands).

Statistical analysis was performed using GraphPad Prism 9.0.2. Pearson’s correlation coefficient was used to determine the relationship between HRR$_{10-20}$ and incomplete versus complete revascularisation, and was also used to determine the relationship between change in HRR$_{10-20}$ from baseline to 12 weeks and upon completion of the rehabilitation programme. Student’s T test used to determine statistical significance of the difference between the two independent groups (p <0.05 was considered statistically significant).
Results

Participants (n= 53) were recruited, 37 of whom had undergone complete revascularisation, while 16 had not. Following initial recruitment, 16 participants elected not to participate in the cardiac rehabilitation stage of the study. The remaining participants (n=37) underwent further assessment in regards to cardiac rehabilitation response. Of these, 25 participated in cardiac rehabilitation versus 12 who did not.

HRR\textsubscript{10-20} was impaired in the incomplete revascularisation group (-3 ± 0.60) compared to the completed revascularisation group (-6.56 ± 0.52) (p<0.0001). Completeness of revascularisation was strongly associated with HRR\textsubscript{10-20} (Pearson’s correlation coefficient 0.529; p <0.0001).

Completion of cardiac rehabilitation also correlated with improvement of HRR\textsubscript{10-20} from baseline to 12 weeks (r=0.6104 p<0.0001).

Through the 6 week and 12-week time periods, differences in HRR\textsubscript{10-20} were noted between the two groups. At the 6-week time point the group who participated in cardiac rehabilitation improved their HRR\textsubscript{10-20} to -5.74±1.91, while the non-rehab group disimproved to 1.85±0.77 (p<0.0001). This pattern was repeated at the 12-week interval, with the rehab group maintaining a marginal improvement of -6.33±2.32, and the non-rehab group deteriorating further to 4.05±1.27 (p<0.0001).

HRR\textsubscript{10-20} in the non-rehab group deteriorated between week 0 and week 6 by 5.94 (p<0.0001), and between week 6 and 3 months by 2.2 (p=0.004).

Conclusions

This study shows a significant correlation between both revascularisation status and completion of cardiac rehabilitation with improved autonomic function as measured with HRR\textsubscript{10-20}.

Impaired autonomic function in the incomplete revascularisation group may be due to residual baseline ischaemia. Augmentation of autonomic function following cardiac rehabilitation may explain in part how cardiac rehabilitation improves prognosis. Furthermore HRR\textsubscript{10-20} may be a modifiable risk factor in high-risk secondary prevention patients.

The main limitation is the limited sample size; the trend observed of improved autonomic function through rehabilitation was in comparison to a group who, through not completing rehabilitation, had a deterioration in autonomic function. The trend of actual improvement in autonomic function may be significant in a larger cohort.
Figure 1. Describing recruitment, cross sectional and longitudinal parts of the study
Lay Abstract

When the human body performs a physical activity, the muscles performing the activity require more oxygen. To achieve this, the rate of breathing and the rate of the heart beat both increase. However, these actions happen in the absence of conscious control, and are instead controlled by the unconscious autonomic nervous system. Through disease processes, the use of medications, aging and hydration status, the autonomic nervous system’s ability to respond to a stimulus can be impaired, but can also be made more effective by regular exercise.

The autonomic nervous system can be monitored and its effectiveness measured by assessing what heart rate and blood pressure do in response to physical activity. This can be performed by measuring the heart rate and blood pressure non-invasively when moving from lying down to standing up – this is called an active stand test. During the first 20 seconds following an active stand, heart rate should initially go up and then come down again, as the autonomic nervous system causes the body to adapt to a more upright posture. HRR_{10-20} measures the heart rate change between the 10 second and 20 second time point after performing an active stand. Blood pressure may also drop giving a dizzy sensation. Additionally, the way in which the heart rate changes from beat to beat, even at rest, can be measured – this is referred to as Heart Rate Variability. Previous research has shown that these assessments, if they show that the autonomic nervous system is not performing effectively, correlate with increased risk of death.

Coronary artery disease is one of the biggest causes of mortality in the Western world, and has several well-known risk factors which we can measure and attempt to influence in order to help guide treatment. As impaired autonomic function is associated with increased risk of death, and coronary artery disease is also associated with increased risk of death, I hypothesised that there would be a similar association between coronary artery disease and autonomic dysfunction, and that through measuring autonomic dysfunction, we can highlight which patients are at higher risk of death in this already high-risk group. I also hypothesised that by completing a structured exercise programme, we would observe an improvement in autonomic function.
**MD Hypothesis**

The main hypothesis of this MD thesis is that autonomic function measured through HRR$_{10-20}$ will initially be impaired in those with coronary artery disease and specifically those who have undergone incomplete coronary artery revascularisation when compared to those who have undergone complete revascularisation. Furthermore, we hypothesise that cardiovascular fitness gained through participation in a cardiac rehabilitation programme results in improved autonomic function.

**Outputs**

**Publications:**

Heart Rate: Control Mechanisms, Pathophysiology and Assessment of the Neurocardiac System in Health and Disease
Armstrong R, Wheen P, Brandon L, Maree A, Kenny RA.

Impaired autonomic function after incomplete revascularisation.

**Papers In Preparation:**

Assessment of Speed of Heart Rate Recovery as a Modifiable Risk Factor Through Cardiac Rehabilitation

**Presentations:**

Impaired Autonomic Function after Incomplete Cardiac Revascularisation
Richard Armstrong
Irish Cardiac Society Congress 2020
CHAPTER ONE:
GENERAL INTRODUCTION
1.1: HEART RATE AND THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system, both sympathetic and parasympathetic systems, is central to the control of heart rate. This vital system cannot be assessed directly, instead we rely on monitoring physiological parameters affected by autonomic function such as heart rate and blood pressure [1]. Heart rate (HR), heart rate variability (HRV), and heart rate recovery time (HRRT) following a stressor are examples of derived physiological indices, beyond simple heart rate, which indirectly measure autonomic tone [1,2,3]. These parameters are under the influence of intrinsic and extrinsic homeostatic control mechanisms in order to allow adequate cardiac output in response to physiological or pathophysiological demands [4]. Intrinsic factors which can impact heart rate include the inherent automaticity of pacemaker cells, which can be influenced by the autonomic nervous system, while extrinsic mechanisms include the delicate balance between parasympathetic and sympathetic tone [5,6].

Pathological processes can influence and be influenced by the physiological processes governing HR, HRV and HRRT [7]. Abnormal HR, HRV and HRRT have been observed in a multitude of pathologies including coronary atherosclerosis, systolic heart failure, sepsis, systemic inflammation and various other pathologies [8,9,10,11]. HR itself can also influence the progression of disease through its effect on vascular shear stress, shear frequency, endothelial function, vascular inflammation, vascular structure, systemic vascular resistance and atherosclerotic plaque stability [12,13,14,15,16,17,18]. This complex relationship between measured autonomic parameters and physiological and pathophysiological demands forms the basis of my hypothesis that autonomic function will be impacted by both revascularisation status and by a structured exercise programme.
1.2: INTRINSIC CONTROL OF HEART RATE

1.2.1 Generation of Cardiac Action Potentials

In order for a contraction to occur, the electrical signal to depolarise and contract cardiac muscle must initiate and propagate throughout the heart. Action potential generation primarily occurs within pacemaker cells of the sino-atrial node (SAN) (figure 1). These specialised cells automatically depolarise due to funny channels- \( (I_r \text{ channels} - \text{a non-selective sodium and potassium cation channel}) \) - which allow slow influx of sodium and potassium ions through the rest period post depolarisation (known as phase 4) [20]. Once the membrane potential reaches -50mV, voltage gated T-type calcium ion channels open, allowing influx of calcium ions [21]. Automaticity may also be influenced by the “calcium clock,” whereby as the sarcoplasmic reticulum fills with calcium, the probability of a spontaneous calcium release increases. The converse is also true; if the sarcoplasmic reticulum is depleted of calcium, the likelihood of spontaneous depolarisation is reduced [22]. Once membrane potential reaches -40mV, L-type calcium ion channels open, and action potential threshold can be reached at around -30mV. Towards the end of this phase, T-type calcium channels close. This then leads to phase 1, with a further influx of calcium ions through the voltage gated L-type calcium channels [23]. Unlike other action potentials (such as myocardial action potential seen in figure 2), there is no phase 2 plateau phase; instead pacemaker cells move directly into phase 3, where potassium ion channels open and L-type calcium ion channels close. This leads to the progressive repolarisation of the cell, until phase 4 begins again [24]. While this intrinsic mechanism impacts heart rate itself, it is influenced by the autonomic nervous system as well. Higher sympathetic tone with reduced parasympathetic tone leads to increased automaticity through increased calcium ion availability.

Intrinsic disease of the sinoatrial node will impact the generation of action potentials, leading to brady-arrhythmia and potentially the need for pacemaker implantation.
Figure 2. Sinoatrial node action potential generation
Figure 3. Myocardial depolarisation
1.2.2 Propagation and Conduction

Local propagation of action potentials leads to a progressive depolarisation of the surrounding myocardium. This occurs primarily as a consequence of free flow of cations between cardiomyocytes though gap junctions of the cellular structure. This wave of depolarisation proceeds quickly through dedicated conductive pathways and slower through cardiomyocytes themselves [25].

Thereafter, the intracardiac conductive system plays a critical role in modulating HR. In a non-pathological state, the sinoatrial node (SAN) – located in the right atrial sulcus terminalis - depolarises, leading to conduction through intranodal pathways leading to the atrioventricular node (AVN), located in at the apex of Koch’s triangle in the right atrium [26]. The wave of depolarisation further progresses down the tree through to the bundle of His, left and right bundles, their respective divisions of fascicles and to the Purkinje fibres, eventually terminating through ventricular myocardium [27]. This is further demonstrated in figure 4.

Similarly to disease of the sino-atrial node, disease of the atrioventricular node may result in the need for a permanent pacemaker implantation.
Figure 4. Intracardiac conductive system
1.2.3 Coronary blood supply to the conductive system

The blood supply of the various stages of the intracardiac conductive system, if disrupted, may lead to development of HR related pathologies [28]. The SAN is usually supplied from a branch of the proximal right coronary artery. The AVN derives its supply from the posterior descending artery (80% from the right coronary artery). The bundle of His receives arterial blood from the AVN arterial supply, but also from septal branches of the left anterior descending artery. Thereafter in the smaller subdivisions of the conductive system, blood is derived from the local surrounding myocardial arterial supply [29].

Patients with coronary artery disease may develop brady-arrhythmias if the blood supply to the sino-atrial node or atrioventricular node is impaired.

1.2.4 Variable Automaticity

The previously described automaticity of myocardial cells, with spontaneous depolarisation occurring at any level of the conductive system, varies throughout the conductive tree. Left to its own devices without external influence, the sinoatrial node would depolarise at a rate of 40 to 60 beats per minute while the spontaneous depolarisation rate in the ventricle would be around 30 beats per minute [30,31].

Spontaneous erratic automatic depolarisation – particularly around the pulmonary veins of the left atrium – may result in atrial fibrillation. Atrial fibrillation can result in variable depolarisation through the atrioventricular node, resulting in tachy-arrhythmias or brady-arrhythmias independent of autonomic tone.
1.3: EXTRINSIC AUTONOMIC CONTROL OF HEART RATE

1.3.1 Opposing forces, homeostasis and feedback

Resting parasympathetic and sympathetic tone act in opposing manners allowing homeostasis to be achieved despite changing physiological demands. HR is altered by various homeostatic control mechanisms [32]. The intrinsic HR drive is extensively innervated and controlled by the autonomic system, and is subject to the homeostatic feedback mechanisms of this system.

1.3.2 Physiological effects of autonomic modulation on the heart

Inotropy (the forcefulness of cardiac contraction), dromotropy (the conduction velocity), lusitropy (myocardial relaxation) and chronotropy (HR) are all influenced by sympathetic and parasympathetic stimulation and withdrawal. HR is a major component of cardiac output. Higher sympathetic drive causes inotropy to be increased by the elevation of intracellular calcium concentration, dromotropy to be increased through increased conduction velocity through the AV node, while chronotropy is increased primarily through stimulation of the SA node [33]. The parasympathetic vagal system has the opposite effect to sympathetic activation. Negative chronotropy is observed due to the innervation of the SA node by the vagus nerve, reducing the HR. Negative dromotropy results from a reduction in AV conduction velocity [34]. The effect of parasympathetic activation on inotropy is less pronounced than that of sympathetic activation, as the parasympathetic system does not directly innervate ventricular myocardium [6].

1.3.3 Autonomic Nervous System Cellular Receptors

The sympathetic system contains receptors for adrenergic agonists such as noradrenaline and adrenaline [6]. The most important adrenoceptor in the heart is the Beta-1 receptor. Upon activation, the B1 receptors induce positive chronotropy, dromotropy, inotropy and lusitropy [35]. The primary parasympathetic receptor involved in modulation of HR is the muscarinic-2 receptor (M2) [6].

The intracellular pathway following activation of adrenergic receptors is via the G protein-cAMP-PKA signalling pathway. Following binding to the receptor, activation of adenylyl cyclase occurs, causing the conversion of ATP to cAMP, which thereafter activates PKA, which has multiple effects, such as on L type Calcium channels and on the Ii ion channels [35]. Muscarinic receptors are also linked to G protein-cAMP-PKA, but in contrast to sympathetic activation, parasympathetic muscarinic activation leads to a reduction of cAMP and the direct opposite
effect on calcium channels [36]. The effects of activation of the various adrenergic and muscarinic receptors are summarised in table 1.
<table>
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<tr>
<th>Receptor</th>
<th>Main locations</th>
<th>Mechanism of action</th>
<th>Effect on heart</th>
<th>Other significant physiological effects</th>
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<td>Alpha 1 adrenergic receptor</td>
<td>Vascular smooth muscle, pupillary dilator muscle, pilomotor smooth muscle, prostate, myocardium</td>
<td>G protein activation of phospholipase C, increasing IP3/DAG</td>
<td>Increased inotropy, coronary vasoconstriction, myocardial hypertrophy and remodelling</td>
<td>Smooth muscle contraction, gluconeogenesis, vasoconstriction, pupil dilation, hairs stand on end</td>
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<tr>
<td>Alpha 2 adrenergic receptor</td>
<td>Adrenergic presynaptic neurons, platelets, vascular smooth muscle, adipose tissue</td>
<td>G protein inhibition of adenyl cyclase, reduction of cAMP</td>
<td>Coronary vasoconstriction</td>
<td>Inhibits release of neurotransmitters, platelet aggregation, lipolysis, weak smooth muscle contraction</td>
</tr>
<tr>
<td>Beta 1 adrenergic receptor</td>
<td>Heart, coronary arteries, kidneys, adipose tissue</td>
<td>G protein activation of adenyl cyclase and PKA, increasing cAMP</td>
<td>Increased chronotropy, dromotropy, inotropy and lusitropy. Myocardial hypertrophy and remodelling</td>
<td>Renin secretion, lipolysis</td>
</tr>
<tr>
<td>Beta 2 adrenergic receptor</td>
<td>Visceral smooth muscle, bronchioles, liver, skeletal muscle</td>
<td>G protein activation of adenyl cyclase, PKA and Ca2+ channels, increasing cAMP</td>
<td>Coronary vasodilation</td>
<td>Vasodilation, bronchodilation, inhibition of insulin excretion</td>
</tr>
<tr>
<td>Beta 3 adrenergic receptor</td>
<td>Adipose tissue</td>
<td>G protein activation of adenyl cyclase and PKA, increasing cAMP</td>
<td>Possible cardioprotective role</td>
<td>Lipolysis</td>
</tr>
<tr>
<td>Muscarinic 1 cholinergic receptor</td>
<td>Mainly neural - Autonomic ganglia, myenteric plexus</td>
<td>G protein modulated increase of IP3/DAG</td>
<td>Increased chronotropy and inotropy</td>
<td>Causes depolarisation of neurones, slows EPSP, increases gastric acid secretion</td>
</tr>
<tr>
<td>Muscarinic 2 cholinergic receptor</td>
<td>Mainly cardiac - Atria, sinoatrial node, presynaptic nerve endings</td>
<td>G protein modulated reduction of cAMP and direct coupling to K+ channel</td>
<td>Negative inotropy, negative chronotropy</td>
<td>Reduces NA or Ach release</td>
</tr>
<tr>
<td>Muscarinic 3 cholinergic receptor</td>
<td>Mainly glandular - Smooth muscle in GIT, bladder, trachea, pupillary dilator muscle, vascular endothelium, smooth muscle, salivary glands, pancreatic beta cells, stomach</td>
<td>G protein modulated increase of IP3/DAG</td>
<td>Mediates acetylcholine induced endothelium dependent coronary arterial dilation, modulates cell-cell communication, regulation of repolarisation</td>
<td>Contraction of visceral smooth muscle, increased gastric acid secretion, vasodilation, salivation, release of insulin</td>
</tr>
<tr>
<td>Muscarinic 4 cholinergic receptor</td>
<td>Uterus, lung</td>
<td>G protein modulated reduction of cAMP</td>
<td>Sympathetic neurotransmitter release in atria and regulation of K+ channels</td>
<td>Contraction</td>
</tr>
<tr>
<td>Muscarinic 5 cholinergic receptor</td>
<td>Brain – substantia nigra</td>
<td>G protein modulated increase of IP3/DAG</td>
<td>Not yet determined</td>
<td>Regulates release of dopamine</td>
</tr>
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Table 1. Adrenergic and muscarinic receptors of the autonomic nervous system [35,36]

1.4: AUTONOMIC CARDIAC INNERVATION

1.4.1 Initial Supply
The intracardiac conductive system is innervated extensively by both sympathetic and parasympathetic fibres. This interface of the nervous system and heart is pivotal in the control of HR. The anatomy of cardiac innervation is summarised in figure 5.
Sympathetic preganglionic fibres arise from the lateral column of the spinal cord at T1 to T4 levels, giving origin to cervical and thoracic ganglia. Cardiac innervation from the superior cervical ganglion is from the superior cardiac nerve, the middle ganglion gives off the middle cardiac nerve, while the inferior ganglion gives off the inferior cardiac nerve. These nerves descend into the thorax to an area near the aortic arch, forming the cardiac plexus [37].
Parasympathetic fibres innervating the heart come from the vagus nerve (X), of which preganglionic craniosacral fibres originate from the brainstem – nucleus ambiguous, reticular nucleus and the dorsal nucleus of the vagus nerve [38].
Figure 5. Schematic of Autonomic Cardiac Innervation.
1.4.2 Local anatomy
The parasympathetic and sympathetic fibres converge into the cardiac plexus, which is situated at the base of the heart, and is further divided into a superficial and a deep cardiac plexus. The superficial plexus is anatomically located inferior to the aortic arch and anterior to the main right pulmonary artery. It is formed from the left sympathetic trunk’s cardiac branches and two branches from the vagus nerve. The deep cardiac plexus is anatomically located anterior to the tracheal bifurcation, posterior to the aortic arch. It is formed from sympathetic branches from the cervical ganglia and parasympathetic branches from the vagus nerve. The deep plexus subdivides further into the left and right plexi, with the right plexus providing innervation to the sinoatrial node and the left plexus providing innervation to the AV node. Fibres from these plexi join again to form a plexus following the territory of the right coronary artery, the left coronary artery and the posterior portion of the heart. These fibres penetrate myocardium providing innervation throughout the ventricles. The AV node is primarily innervated by parasympathetic fibres, while the ventricles are primarily innervated with sympathetic fibres. [37,38,39]

1.4.3 Feedback Mechanisms
Homeostatic feedback mechanisms monitor flow, pressure and oxygenation of blood. These are subdivided into baroreceptor and chemoreceptor systems. Baroreceptors are found in the carotid body, aortic arch and in the vascular pedicle of the neck [40]. They are richly innervated from sympathetic and parasympathetic fibres. Efferent fibres from baroreceptors travel to the brainstem – the solitary tract nucleus, nucleus ambiguous, dorsal nucleus of the vagus nerve and the bulbar reticular formation. Baroreceptors are located in the aortic arch and in carotid sinuses and are sensitive to changes in blood pressure. When distended, they are activated, leading to inhibition of the sympathetic system - reducing peripheral vascular resistance through vasodilation, reducing cardiac output through negative chronotropy and inotropy [41]. Additionally, there are baroreceptors in the atria, which again are activated upon distension. When atrial baroreceptors are activated, the reflex activated increases HR through sympathetic activation, increasing cardiac output [42]. Pathology is encountered in relation to the baroreceptor reflex given the degree of innervation in the carotid body. In the event of carotid sinus hypersensitivity, inappropriate activation of the homeostatic feedback mechanism by pressure placed upon the carotid body may lead to a syncopal event [32,33,40]. Clinically this can be assessed by performing a carotid sinus massage in a controlled environment.
Chemoreceptors may be peripheral - located in the aorta and carotid bodies – or central, located in the ventrolateral medulla. They assess the concentration of carbon dioxide and oxygen along with pH of blood. Upon activation due to low oxygen concentration, high carbon dioxide concentration or low pH, parasympathetic tone is decreased and sympathetic tone is increased, resulting in higher HR [40,41,42]. These feedback mechanisms may be impacted by disease processes directly – such as carotid sinus hypersensitivity – or respond to pathological processes downstream, resulting in increased or decreased heart rate.

1.5: THE IMPACT OF HEART RATE ON PATHOLOGICAL PROCESSES

1.5.1 Heart Rate and Mortality
There is an established link between heart rate - along with heart rate derived physiological parameters - and mortality. The TILDA group have shown a link between HRR10-20 and all-cause mortality amongst an otherwise healthy cohort. Additionally, patients post myocardial infarction have been shown to have a lower mortality if they have a lower resting heart rate. This relationship between heart rate and mortality may be explained through heart rate’s impact on various pathological processes including shear stress and frequency, endothelial dysfunction, vascular inflammation, vascular structure, systemic vascular resistance, atherosclerosis, coronary hypoxia, ischaemia and atherosclerotic plaque stability.

1.5.2 Shear stress and shear frequency
Shear stress on the vascular endothelium is the tangential force generated by velocity of blood flow. Each lamina of blood flow exerts a degree of shear stress on neighbouring lamina (liquid shear stress), while the vessel wall additionally exerts shear stress on blood flowing past (wall shear stress). The response of the endothelium to this force is involved in the pathogenesis of atherosclerosis [43,44,45]. There is evidence suggesting a close correlation with HR, in that with a higher frequency of HR there is a greater force over time leading to further expression of proinflammatory, proapoptotic and procoagulant genes, along with a reduction of nitric oxide synthase production [46]. This may also be related to the waveforms of arterial pulsation, with pulsatile 2Hz shear frequency specifically generating a proinflammatory phenotype, whereas a more normal physiological 1Hz reduces expression of proinflammatory genes [47]. It can therefore be hypothesised that in patients who have higher shear frequencies caused by a higher HR, there is an increased risk of atherosclerosis. Mechanical forces of cyclical strain are additionally associated with increased vascular stiffness [48].
Mechanical stress may additionally play a role in so called vascular “fatigue” – whereby a cumulative vascular injury is caused by pulsatile pressure [49]. This can be particularly evident in areas where flow disturbance is greatest – namely at the os and bifurcations of arteries [50]. The overall movement of the artery must be taken into consideration as well – with some segments of arteries moving quite significantly (for example the mid right coronary artery’s “elbow”). Bassiouney et al have suggested using a rate-pressure product (mean blood pressure x mean HR) to quantify the burden of haemodynamic stress in an animal model – demonstrating a correlation between haemodynamic stress and atherosclerosis in the aorta [50]. Furthermore, reduction of HR using ivabradine has been demonstrated in a rat model to reduce the medial cross-sectional area of the thoracic aorta [51].

Coronary arterial shear stress is low and oscillatory during systole, followed by an increase to maximum during diastole [52]. In anatomical areas demonstrating low shear stress, progression of atherosclerosis and positive remodelling of the vasculature can ensue [53]. With high resting HR there is a reduction of diastolic time with its protective high diastolic shear stress, and longer periods of systolic shear stress, possibly contributing to the development of progressive atheroma formation [54].

1.5.3 Endothelial dysfunction
The endothelium is particularly sensitive to vascular pathological processes due to exposure to the haemodynamic stress of blood flow, with disturbance of normal endothelial function being an important step in the development of atherosclerosis [55]. The primary characteristic of impaired endothelial function is reduced production of endothelial NO [56]. Conversely, greater production of endothelial NO indicates improvement in endothelial function [57]. The dual effect of HR and endothelial dysfunction has been investigated in mouse models showing that ivabradine treatment reduces HR (by 13.4%) coupled with enhanced endothelial dependent vasorelaxation [58]. Further studies using ivabradine in dyslipidaemic mice showed a reduction in endothelial dysfunction in renal and cerebral arteries [59].

Despite animal data, no studies have demonstrated real world clinical data linking HR and endothelial function. The Framingham study has shown a correlation between HR and brachial artery flow mediated dilation; other smaller studies have been limited by sample size [60]. Hohneck et al demonstrated in a prospective placebo controlled clinical crossover study of 23 patients that with an average reduction in HR of 11.4, the use of ivabradine was associated with
endothelium dependent vasodilation (flow mediated dilation of the brachial artery), and reduced arterial stiffness in patients with known coronary artery disease [61].

1.5.4 Vascular Inflammation
There is a causal relationship between vascular inflammation, endothelial dysfunction and atherosclerosis [62]. This can be seen in blood biomarkers, with elevated levels of CRP and high WCC being correlated with cardiovascular risk [63,64,65]. There additionally exists a relationship between markers of vascular inflammation and HR. Two large studies show a correlation of CRP, WCC and fibrinogen with HR in otherwise healthy individuals [66,67]. In the I-SEARCH study, higher resting HR was a predictor for the presence of microalbuminuria in a hypertensive cohort [68]. Ulleryd et al added to the evidence base by demonstrating a correlation in 124 men between reduced parasympathetic activity, CRP, white cell count and carotid atheroma area. Neurological control of inflammation, along with potential modulation in a clinical setting, is an area which requires further research [69].

1.5.5 Vascular structure
The elastic ability of a blood vessel to adapt to mechanical stress by changing geometry is described as vascular compliance. This is determined by change in volume over change in pressure, and the value reduces with age [70]. This “hardening of the arteries” is a predictor for cardiovascular mortality [71]. There does exist experimental evidence supporting a link between vascular compliance and HR. In an animal model, higher HR caused by atrial pacing in rats led to reduction in carotid artery compliance, independent from sympathetic tone [72]. This has additionally been demonstrated in humans using pulse wave velocity Doppler and echo tracking measurements to assess central, lower limb, radial and carotid artery distensibility in relation to pacing [73]. On the contrary, other studies have shown the opposite effect, with a correlation reported between incremental increased pacing rates and an improved augmentation index (a pulse wave Doppler analysis of arterial stiffness) [74]. These conflicting results may be as a consequence of differing methods of analysis- augmentation index, pulsed wave Doppler and echo tracking. Regardless of whether the correlation is positive or negative, there is an association between HR and vascular compliance.

1.5.6 Hypertension and Systemic Vascular Resistance
The phenomenon of lower HR potentiating negative vascular compliance is further assessed in the CAFE study, whereby it was noted that a lower HR as caused by beta blockade with atenolol
was associated with higher central aortic systolic and pulse pressure [17]. This was postulated to be as a consequence of increased central pressure waveform reflections when the HR was lower or a consequence of increased stroke volume with better diastolic filling [75]. Additionally, vasoconstriction in the peripheral arterioles caused by beta blockers increases systemic vascular resistance, increasing central systolic blood pressure [76,77,78].

1.5.7 Atherosclerosis

The initial observations of a link between higher HR and the development of atherosclerosis were in a monkey animal model. At first, SA node ablation was used to iatrogenically lower HR, which was observed to reduce the amount of coronary and carotid atherosclerosis compared to controls [79]. This was further demonstrated in an observational study whereby monkeys with a higher resting HR were observed to develop coronary atherosclerosis at more than double the rate of those with a lower resting HR [80]. The effect of stress on HR response has also seen to be a risk factor for the development of coronary atheroma [81]. Further animal studies in ApoE knockout mice have demonstrated that through the use of ivabradine to lower HR, there was a reduction in atherosclerotic plaque burden in the ascending aorta [58]. This may be due to a reduction in the expression of monocyte chemoattractant protein-1, of which regulation is normally controlled by shear patterns and cyclical strain [82]. Outside of animal models, it has been observed that there is a significant correlation between high resting HR and development of increasingly severe coronary atheroma [83].

It has been established that reducing HR as a secondary prevention measure following myocardial infarction improves survival. The positive impact of beta blockade following myocardial infarction may be secondary to the primary effect of reducing HR, but additionally synergistic secondary effects including possibly the reduction of endothelial permeability for low density lipoprotein cholesterol [84,85]. As previously discussed, although beta blockers reduce HR, the impact of peripheral vasoconstriction caused by beta blockade specifically in already hypertensive patients may lead to increased risk of cardiovascular death [78]. This has particularly been observed in non-vasodilating beta blockers such as atenolol, and these data cannot be extrapolated out to a class-wide judgement [86]. While the effects of HR reduction using ivabradine on atheroma formation have been observed in mice [59], a prospective randomised trial assessing the impact on atherosclerotic plaque development in humans has not yet been performed.
1.5.8 Coronary hypoxia and ischaemia
Within the coronary arterial tree, flow of blood is driven by the gradient of pressure between the proximal aorta, the right atrial pressure and the length of time in diastole. Coronary flow is phasic with the majority of flow occurring in diastole. Higher HR leads to a reduction of diastolic filling time, therefore reducing the amount of time for coronary perfusion with oxygenated blood. Reduction in HR allows greater time for diastolic flow in the coronary arteries to occur, allowing greater perfusion [87]. Clinically this physiological effect can be mimicked as an anti-anginal stratagem, with the introduction of beta blockers, calcium channel blockers and If (funny) channel blockers [88].

1.5.9 Coronary Atherosclerotic Plaque stability
Atheromatous plaque rupture with subsequent coronary thrombosis is the most commonly observed cause of myocardial infarction [89]. The stability of the fibrous cap determines the likelihood of plaque rupture. This is influenced by the thickness of the cap, and additionally by the haemodynamic stress placed upon it [90,91]. There are retrospective analyses suggesting a positive correlation between a resting HR in excess of 80bpm and progression of initially angiographically stable atheroma to plaque disruption [18] - Heidland et al observed that in those using beta blockers to reduce resting HR, plaque disruption rates were reduced[18]. Furthermore, Diaz et al reported on 24,913 patients that elevated average HR of greater than 83bpm positively correlated with all-cause mortality, cardiovascular death and cardiovascular hospitalisation, with a relative risk of 1.23 compared with controls [92].

Shear stress and shear stress frequency have previously been discussed, but are of particular significance when it comes to their influence on atheromatous plaque disruption. Segments of coronary arteries where atheroma is most likely to form: bifurcations, ostia of branches – are also the most likely areas to be under shear and mechanical stress [93]. These stressors are influenced at least partly by resting HR. Additionally, circumferential wall stress and repetitive tensile stress are also influenced by pulsatility and frequency of mechanical stress – these factors stimulate the production of matrix metalloproteinase-1, a major component of extracellular matrix degradation and weakening of atheromatous caps[94].

HR of patients following myocardial infarction is significantly higher than normal. High HR at discharge is linked to a higher mortality rate at one to three years [95,96]. A meta-analysis of the GISSI trials of around 20,000 patients showed that in hospital mortality rate of patients with
resting HR <60bpm was 3.3% versus 10.1% for patients with a resting HR of >100bpm. These, along with the beta blocker trials, have led to beta blockade following myocardial infarction being “gold standard” therapy [97].
1.6: MEASURING AUTONOMIC FUNCTION USING HEART RATE

1.6.1 Measuring Autonomic Function by Proxy

Autonomic function, as previously mentioned, cannot be directly measured, and so instead we can use heart rate and its derived parameters as surrogate indices. Beyond simply measuring heart rate in beats per minute, there are the derived indices; heart rate variability and heart rate recovery time. Heart rate recovery time between 10 and 20 seconds following orthostatic challenge is of particular relevance as this novel parameter was the focus of this research project, having previously been demonstrated to be correlated with all-cause mortality.

1.6.2 Heart Rate Variability

The measurement of HRV can be used to assess the balance between sympathetic and parasympathetic stimulation – both of which exert extrinsic control of heart rate. It is physiologically described as the fluctuation in length of heart beat intervals, and is a non-invasive ECG based index [2,98]. HRV represents the capacity of the autonomic nervous system to respond to physiological or pathophysiological demands – both psychological and physical.

The significance of this physiological variable was initially noted in 1965 when it was observed that HRV fluctuations were present before fluctuations in HR in episodes of fetal distress [99]. HRV has been observed to decline with age, and age adjusted HRV has additionally been observed to correlate with all-cause mortality [100]. Huikuri et al demonstrated in a longitudinal study that low HRV is a strong independent predictor of coronary atherosclerosis progression [101].

There is a normal balance between HR and HRV. As HR increases, and R-R intervals shorten, there is less capacity for additional variation to occur, and HRV will correspondingly fall [102,103]. As HR slows, there is conversely more capacity between R-R intervals for variability, and HRV therefore is higher. This relationship is described as cycle length dependence, and is normal in a physiologically healthy heart [104]. In the case of coronary artery disease or indeed other cardiac pathologies, this relationship may be lost. Due to this phenomenon, when HRV is assessed, HR should be reported in order to interpret the data [102,103,104].

HRV can be measured through time domains, frequency domains or through non-linear indices. Time domains may be statistical or geometric, and involve the calculation of mean NN (normal to normal) intervals and their variance [104].
Frequency, or power spectral density domains may be analysed over short (5 minute) or longer (24 hour) intervals. Longer monitoring intervals allow diurnal variation of homeostasis to be taken into account. Frequency domain analyses are preferred for short term analyses of 5 minutes or so compared to time domain analyses. The differing frequency bands are associated with either sympathetic (low frequency (LF), very low frequency (VLF) and high frequency (HF)) or parasympathetic activation and tone [2,104,105].

Nonlinear indices of HRV assess the quality, scaling and correlation of the signals rather than the magnitude of variability assessed in more traditional HRV indices [105]. It is important to keep in mind that these measurements are of HR rather than a direct measurement of autonomic activity, and that various systems can impact upon the indices beyond the influence of the neurocardiac system (circadian rhythm, hormones, temperature). The various methods of analysing HRV along with their correlation to autonomic function and the neurocardiac axis are summarised in tables 2a, 2b and 2c.

HRV indices have been used as a surrogate marker for vagal tone and autonomic function in clinical research. Studies have observed an inverse correlation between low LF-HRV (primarily associated with low parasympathetic tone) with increased markers of inflammation such as fibrinogen, CRP, IL-6, and additionally an inverse correlation between HF-HRV (associated with low parasympathetic tone and higher sympathetic tone) with fibrinogen and CRP [106]. This allowed investigators to conclude that the parasympathetic system has anti-inflammatory effects. Within a patient group who had ischaemic heart disease, the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study assessed HRV in 1284 patients, demonstrating higher mortality in patients whose standard deviation of normal to normal intervals (SDNN [a time index of HRV]) was less than 70ms [107]. Further studies assessing LF-HRV and HF-HRV demonstrated that low values were predictive of all-cause mortality, cardiac death and arrhythmic death over 4 years [108,109]. Various prognostic cut-offs of SDNN have been suggested, varying between 50 and 100, due to confounders such as age, gender along with infarct size and location [103-112].

The impact of exercise and rehabilitation on HRV indices has also been used as a surrogate for the measurement of vagal and autonomic tone in general. Rehabilitation and exercise training programmes are postulated to decrease catecholamines, beta adrenergic receptor density,
angiotensin II, renin, and increase availability of nitric oxide [113]. These mechanisms lead to increased vagal activity and a reduction in sympathetic drive, observed as an improvement in HRV indices. The use of HRV to assess success of cardiac rehabilitation again raises the question within our hypothesis; if the same correlation may be seen using heart rate recovery velocity.
<table>
<thead>
<tr>
<th>Index</th>
<th>Type of measurement</th>
<th>Unit of measurement</th>
<th>Definition of abbreviation</th>
<th>Part of Autonomic/Neurocardiac System Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>statistical</td>
<td>ms</td>
<td>Standard deviation of NN intervals</td>
<td>Sympathetic and parasympathetic</td>
</tr>
<tr>
<td>SDRR</td>
<td>statistical</td>
<td>ms</td>
<td>Standard deviation of RR intervals</td>
<td>Sympathetic and parasympathetic</td>
</tr>
<tr>
<td>SDSD</td>
<td>statistical</td>
<td>ms</td>
<td>Standard deviation of differences between adjacent NN intervals</td>
<td>Sympathetic and parasympathetic</td>
</tr>
<tr>
<td>SDANN</td>
<td>statistical</td>
<td>ms</td>
<td>Standard deviation of the average NN intervals for each 5 minute segment of a 24 hour HRV recording</td>
<td>Sympathetic and parasympathetic</td>
</tr>
<tr>
<td>SDNN index</td>
<td>statistical</td>
<td>ms</td>
<td>Mean of the standard deviations of all of the NN intervals for each 5 minute segment of a 24 hour HRV recording</td>
<td>Sympathetic and parasympathetic</td>
</tr>
<tr>
<td>pNN50</td>
<td>statistical</td>
<td>%</td>
<td>Percentage of successive RR intervals that differ by more than 50ms</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td>NN50 count</td>
<td>statistical</td>
<td>bpm</td>
<td>Numbers of pairs of adjacent NN intervals differing by more than 50ms in the entire recording</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td>HR max – HR min</td>
<td>statistical</td>
<td>bpm</td>
<td>Average difference between the highest and lowest heart rates during each respiratory cycle</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td>RMSSD</td>
<td>statistical</td>
<td>ms</td>
<td>Root mean square of successive RR interval differences</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td>HRV triangular index</td>
<td>geometric</td>
<td></td>
<td>Integral of the density of the rr interval histogram divided by its height</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td>TINN</td>
<td>geometric</td>
<td>ms</td>
<td>Baseline width of the RR interval histogram</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td>Differential index</td>
<td>geometric</td>
<td></td>
<td>Difference between the widths of the histograms of differences between adjacent NN intervals measured at selected heights</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td>Logarithmic index</td>
<td>geometric</td>
<td></td>
<td>Coefficient of the negative exponential curve which is the best approximation of the histogram of absolute differences between adjacent NN intervals</td>
<td>Parasympathetic</td>
</tr>
</tbody>
</table>

Table 2a. Heart Rate Variability – Time Indices [104]
<table>
<thead>
<tr>
<th>Index</th>
<th>Unit</th>
<th>Definition of abbreviation</th>
<th>Part of Autonomic/Neurocardiac System Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULF Power</td>
<td>ms²</td>
<td>Absolute power of the ultra-low frequency band (≤0.003Hz)</td>
<td>Possibly parasympathetic and sympathetic</td>
</tr>
<tr>
<td>VLF Power</td>
<td>ms²</td>
<td>Absolute power of the very low frequency band (0.0033-0.04Hz)</td>
<td>Intrinsic cardiac nervous system and efferent sympathetic activity</td>
</tr>
<tr>
<td>LF Power</td>
<td>ms²</td>
<td>Absolute power of the low frequency band (0.04-0.15Hz)</td>
<td>Parasympathetic and sympathetic (with some variation) activity</td>
</tr>
<tr>
<td></td>
<td>nu</td>
<td>Relative power of the low frequency band (0.04-0.15Hz) in normal units</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>Relative power of the low frequency band (0.04-0.15Hz)</td>
<td></td>
</tr>
<tr>
<td>LF Peak</td>
<td>Hz</td>
<td>Peak frequency of the low frequency band (0.04-0.15Hz)</td>
<td>Parasympathetic and sympathetic (with some variation) activity</td>
</tr>
<tr>
<td>HF Power</td>
<td>ms²</td>
<td>Absolute power of the high frequency band (0.15-0.4Hz)</td>
<td>Parasympathetic activity</td>
</tr>
<tr>
<td></td>
<td>nu</td>
<td>Relative power of the high frequency band (0.15-0.4Hz) in normal units</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>Relative power of the high frequency band (0.15-0.4Hz)</td>
<td></td>
</tr>
<tr>
<td>HF Peak</td>
<td>Hz</td>
<td>Peak frequency of the high frequency band (0.15-0.4Hz)</td>
<td>Parasympathetic activity</td>
</tr>
<tr>
<td>LF/HF</td>
<td>%</td>
<td>Ratio of LF to HF power</td>
<td>A ratio thought to compare sympathetic and parasympathetic activity</td>
</tr>
</tbody>
</table>

Table 2b. Frequency Domain Indices of Heart Rate Variability [104]
<table>
<thead>
<tr>
<th>Index</th>
<th>Unit</th>
<th>Description</th>
<th>Part of Autonomic/Neurocardiac System Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>ms</td>
<td>Area of the ellipse which represents total HRV</td>
<td>Parasympathetic and sympathetic</td>
</tr>
<tr>
<td>SD1</td>
<td>ms</td>
<td>Poincare plot standard deviation perpendicular to the line of identity</td>
<td>Parasympathetic</td>
</tr>
<tr>
<td>SD2</td>
<td>ms</td>
<td>Poincare plot standard deviation along the line of identity</td>
<td>Parasympathetic and sympathetic (with some variation) activity</td>
</tr>
<tr>
<td>SD1/SD2</td>
<td>%</td>
<td>Ratio of SD1 to SD2</td>
<td>A ratio thought to compare sympathetic and parasympathetic activity</td>
</tr>
<tr>
<td>ApEn</td>
<td></td>
<td>Approximate entropy measuring the regularity and complexity of a time series</td>
<td>Low entropy implies regularity – possibly high parasympathetic activity</td>
</tr>
<tr>
<td>SampEn</td>
<td></td>
<td>Sample entropy measuring the regularity and complexity of a time series</td>
<td>Low entropy implies regularity – possibly high parasympathetic activity</td>
</tr>
<tr>
<td>DFA alpha1</td>
<td></td>
<td>Detrended fluctuation analysis, describing short term fluctuation</td>
<td>Baroreceptor reflex</td>
</tr>
<tr>
<td>DFA alpha2</td>
<td></td>
<td>Detrended fluctuation analysis, describing long term fluctuation</td>
<td>Baroreceptor reflex</td>
</tr>
<tr>
<td>D2</td>
<td></td>
<td>Correlation dimension, estimating the minimum number of variables required to construct a model of system dynamics</td>
<td></td>
</tr>
</tbody>
</table>

Table 2c. Non Linear Indices of Heart Rate Variability [105]
1.6.3 Heart Rate Recovery

Heart rate recovery to a resting state following a stimulus can be used to assess the integrity of the autonomic nervous system. The stimulus to provoke an increased HR may be exercise (treadmill/exercise bike) or orthostatic change (active stand) [3,114].

Post exercise, the recovery of HR to baseline value is a known prognostic indicator. Multiple studies have demonstrated that if HRR is reduced, this is a marker of reduced parasympathetic activity – which can lead to increased rates of mortality in various patient populations, including patients without clinically evident cardiovascular disease [3,114,115]. This has primarily been studied and validated at the 1- and 2-minute mark, with Cole et al demonstrating a 10% mortality rate at 12 years in patients with abnormal 2-minute HRR versus 4% in patients with normal HRR [3,115]. In patients with known cardiovascular disease, HRR has been shown to correlate with rate of further cardiovascular events in a series of large population studies [116,117]. Significant studies in this field are summarised in table 3.

Several studies have demonstrated improvement in exercise provoked HRR following cardiac rehabilitation. This is postulated to be a reflection of improved autonomic function following the rehabilitation exercise programme [118,119,120,121].

More recently, HRR after orthostatic challenge has been reported as a predictor of CV disease and mortality. HR initially increases upon moving from lying to standing position, due to inhibition of vagal tone [122]. A peak of HR is observed at approximately 10 seconds, with a reduction thereafter to around 20 seconds [123]. The velocity of HRR, between 10 and 20 seconds following orthostatic challenge, predicts all-cause mortality in a population study of adults 50 years and older (mean age 64 years). Remarkably, participants in the slowest recovery quartile were 2.3 times more likely to die within 4 years than those in the fastest recovery group, independent of other risk factors [114]. HRR_{10-20} has further been shown to correlate with educational attainment level, showing that in less educated groups there is a significant impairment in autonomic function – shown in figure 6 [124].
Figure 6. Speed of heart rate recovery in beats per minute in response to postural challenge by highest level of educational attainment, after controlling for age, sex, existing cardiovascular disease burden, use of cardiovascular medications, and height. Difference in HRR_{10-20} between primary and tertiary educated groups 1.15, p<0.01 [124]
<table>
<thead>
<tr>
<th>n</th>
<th>Physiological challenge</th>
<th>Measurement</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cole et al, 1999 [3]</td>
<td>2428 Exercise stress test – standard Bruce protocol</td>
<td>Heart rate recovery at 1 minute post cessation of exercise</td>
<td>Impaired heart rate recovery in a population without previous diagnosed cardiovascular disease is associated with increased all-cause mortality</td>
</tr>
<tr>
<td>Cole et al, 2000 [125]</td>
<td>5234 Exercise stress test – standard and modified Bruce protocols</td>
<td>Heart rate recovery at 2 minutes post cessation of exercise</td>
<td>Impaired heart rate recovery, even following submaximal exercise, is associated with increased all-cause mortality</td>
</tr>
<tr>
<td>Morshedi-Medibodi et al, 2002 [126]</td>
<td>2967 Exercise stress test – standard Bruce protocol</td>
<td>Heart rate recovery, and velocity of recovery, between 1 to 4 minutes</td>
<td>Impaired heart rate recovery is associated with higher rates of cardiovascular events as well as all-cause mortality</td>
</tr>
<tr>
<td>Lipinski et al, 2004 [127]</td>
<td>2193 Exercise stress test – USAFSAM or individualised ramp protocol</td>
<td>Heart rate recovery at 1,2,3 and 5 minutes following cessation of exercise</td>
<td>Impaired heart rate recovery is associated with the presence of coronary artery disease</td>
</tr>
<tr>
<td>Aktas et al, 2004 [128]</td>
<td>3554 Exercise stress test – standard Bruce or modified Bruce protocols</td>
<td>Heart rate recovery at 1 minute following cessation of exercise</td>
<td>Impaired heart rate recovery may be used in addition to cardiovascular risk calculations to increase sensitivity and specificity</td>
</tr>
<tr>
<td>Myers et al, 2007 [129]</td>
<td>1910 Exercise stress test – individualised</td>
<td>Heart rate recovery at 2 minutes following cessation of exercise</td>
<td>Impaired heart rate recovery and chronotropic incompetence are associated with cardiovascular mortality</td>
</tr>
<tr>
<td>Savonen et al, 2011 [133]</td>
<td>1102 Exercise stress test – cycle ergometer</td>
<td>Heart rate recovery at 2 minutes following cessation of exercise</td>
<td>Impaired heart rate recovery following cycle-based exercise stress test is associated with increased risk of all-cause mortality in an otherwise healthy cohort</td>
</tr>
<tr>
<td>Johnson et al, 2012 [132]</td>
<td>2082 Exercise stress test – standard Bruce protocol</td>
<td>Heart rate recovery at 5 minutes following cessation of exercise</td>
<td>Impaired late heart rate recovery adds prognostic value for all-cause mortality to a multivariate model including earlier 1 minute heart rate recovery</td>
</tr>
<tr>
<td>Park et al, 2015 [131]</td>
<td>898 Exercise stress test – submaximal workload</td>
<td>Heart rate recovery at 2 minutes following cessation of exercise</td>
<td>Impaired heart rate recovery is associated with long term myocardial ischaemia</td>
</tr>
<tr>
<td>McCrory et al, 2016 [114]</td>
<td>4475 Orthostatic challenge</td>
<td>Velocity of heart rate recovery between 10 and 20 seconds following orthostatic challenge</td>
<td>Impaired heart rate recovery velocity following orthostatic challenge is associated with increased all-cause mortality</td>
</tr>
<tr>
<td>Van de Vegte et al, 2018 [130]</td>
<td>40,72 Exercise stress test – UK Biobank cardio assessment</td>
<td>Heart rate recovery at 10, 20-, 30-, 40- and 50-seconds following cessation of exercise</td>
<td>Impaired heart rate recovery at 10 seconds is a strong predictor of all-cause mortality and cardiovascular mortality</td>
</tr>
</tbody>
</table>

**Table 3. Studies detailing heart rate recovery time after exercise and orthostatic challenge**
1.7: BLOOD PRESSURE, FINAPRES AND THE ACTIVE STAND

1.7.1 Deriving HRR_{10-20}
Previous studies from the TILDA group using HRR_{10-20} used specific protocols to ensure experimental accuracy in measurements obtained and replicability over time. Their protocols of performing an active stand while continually measuring heart rate and phasic blood pressure were replicated in this project, and as I have used their protocols, I will review the methods which were employed and the scientific justification for these methods.

1.7.2 Methods of Monitoring Blood Pressure
Arterial blood pressure may be measured invasively or non-invasively, with non-invasive monitoring being the modality of choice in a non-critical care setting [134,135]. Standard non-invasive blood pressure measurement is primarily done via a sphygmomanometer, either manually with a stethoscope or automatically. This method provides a single reading of systolic and diastolic blood pressure, and may be repeated many times over a period in order to provide more information, such as that seen in a 24-hour ambulatory blood pressure reading. A drawback of this method is that it does not provide beat-to-beat continuous data; however, other methods may provide this information [136].

1.7.3 Continuous Phasic Beat-to-beat Blood Pressure Measurement
The gold standard of continuous phasic beat-to-beat blood pressure monitoring is via invasive direct arterial observation. This is usually performed via the radial, brachial or femoral arteries, where a catheter is inserted and connected to a pressure transducer, allowing real time pressure waveform observation.

Invasive monitoring of blood pressure has the disadvantage of complications derived from the invasive nature of the process; access site complications such as dissection, thrombosis and infection risk. The accuracy of the readings may be impacted by the size of the vessel which is being cannulated and the overall clinical state of the patient, with ascending aorta pressure being different to abdominal aortic or radial arterial pressure – see figure 7. Due to the risk to benefit ratio, this method is primarily reserved for patients in a critical care or intra-operative setting. [137,138]

An alternative to invasive assessment while still allowing continuous phasic beat-to-beat blood pressure recordings is via the volume-clamp method, initially developed by Penaz [139]. The
Finometer (Finapres Medical Systems BV, Arnhem, the Netherlands) is an example of a device which employs this method [140]. A cuff containing an inflatable bladder is placed around the patient’s finger, which inflates to the point of clamping the digital arteries creating pressure equalisation on both sides of the arterial wall. Counter-pressure is applied through the inflatable bladder which is adjusted continuously in order to keep the arterial volume at a constant level. The volume of blood flowing through the artery can then be measured using an infrared photoplethysmograph built into the cuff itself. The waveforms of the recordings from this form of assessment are similar to direct atrial pressure waveforms, however, inaccuracies may develop due to changes in vascular tone and unloaded digital arterial pressure and must be adjusted for, such as with the automatic proprietary Physiocal seen on the Finometer device [140,141]. In order to further improve the accuracy of the readings, height correction sensors, regression and signal filtering methods can be used – these will specifically allow correction for differences in waveforms between the small digital arteries and larger calibre arteries [142].

Blood pressure measurements derived from the volume-clamp method are susceptible to error due to the non-invasive nature of the reading, and as such, care must be taken to ensure that the system is properly calibrated and that the various monitoring hardware is applied appropriately [142].

Due to the continuous and non-invasive nature of the recordings, this method of assessment can be used in stable out-patients, such as in a falls and syncope assessment, whereby an active stand may be performed with continuous blood pressure assessment allowing the diagnosis of orthostatic hypotension to be made [143]. In order to allow accurate diagnoses to be made using this assessment tool, a standardised protocol should be followed to allow comparison of readings both in a time interval and between separate patients [142].
Figure 7. Differences in invasively obtained arterial waveforms depending on site of measurement
Figure 8. Volume clamp method of Blood Pressure measurement
Figure 9. Example of Finometer Trace During Active Stand
1.7.4 Active Stand Protocol

As described above, the use of the Finometer to non-invasively monitor phasic blood pressure may be prone to error. Furthermore, the time of day, temperature, hydration status, and use of nicotine and caffeine may also affect the results. Due to this, a standardised protocol to perform an active stand was developed in order to allow comparison with previous results from the same patient and between patients even if a different clinician or researcher is performing the test [142].

An example of a standardised protocol used in previous research, and additionally in this project includes;

1. Performing the active stand in the morning, in a quiet room at a temperature between 21 to 23 degrees centigrade.
2. The patient should be fasted for 2 hours before the active stand, and abstain from caffeine, nicotine and exercise for the preceding 12 hours.
3. The patient should remain in a supine position for 10 minutes prior to changing posture to standing to allow system calibration, cardiovascular stabilisation and baseline recordings of heart rate and blood pressure to be made.
4. The patient is instructed to stand up as fast as possible and remain standing for 3 minutes.
5. Throughout the active stand, phasic blood pressure and heart rate recordings are taken. The patient is asked in regards to symptoms of dizziness and light-headedness at the 1- and 3-minute time intervals, and otherwise should remain silent in order to prevent interference with recordings.
1.8: CORONARY ARTERY DISEASE AND REVASCULARISATION

1.8.1 Coronary Artery Disease and Autonomic Function
Coronary artery disease has both a cause and an effect relationship with autonomic dysfunction. As previously described, there is a strong correlation between resting heart rate and atheromatous plaque formation and rupture, likely due to increased heart rate causing increased shear stress and shear frequency on thin-capped fibroatheroma [83, 90, 91]. Furthermore, increased heart rate as previously discussed will also result in endothelial dysfunction, with a reduction in NO production, resulting in vasoconstriction and negative vessel remodelling [60,61]. Additionally, ischaemia in the myocardium following either plaque rupture or following chronic obstruction will be acted upon by the autonomic system, with increased sympathetic and decreased parasympathetic tone. This resultant negative feedback cycle can lead to progressive ischaemia and infarction in the downstream myocardial territory, and may result in an increased risk of ventricular arrhythmia and death [108,109].

1.8.2 Acute and Chronic Coronary Syndromes
Coronary artery disease is one of the leading causes of morbidity and mortality throughout the world. The primary pathophysiology is of coronary atherosclerosis, whereby atheroma formation within the coronary arteries can impact flow of blood to the myocardium. This disease process may present in two main distinct ways, described by the European Society of Cardiology as Acute Coronary Syndrome (ACS) and Chronic Coronary Syndrome (CCS) [144,145, 146].

In ACS, the fibrous cap of the atheromatous plaque within the coronary artery ruptures, leading to thrombus formation. This may occlude the artery completely, which may cause an ST segment Elevation Myocardial Infarction (STEMI), or occlude partially or transiently, leading to a Non-ST segment Elevation Acute Coronary Syndrome (NSTEMI). In the setting of ACS, the acute management is focused at revascularizing the impaired myocardium in order to limit morbidity and mortality [144,145].

In CCS, the atheroma formation follows a more stable path, which may lead to progressive calcification and negative remodelling of the arterial structure, eventually leading to obstructed flow to the distal myocardial tissue. This syndrome presents, as its name suggests, as a chronic presentation of exertional angina. In the setting of CCS, management is primarily focused at
reducing the morbidity of the symptom burden, with adequate anti-anginal medication therapy along with potential revascularisation [146].

1.8.3 Revascularisation Strategy
The revascularisation strategy of both of these distinct clinical syndromes is determined by the patients themselves; the anatomy of the coronary artery disease, their comorbid status and the nature of presentation, and can include percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or a hybrid of both of these modalities.

PCI is performed in the cardiac catheterisation laboratory by the interventional cardiology team. It involves arterial access (radial or femoral), the placement of guiding catheters in the aorto-ostium of the coronary arteries, wiring the stenosed or occluded segment of the artery, and thereafter restoring flow with balloon angioplasty and implantation of stents to prevent arterial recoil. Since the first coronary angioplasty was performed by Andreas Gruntzig in 1977, the procedure has improved with the development of initially bare metal and eventually drug eluting stents, along with intracoronary imaging techniques (such as intravascular ultrasound), intracoronary physiological assessments (such as fractional flow reserve) and calcium modification techniques (such as intracoronary lithotripsy) [147, 148, 149, 150]. PCI is the treatment strategy of choice for STEMI and for more approachable coronary lesions, as the technology can be limited by anatomical considerations.

CABG procedures are performed in an operating theatre by the cardiothoracic surgery team. It involves performing a sternotomy, mobilising saphenous veins from the leg and/or arterial grafts such as the left internal mammary artery from the chest wall, and the anastomoses of these conduits to the coronary arteries distal to the occluded or stenosed segment. This can be performed with full bypass and aortic cross clamping, or off pump [151]. Following the surgery, the patient is admitted to the intensive care unit for a period of recovery. Due to the need for a sternotomy and post-operative intensive care unit stay, CABG is reserved for participants whose coronary anatomical considerations would limit the effectiveness of a PCI option.

1.8.4 The SYNTAX score
Coronary anatomical considerations which increase the complexity of a PCI and may lead to the decision being made to proceed with CABG include: if the coronary lesion is a chronic total occlusion, a trifurcation or bifurcation, aorto-ostial site of the stenosis, presence of severe tortuosity, length of lesion greater than or equal to 20mm, heavy vessel calcification, presence of thrombus, and if the pattern of disease is diffuse. One of the most widely used scoring
systems to aid in decision making regarding PCI or CABG for revascularisation was developed as part of the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial (SYNTAX), and is referred to as the SYNTAX score [152]. This scoring system uses the above anatomical considerations to give a numerical score to the complexity of the underlying coronary artery disease. The SYNTAX trial and subsequent follow-on research showed that this anatomical SYNTAX score differentiated between low complexity (SYNTAX score less than or equal to 22), intermediate complexity (SYNTAX score 23-32) and high complexity coronary artery disease (SYNTAX score greater than or equal to 33). In low complexity lesions PCI was non-inferior to CABG, high complexity showed better outcomes with CABG, and intermediate complexity showed non inferiority of PCI at 1 year follow-up, with some divergence favouring CABG thereafter. Follow-on trials improving the SYNTAX score to the functional SYNTAX and SYNTAX score 2 involved incorporating comorbidities and invasive coronary physiological assessment, along with intracoronary imaging guided optimisation of implanted stents [153, 154]. Despite the added benefit of these variables in the updated scoring systems, the anatomical SYNTAX score is often used in clinical practice to describe the overall complexity of underlying coronary artery disease.

1.8.5 Incomplete Revascularisation
Following completion of PCI or CABG, the degree of underlying residual coronary artery disease allows the disease pattern to be considered as either complete revascularisation (CR) or incomplete revascularisation (ICR). The definition of these terms has been subject to debate and depends on if invasive physiological assessment with fractional flow reserve or instantaneous free wave ratio has been carried out, if angiographic findings alone define the status or if all reasonable revascularisation targets have been achieved [155]. Regardless, both residual angiographic anatomical coronary artery disease and residual functionally proven myocardial ischaemia have both been shown to correlate with higher rates of cardiac and all-cause mortality, be the initial revascularisation strategy PCI or CABG (as further described in figure 8 from the randomised Second Medicine, Angioplasty, or Surgery Study [156]). A method of quantifying the degree of ICR is through the use of the residual SYNTAX score (rSS) – which is a calculation of the anatomical SYNTAX score following completion of the revascularisation procedure. Residual SYNTAX score of greater than 8 is associated with higher rates of long-term mortality [157].
Figure 10. Probability of survival free of cardiovascular mortality among patients in the complete and incomplete revascularization groups. Difference in mortality $p=0.04$ [156].
1.9: CARDIAC REHABILITATION

1.9.1 Cardiac Rehabilitation and Autonomic Function
Completion of a cardiac rehabilitation programme has previously been demonstrated to be associated with improved HRV (RR, LF, HF, LF/HF) and exercise based HRR [158, 159]. This is therefore postulated to be a sign that completing cardiac rehabilitation modulates the autonomic nervous system.

1.9.2 What is Cardiac Rehabilitation?
Cardiac rehabilitation was defined by the World Health Organisation as “‘the sum of activities required to influence favourably the underlying cause of the disease and to ensure cardiac patients the best possible physical, mental and social conditions so that they may, by their own efforts, preserve or resume as normal a place as possible in the community.” [160]
It entails a structured supervised exercise programme (including cardiovascular exercise such as treadmill or exercise bicycle along with isometric weight-based exercises), psychological support, risk factor modification along with educational sessions from nurses, doctors, social workers, physiotherapists, pharmacists, occupational therapists and clinical nutritionists among others. It carries a class 1 treatment indication from the ESC for patients with coronary artery disease and heart failure [144, 145, 146, 161].

1.9.3 Impact of Cardiac Rehabilitation
Cardiac rehabilitation is a form of secondary prevention of further cardiac events. Through the programme, the aim is to tackle the risk factors for disease progression: hypertension, smoking, diabetes, obesity and dyslipidaemia among others. By affecting each individual risk factor in an ongoing way, the overall risk for further events should reduce. Suaya et al demonstrated a 25% reduction in all-cause mortality in patients who had completed cardiac rehabilitation [162]. This benefit has been shown to extend up to 5 or even 10 years in previous research [163,164]. Additionally, symptom burden of angina and dyspnoea is decreased, there is improved adherence with medication, increased exercise capacity, and demonstrable improvement in both blood pressure and plasma lipid profile [165-169].
CHAPTER TWO:
Aims, Hypothesis, General Methodology
2.1 AIMS
Heart rate can be modulated through pathological and physiological demands on the central nervous system, the autonomic nervous system itself, the homeostatic feedback mechanisms, and the heart itself, as shown in figure 11.

This project aims to compare the usage of a novel autonomic function index, HRR_{10-20}, to assess its possible clinical uses in patients with cardiac pathologies. We aim to assess the difference in autonomic function in complete revascularisation and incomplete revascularisation, by assessing two separate groups of patients with totally revascularized coronary arteries versus those with residual disease. Following on from this, we aim to assess the impact of the increased physiological demand of exercise through cardiac rehabilitation, by following patients as they complete a six week structured exercise programme and assessing their autonomic function at set time points along the way. This will be in comparison to a group of patients who elected to not participate in a structured exercise programme.

2.2: HYPOTHESIS
The hypothesis of this MD thesis is that autonomic function measured through HRR_{10-20} will initially be impaired in those with coronary artery disease, specifically those with incomplete revascularisation - determined by residual SYNTAX score – and that thereafter following completion of cardiac rehabilitation, autonomic function will improve.

2.3: GENERAL METHODOLOGY
In order to address our hypothesis, we elected to perform both a cross sectional and longitudinal assessment of the same patient cohort as a case: case/control nested longitudinal study. Initially, the effect of revascularisation was assessed by comparing HRR_{10-20} in patients who had successful complete revascularisation with those who had not had complete revascularisation. These same patients were then be followed up throughout a period of cardiac rehabilitation. There are inevitably patients who drop out of cardiac rehabilitation at the commencement of the exercise programme due to various factors such as commute to the centre, family or work commitments. We aimed to assess both the patients who had successfully completed the structured exercise programme and those who did not commence the structured exercise period. The recruitment period was from 1st August 2019 until 1st March 2020 before being curtailed due to the SARS-CoV-2 pandemic.
The same active stand protocol was used throughout, with real time heart rate, blood pressure and ECG recordings taken. Analysis of these readings provided the variable which we are assessing, HRR_{10-20}. Further detail on the cross-sectional methodology can be seen in chapter 3.2, while further detail on the longitudinal methodology can be seen in chapter 4.2.

**Inclusion criteria**

Inclusion criteria were that the patient needed to be >18 years of age and had been enrolled in phase 2 cardiac rehabilitation. The participant additionally needed to have the ability to perform an active stand from supine to standing within 5 seconds, have resting sinus rhythm and the ability to provide informed consent.

**Exclusion criteria**

Participants were determined to be ineligible if they had a paced cardiac rhythm, atrial fibrillation and if they were unable to move from supine to standing within 5 seconds. These criteria would prevent a Finometer trace from being clean enough to provide an accurate HRR_{10-20}. Furthermore, if the participant was unable to provide consent, they were not considered for the study.

Additional inclusion and exclusion criteria for the individual arms of the research can be seen in chapters 3.2 and 4.2.

Assessment of autonomic function was performed by determining speed of heart rate recovery between 10 and 20 seconds post orthostatic challenge (HRR_{10-20}). A pressure cuff was applied to the participant’s finger, which measures phasic blood pressure. Following a 10-minute rest period in a supine position, participants were instructed to stand promptly (within 5 seconds). The zero-time point was set at the point where the participant began to rise from supine. Beat to beat variability in heart rate and blood pressure during the change in posture was measured via non-invasive digital photoplethysmography (Finometer, Finapres Medical systems, Arnhem, The Netherlands). Data collected were corrected for height using a height correction device applied automatically by the Finometer. During the active stand, real time heart rate, blood pressure and ECG recordings were taken and HRR_{10-20} extrapolated as follows; Heart rate after 10 and 20 seconds were calculated using a non-stationary moving average window, with window width set at +/- 5 seconds to filter the heart rate from the Finometer heart rate signal, from which the velocity of change within that timeframe was calculated. Waveform graphs of ECG and phasic blood pressure were assessed for reliability to ensure accuracy of derived
physiological parameters, while additionally a signal abnormality index was used to quantify the quality of the signal data within the active stand record. This calculates the proportion of beats that are noisy within the timeframe of the stand, whereby 0 implies a clean record with no detected abnormal beats, and 1 implies a very noisy record with all beats identified as abnormal. All study participants were included regardless of the signal abnormality index in an intention to treat analysis.

**Active stand protocol**

Participants all underwent active stand (AS) in early afternoon between hours of 12noon and 3pm, with measurements being taken following abstention from caffeine, nicotine and exercise for the previous 12 hours. Participants had additionally been instructed to fast for 2 hours prior to the AS occurring. Participants underwent AS following approximately 10 minutes of supine rest. Baseline BP was calculated as the mean value between 60 and 30 seconds before stand. Data was down-sampled to 1 Hz. Two smoothing filters were applied, a 10-point moving average filter and an 11-point median filter. Onset of the stand was detected via an algorithm using data from the Finometer height correction unit. Participants were instructed to remain standing for 3 minutes following moving from supine, with continuous phasic BP and ECG tracings throughout. This protocol has been used and validated previously [114, 123, 124, 142].
Figure 11. Physiological and Pathophysiological Impact on the Neurocardiac Axis
CHAPTER THREE:
Impaired Autonomic Function after Incomplete Revascularisation
CHAPTER 3.1: INTRODUCTION

Autonomic function plays a central role in control of homeostatic mechanisms governing heart rate. This can be assessed clinically using various indices including: heart rate recovery time following either exercise or orthostatic challenge, and various metrics of heart rate variability. Studies have previously shown in a non-standardised manner that heart rate recovery time following exercise (varying between 1- and 5-minutes following cessation of exercise) correlates with increased rates of mortality in various patient populations, including patients without clinically evident cardiovascular disease [3, 126, 127]. Heart rate recovery time after orthostatic challenge has also been reported as a predictor of CV disease and mortality. HR initially increases upon moving from lying to standing position, due to inhibition of vagal tone. A peak of HR is observed at approximately 10 seconds, with a reduction thereafter to around 20 seconds. This pattern of HR and BP change following orthostatic challenge is shown in figure 12 [114]. Our group has previously demonstrated that the velocity of HRR, between 10 and 20 seconds following orthostatic challenge (HRR10-20), predicts all-cause mortality in adults 50 years and older (mean age 64years) in a general population. Participants in the slowest recovery quartile were 2.3 times more likely to die within 4 years than those in the fastest recovery group, independent of other risk factors [114].

Both heart rate variability metrics and heart rate recovery have been used previously in clinical research as a surrogate marker of autonomic tone, as no direct measurements of the autonomic system are possible. This can mean that other factors can influence the extrapolated results; for example, circadian rhythm, hormones and temperature. Furthermore, time and frequency HRV indices such as PNN50, SDNN, SDANN and rMSSD, along with HRR following exercise stress testing have demonstrated a correlation between the presence of coronary artery disease, mortality, and impaired autonomic function [107-109].

Incomplete revascularisation (ICR) is associated with increased 5-year mortality. Various trials have attempted to elucidate the benefit of a complete revascularisation (CR) strategy in patients with complex coronary artery disease [156, 170-172]. The SYNTAX score is an objective, quantitative and widely used tool used to demonstrate the burden and complexity of coronary artery disease, while the residual SYNTAX score (rSs) has additionally been used to describe residual coronary artery disease – indicative of ICR- following percutaneous coronary intervention (PCI) [157].
Previous research has demonstrated a correlation between time and frequency domain variables of HRV with percutaneous revascularisation, but the use of heart rate recovery velocity has not been previously described [107, 173, 174]. Given that both impaired autonomic function and incomplete revascularisation are both associated with increased mortality, we aimed to assess the novel metric HRR\textsubscript{10-20} in a high risk, incompletely revascularized group compared to a lower risk, completely revascularized group. We hypothesised that ICR would be associated with impaired autonomic function derived from the novel variable HRR\textsubscript{10-20}. 

Figure 12. Mean heart rate and systolic blood pressure (SBP) and diastolic blood pressure (DBP) values across the stand (including baseline) in a healthy control [114]
3.2: METHODS

Study Design
We conducted a prospective case: control study from 1st August 2019 until 1st March 2020 in a secondary and tertiary referral university teaching hospital and a supra-regional referral centre for coronary intervention. Written informed consent was obtained from all participants. Ethical approval was confirmed by the St James’s Hospital/Tallaght University Hospital Joint Research and Ethics Committee, Dublin, Ireland (REC: 2019-07 List 27 (19)).

Study Participants

Cases
Cases were patients aged >18 years of age who had undergone PCI for stable or unstable coronary syndromes performed within the previous 3 months and had been referred for phase 2 cardiac rehabilitation. Inclusion criteria beyond those described in chapter 2.3 additionally included ICR determined by a rSs of >0.

Case/Controls
Case/Controls were patients aged >18 years of age who had undergone PCI for stable or unstable coronary syndromes performed within the previous 3 months and had been referred for phase 2 cardiac rehabilitation. Inclusion criteria in addition to those described in chapter 2.3 included CR determined by a rSs of 0.

Exclusion Criteria
There were no additional exclusion criteria beyond those described in the general methodology chapter 2.3.

Data Collection and Validation
All eligible participants were recruited consecutively post-revascularisation through the cardiac rehabilitation programme, and informed consent obtained. Participants answered a baseline semi structured questionnaire, including self-reported answers with investigator assistance to complete, containing demographic data, comorbidities including diabetes, smoking history and family history of premature coronary artery disease along with medication usage - including rate limiting or autonomic modulating medications (beta blockers, ivabradine, calcium channel blockers, salbutamol). Participants additionally underwent a physical examination including
height and weight. Medical records were reviewed to determine the type of stent used, where
the stent was placed and the indication for PCI.

Both pre and post procedural angiograms of the participants were reviewed by independent
reviewers (Dr Peter Wheen, Dr Lisa Brandon) and SYNTAX scores determined using the SYNTAX
calculator (www.syntaxscore.com). Patients with an rSs > 0 were considered incompletely
revascularized and those with an rSs of 0 fully revascularized.

**Active stand protocol**

Participants all underwent AS in early afternoon between hours of 12noon and 3pm, with a
previously validated protocol described in chapter 2.3 above. This protocol has been used and
validated in previous research [114, 123, 124, 142].

**Statistical Methodology**

Statistical analysis was performed using GraphPad Prism 9.0.2. Pearson’s correlation coefficient
was used to determine the relationship between HRR_{10-20} and incomplete versus complete
revascularisation, Shapiro-Wilk test to assess for normality of distribution, and a Student’s T test
used to determine statistical significance of the difference between the two independent groups
(p < 0.05 was considered statistically significant).

Detailed sample size calculations are outlined on the next page. A sample size of 48, with a 1:2
ratio of patients with ICR vs. CR, was calculated to provide 90% power to detect a difference in
HRR_{10-20} of 2 beats per minute between groups, with a p value of <0.05 denoting statistical
significance. Estimates of difference in HRR_{10-20} were based upon previous studies of HRR_{10-20}. We
aimed to recruit 60 cases (20 ICR versus 40 CR) over a 6-month period.
Sample size calculation

3.3: RESULTS
A total of 113 participants were screened across the 6 months of recruitment, with 78 participants meeting inclusion criteria, of whom 53 consented to participation. Of those recruited, 16 were cases with ICR and 37 were case/controls with complete revascularisation.

Demographic Characteristics
Cases and case/controls did not differ significantly in baseline demographic and background medical characteristics (see table 4). Use of rate limiting or autonomic modulating medications was similar between groups.

Data Quality
Signal average index of phasic blood pressure during active stand was similar between groups: 0.093 in the ICR group and 0.09 in the CR group. The signal average index of ECG was also similar between the groups: 0.011 in the ICR group; 0.013 in the CR group.
Figure 13. Flow diagram of Participant Recruitment

Assess for eligibility n=113

Did not meet inclusion criteria n=38
atrial fibrillation n=20
permanent pacemaker n=14
could not perform active stand n=4

Consent requested n=78

Did not consent n=25

Assessed for completeness of revascularisation n=53

Incomplete Revascularisation r'SS>=0 n=10

Complete Revascularisation r'SS=0 n=37

Active stand carried out

Analysis for HRR10-20
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Complete Revascularisation</th>
<th>Incomplete Revascularisation</th>
<th>P Value</th>
</tr>
</thead>
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<td>n</td>
<td>37</td>
<td>16</td>
<td></td>
</tr>
<tr>
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<td>0.17</td>
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<td>Procedures Implanting EES (no)</td>
<td>33</td>
<td>12</td>
<td>0.98</td>
</tr>
<tr>
<td>Stents Implanted (no)</td>
<td>1.7</td>
<td>1.8</td>
<td>0.99</td>
</tr>
<tr>
<td>LMS PCI (no)</td>
<td>3</td>
<td>1</td>
<td>0.98</td>
</tr>
<tr>
<td>LAD PCI (no)</td>
<td>22</td>
<td>7</td>
<td>0.97</td>
</tr>
<tr>
<td>LCx PCI (no)</td>
<td>12</td>
<td>4</td>
<td>0.97</td>
</tr>
<tr>
<td>RCA PCI (no)</td>
<td>26</td>
<td>9</td>
<td>0.97</td>
</tr>
<tr>
<td>Time from revascularisation to AS (weeks)</td>
<td>10.4</td>
<td>11.1</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Table 4. Baseline Demographics

**Autonomic Function and Revascularisation status**

$HRR_{10-20}$ was impaired in the ICR group (-3 ± 0.60) contrasting to the CR cohort (-6.56 ± 0.52) (p<0.0001) (figure 14). Completeness of revascularisation was strongly associated with $HRR_{10-20}$ (Pearson’s correlation coefficient 0.529; p<0.0001).

No significant difference was observed between groups in relation to resting or peak systolic blood pressure, resting or peak diastolic blood pressure and resting or peak heart rate, as described in table 5.
Figure 14 – Impact of revascularisation status on HRR$_{10-20}$
### Table 5. Measured physiological indices; complete revascularisation versus incomplete revascularisation cohorts

<table>
<thead>
<tr>
<th>Physiological Index</th>
<th>Complete Revascularisation</th>
<th>Incomplete Revascularisation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRR&lt;sub&gt;10-20&lt;/sub&gt; (bpm)</td>
<td>-6.56 ± 0.52</td>
<td>-3 ± 0.60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HR rest (bpm)</td>
<td>66.36 ± 2.96</td>
<td>66.63 ± 5.67</td>
<td>0.93</td>
</tr>
<tr>
<td>HR peak (bpm)</td>
<td>82.74 ± 4</td>
<td>83.89 ± 7.55</td>
<td>0.77</td>
</tr>
<tr>
<td>SBP rest (mmHg)</td>
<td>136.56 ± 5.29</td>
<td>139.53 ± 8.38</td>
<td>0.55</td>
</tr>
<tr>
<td>SBP peak (mmHg)</td>
<td>127.31 ± 8.97</td>
<td>109.95 ± 12.8</td>
<td>0.75</td>
</tr>
<tr>
<td>DBP rest (mmHg)</td>
<td>78.85 ± 3.83</td>
<td>80.63 ± 5.77</td>
<td>0.61</td>
</tr>
<tr>
<td>DBP peak (mmHg)</td>
<td>69.97 ± 5.31</td>
<td>63.79 ± 9.96</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Mean values with 95% CI
3.4: DISCUSSION

Our data confirm significant correlation between revascularisation status and autonomic function determined by speed of heart rate recovery. Given the previously established correlation between impaired autonomic function and all-cause mortality and also the correlation between incomplete revascularisation and all-cause mortality, our data support the hypothesis that increased mortality due to incomplete revascularisation may be as a result of impaired autonomic function and sequelae to which this pertains.

We have also demonstrated that assessment of autonomic function may facilitate risk stratification among a high-risk group of patients who have undergone percutaneous coronary interventions.

Our findings indicate that autonomic function correlates with completeness of revascularisation. We postulate that this may be due to myocardial ischaemia leading to homeostatic feedback through the neurocardiac system causing reduced vagal tone. In the event that myocardium is ischaemic, hypoxia and metabolic stress may cause differences in efferent signalling through the vagus nerve and cardiac plexus when compared to non-ischaemic myocardium. As a result, homeostatic afferent signalling to the sinoatrial and atrioventricular nodes may differ, resulting in the observed differences in $\text{HRR}_{10-20}$.

Extrapolating from these findings we can additionally consider that overall complexity of coronary artery disease may also correlate with autonomic function. We have observed that a SYNTAX score of >0 correlates with impaired autonomic tone, and we suggest that given our theory that myocardial ischaemia is the causative factor in this dysregulation, we also suggest that as SYNTAX scores increase, greater impairment in autonomic function may result. This theory should be tested in a larger patient cohort.

Furthermore, our postulation that ischaemia is the causative factor of impaired autonomic function leads to the theory that autonomic function may improve following coronary revascularisation, and that autonomic function could be a measure of procedural success. This additionally requires validation, and can be assessed by performing autonomic assessments prior to and post revascularisation.
The data which we have collected correlate with results from previous research Bonnemeier et al demonstrated that primary PCI for STEMI positively impacted upon autonomic function as determined by the SDNN HRV parameter, while Sedziwy et al further showed that HRV as described by PNN50, SDNN, SDANN and rMSSD improves following PCI in patients with stable coronary artery disease [173, 174]. Our data are the first to show a correlation between revascularisation status and autonomic function determined by the novel parameter HRR$_{10-20}$.

The main limitation of this study is that we measured surrogate markers of autonomic function through HRR$_{10-20}$. It may be more suitable in a future study to perform multiple assessments of autonomic function including HRR$_{10-20}$ as part of a suite of autonomic assessments, such as multiple HRV indices along with non-vascular assessments such as sweat tests. Future studies which include comprehensive assessment of autonomic function should include HRR$_{10-20}$ as part of the testing paradigm, because the HRR$_{10-20}$ has the potential to provide additional clinically-informative data.

The case-control design of the study is also a limitation. This allowed determination that there is a correlation between revascularisation status and heart rate autonomic variables, but does not definitively determine how they are linked. A prospective study assessing autonomic function prior to and post revascularisation would enable one to determine whether successful revascularisation improves autonomic function in individual patients with IHD. Furthermore, performing quantitative assessment of ischaemia such as perfusion imaging may validate the theory that myocardial ischaemia is the causative factor of impaired autonomic function.

Additionally, patients who had been revascularized through percutaneous intervention were primarily assessed. The impact of coronary artery bypass surgery has not been assessed; the impact of sternotomy, intensive care post-operative stay, saphenous venous grafts versus arterial grafts and other surgical variables was not reviewed as part of this study and thus our findings cannot be extrapolated to include them. Additionally, the relative impact of percutaneous versus surgical revascularisation upon autonomic function was not assessed.
Conclusions

The data support the hypothesis that incomplete revascularisation is associated with impaired autonomic function determined by HRR_{10-20}. This association has not previously been described and requires further study to elucidate physiological and pathophysiological causes.
CHAPTER FOUR:
Assessment of Speed of Heart Rate Recovery as a Modifiable Risk Factor Through Cardiac Rehabilitation
4.1: INTRODUCTION

Vascular health can be assessed by measuring baseline physiology to ensure normal function. Diametrically, vascular pathology can be assessed by measuring the effect of the pathology on physiological parameters. Commonly, blood pressure is used as a modifiable physiological parameter that is a risk factor for coronary artery disease amongst other vascular pathologies. Of other measurable physiological parameters, heart rate recovery time (HRRT) has previously been studied and ascertained to also correlate with both mortality and risk of coronary artery disease [114-117].

The physiology of heart rate is controlled by various methods, including intrinsic cardiac and extrinsic control mechanisms. These are often acting in opposing manners to achieve a balance which allows various feedback cycles to achieve homeostasis despite differing physiological demands. Heart rate is a major component of cardiac output and is a variable which can be easily altered by the body’s various homeostatic control mechanisms [4-6].

The autonomic nervous system’s effect on vascular tone and on the electrical conductive system of the heart is a key extrinsic control mechanism involved in modulating heart rate. Elevation of heart rate during exertion results from a reduction in vagal tone and activation of the sympathetic nervous system. Decline in heart rate post exertion is caused by the resumption of vagal tone.

Pathology can modulate the physiology of heart rate control through ischaemia and infarction, direct effect on the autonomic nervous system, tachyarrhythmias/bradyarrhythmias, via other neurohormonal imbalances such as seen in heart failure and in acute or chronic inflammatory conditions [8-11].

Pharmacological modulation of heart rate can be performed using beta blockers, calcium channel blockers, ivabradine and digoxin amongst other agents commonly used in clinical practice. The effect of the autonomic nervous system on the heart has previously been studied in patients post myocardial infarction, with prior studies determining that baroreceptor sensitivity, indicating reduced parasympathetic tone, predicts ventricular arrhythmia [107].

Additionally, it has been previously established that speed of heart rate recovery between 10 and 20 seconds post orthostatic challenge (HRR\textsubscript{10-20}) correlates with all-cause mortality in a general population [114]. This can be assessed by using a Finometer device during an active
stand assessment. We have also previously demonstrated that HRR10-20, as a marker of impaired autonomic function, may be seen in patients with incomplete vs. complete coronary revascularisation.

Measuring physiological response to treatment is a common measure of successful treatment, such as by successfully lowering blood pressure by prescribing anti-hypertensives, but assessing success or indeed identifying patients in whom further intervention is needed remains an ongoing problem in high-risk patient groups with IHD. The patients at highest risk of future events are those who have had previous events, and secondary prevention strategies commence at the onset of initial symptoms. This continues through cardiac rehabilitation and on to both general cardiology clinics and to primary care [160].

Cardiac rehabilitation is a structured multidisciplinary physical training and education programme designed to reduce risk of future cardiovascular events through multi-faceted risk factor modification. Physiotherapists and specialist nurses oversee a warm-up and various aerobic exercises, including treadmill, exercise bike and light isometric exercises. Sessions continue over a period of 6 to 8 weeks, along with additional educational sessions with the aim of other risk factor modification, including improved diet, smoking cessation and medication adherence. Cardiac rehabilitation itself has been proven to improve prognosis in patients post cardiac intervention but physiological measures of cardiovascular training response are lacking [161-169]. This aspect of our study aimed to determine whether a cardiac rehabilitation programme could alter autonomic function, quantified by longitudinal assessment of the HRR10-20, in patients with cardiac disease. The ultimate aim of this work is to determine whether measurement of autonomic function could be used as an in vivo marker to identify patients at higher risk of recurrent vascular events or vascular death during follow up, and whether such data could facilitate optimised secondary preventive therapy to reduce the risk of adverse outcomes in individuals/populations of patients with cardiac disease. We hypothesize that by successfully completing a structured cardiac rehabilitation programme, patients with IHD would see an improvement in their autonomic function as assessed by HRR10-20.
4.2: METHODS

Study Design

We conducted a prospective case: case/control study from 1st August 2019 until 1st March 2020 in a secondary and tertiary referral university teaching hospital and a supra-regional referral centre for coronary intervention. Written informed consent was obtained from all participants. Ethical approval was confirmed by the St James’s Hospital/Tallaght University Hospital Joint Research and Ethics Committee, Dublin, Ireland (REC: 2019-07 List 27 (19)). Written informed consent was obtained from all participants. Ethical approval was confirmed by the St James’s Hospital/Tallaght University Hospital Joint Research and Ethics Committee, Dublin, Ireland (REC: 2019-07 List 27 (19)).

Cases

Cases were patients aged >18 years of age who had undergone percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) surgery, transcatheter aortic valve implant (TAVI), surgical aortic valve replacement (SAVR) or other interventional or surgical cardiac intervention at the beginning of phase 2 of cardiac rehabilitation, thereafter reassessed at completion of 6 weeks of cardiac rehabilitation, and again after a further 6 week interval.

Case/Controls

The case/control group were a group of patients aged >18 years of age who had undergone percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) surgery, transcatheter aortic valve implant (TAVI), surgical aortic valve replacement (SAVR) or other interventional or surgical cardiac intervention referred for cardiac rehabilitation who did not commence the structured exercise component of the rehabilitation programme. These were a self-selected group of patients who attended for an educational session at the beginning of a rehabilitation programme, but elected to not proceed with the physical exercise component. The case/control group of participants were assessed with similar time periods between measurements – on recruitment, at 6 weeks and at 12 weeks.

Other inclusion and exclusion criteria were as previously described in chapter 2.3.

Data Collection and Analysis

All eligible participants were recruited at the beginning of phase II of the cardiac rehabilitation programme, and informed consent obtained. Participants answered a baseline semi structured questionnaire, including self-reported answers with investigator assistance to complete,
containing demographical data, comorbidities including diabetes, smoking history and family history of premature coronary artery disease along with medication usage - including rate limiting or autonomic modulating medications (beta blockers, ivabradine, calcium channel blockers, salbutamol, antithrombotics). Participants additionally underwent a physical examination including height and weight. Medical records were reviewed to determine the cardiac intervention which was performed, along with any salient details regarding the procedure.

Assessment of autonomic function was performed by determining speed of heart rate recovery between 10 and 20 seconds post orthostatic challenge (HRR\textsubscript{10-20}) with identical methodology to that described detail in chapter 2.3 above. All study participants were included regardless of the signal abnormality index.

Physical activity levels were assessed at the three data collection time points by using the IPAQ physical activity questionnaire (included in appendix). Continuous data were quantified using the IPAQ methodology to derive MET-mins per week. Categorical analysis was performed by dividing the groups into sedentary (<600 METs/min/week); moderate activity (600–3000 METs/min/week); and vigorous activity (>3000 METs/min/week) subgroups [175].

**Active stand protocol**

Participants all underwent AS in early afternoon between hours of 12noon and 3pm, with an identical, previously validated protocol to that described in chapter 2.3 above. This protocol has been used and validated in previous research [114, 123, 124, 142].

**Statistical Methodology**

A sample size of 39 was calculated to provide 85% power to enable us to detect a difference in HRR\textsubscript{10-20} of 3 beats per minute between groups (shown underneath). Estimates of difference in HRR\textsubscript{10-20} was based on previous studies of HRR\textsubscript{10-20}. The aim was to recruit 40 participants over the recruitment period.

Statistical analysis was performed using GraphPad Prism 9.0.2. Pearson’s correlation coefficient was used to determine the relationship between the change in HRR\textsubscript{10-20} from baseline to 12 weeks and completion of the rehabilitation programme, and unpaired t-tests were used to assess differences between the two groups. P <0.05 was considered statistically significant.
Paired student’s t-tests were used to assess whether changes in HRR\textsubscript{10-20} over the rehabilitation period were statistically significant. The correlation between the IPAQ activity score and the change in HRR\textsubscript{10-20} over the rehabilitation period was also assessed using Pearson’s correlation coefficient.

<table>
<thead>
<tr>
<th>Continuous Endpoint, Two Independent Sample Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Size</strong></td>
</tr>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Study Parameters</strong></td>
</tr>
<tr>
<td>Mean, group 1</td>
</tr>
<tr>
<td>Mean, group 2</td>
</tr>
<tr>
<td>Alpha</td>
</tr>
<tr>
<td>Beta</td>
</tr>
<tr>
<td>Power</td>
</tr>
</tbody>
</table>

\[
k = \frac{n_2}{n_1} = 2
\]
\[
n_1 = \left(\sigma_1^2 + \sigma_2^2 / K(z_{1-\alpha/2} + z_{1-\beta})^2\right) / \Delta^2
\]
\[
n_1 = \left(3^2 + 3^2 / 2(1.645 + 1.04)^2\right) / 3^2
\]
\[
n_1 = 13
\]
\[
n_2 = K \ast n_1 = 26
\]

- $\Delta = |\mu_1 - \mu_2|$ = absolute difference between two means
- $\sigma_1, \sigma_2$ = variance of mean #1 and #2
- $n_1 = $ sample size for group #1
- $n_2 = $ sample size for group #2
- $\alpha =$ probability of type I error (usually 0.05)
- $\beta =$ probability of type II error (usually 0.2)
- $z =$ critical $Z$ value for a given $\alpha$ or $\beta$
- $K =$ ratio of sample size for group #2 to group #1

**Power calculation**

4.3: RESULTS

During the recruitment period, 37 participants were recruited, 63.25% of whom were male; 25 commenced and completed full rehabilitation, whereas 12 did not commence the exercise component of rehabilitation by self-selection. Recruitment is summarised in figure 15. Of the 12 who did not complete the exercise component of the programme, 9 were due to time limitations because of family or work commitments, 2 were due to distance/commute to the centre, and 1 was due to not wishing to exercise.

At baseline, there were no differences in demographic or vascular risk factors between patients who did and did not commence rehabilitation (table 6). The vast majority of patients had IHD and underwent PCI, with 2 undergoing CABG and 3 having other surgical procedures (1 patient...
undergoing pericardectomy and 2 undergoing aortic valve replacement). Baseline demographics and characteristics are described in table 6.

Autonomic function as determined by HRR\textsubscript{10-20} at baseline was not significantly different between the groups (-4.09±2.02 in the group which did not commence rehab and -3.53±2.54 in the group which completed rehab, p=0.781).

Activity levels were also similar as determined by IPAQ derived weekly activity measured in MET-min/week (1160.56± 659 in the group which did not commence rehab, 1140.25± 383 in the group which completed rehab, p=0.956).

Through the 6 week and 12-week time periods, statistically significant differences in HRR\textsubscript{10-20} were noted between the group which completed rehabilitation versus the group which did not complete rehabilitation. At the 6-week time point, the group which completed rehabilitation improved their HRR\textsubscript{10-20} to -5.74±1.91, while the group which did not complete rehabilitation disimproved to 1.85±0.77; this difference between the rehabilitation group and the group which did not complete rehabilitation was statistically significant (p<0.0001). This pattern was repeated at the 12-week follow-up timepoint, with the rehabilitation group maintaining a marginal improvement in autonomic function (HRR\textsubscript{10-20} -6.33±2.32), and the group which did not complete rehabilitation deteriorating further (HRR\textsubscript{10-20} 4.05±1.27), with a statistically significant difference between groups (p<0.0001) (figure 16 and table 7).

The group which did not complete rehabilitation showed a deterioration in HRR\textsubscript{10-20} during follow-up between week 0 and 6 (+5.94 (p=<0.0001)), and between week 6 and 12 (+2.2 (p=0.004)). There was no significant change in HRR 10-20 amongst patients who completed rehabilitation over time, with stable results between week 0 and 6 (-2.21 (p=0.1799), and between week 6 and 12 (0.6 (p=0.58)) (table 8).

Completion of cardiac rehabilitation was strongly correlated with improvement of HRR\textsubscript{10-20} from baseline to 12 weeks (r=0.6104 p=<0.0001).

Activity levels as determined by IPAQ in MET-min/week were shown to be statistically different between the 2 groups at both time intervals: Activity levels were higher in those who completed rehabilitation compared with those who did not complete rehabilitation at both 6 weeks.
Improvement in activity levels in the rehabilitation group shown to correlate strongly with improved HRR$_{10-20}$ (at 6-weeks $r=-0.421$ $p=0.0068$; at 12-weeks $r=-0.315$ $p=0.0477$) (table 10). The rate of improvement of activity levels was additionally shown to strongly correlate with the rate of improvement of HRR$_{10-20}$ between baseline and both 6 and 12 weeks (from 0 to 6 weeks: $r=0.8778$ $p=<0.0001$, from 6 to 12 weeks: $r=0.178$ $p=0.2718$, from 0 to 12 weeks $r=0.7907$ $p=<0.0001$) (table 11).

Reliability of the measurements was similar both between the two groups and during follow-up over time, with comparable signal average index of ECG recordings (from which the HRR$_{10-20}$ analysis was performed). Week 1 measurements across all groups showed a signal average index of 0.09; at week 6 it was 0.087, and it was 0.10 at the week 12 timepoint. The rehabilitation group mean signal average index was 0.091, while the non-rehabilitation group was 0.095. This demonstrates background noise of all measurements using the Finometer was broadly similar.
Figure 15. Flow diagram of participant recruitment
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Did Not Complete Rehabilitation</th>
<th>Completed Rehabilitation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age - mean (years)</td>
<td>62.78</td>
<td>61.5</td>
<td>0.68</td>
</tr>
<tr>
<td>Age - &gt;65 (%)</td>
<td>44.44</td>
<td>45</td>
<td>0.71</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>64</td>
<td>62.5</td>
<td>0.49</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168</td>
<td>172</td>
<td>0.19</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.2</td>
<td>76.2</td>
<td>0.18</td>
</tr>
<tr>
<td>Never smoked (%)</td>
<td>48</td>
<td>51</td>
<td>0.63</td>
</tr>
<tr>
<td>Former smoker (%)</td>
<td>47</td>
<td>45</td>
<td>0.59</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>5</td>
<td>4</td>
<td>0.91</td>
</tr>
<tr>
<td>Diabetic (%)</td>
<td>11.1</td>
<td>12.5</td>
<td>0.77</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>94.4</td>
<td>95</td>
<td>0.84</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>94.4</td>
<td>95</td>
<td>0.84</td>
</tr>
<tr>
<td>Family history CAD (%)</td>
<td>64</td>
<td>60</td>
<td>0.39</td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>33.3</td>
<td>27.5</td>
<td>0.72</td>
</tr>
<tr>
<td>NSTEMEACS (%)</td>
<td>33.3</td>
<td>32.5</td>
<td>0.81</td>
</tr>
<tr>
<td>CCS (%)</td>
<td>33.3</td>
<td>40</td>
<td>0.7</td>
</tr>
<tr>
<td>EF (%)</td>
<td>51.67</td>
<td>49</td>
<td>0.32</td>
</tr>
<tr>
<td>Initial SYNTAX score</td>
<td>15.82</td>
<td>14.97</td>
<td>0.83</td>
</tr>
<tr>
<td>Residual SYNTAX score</td>
<td>3.36</td>
<td>1.83</td>
<td>0.4</td>
</tr>
<tr>
<td>Antithrombotic Rx (no)</td>
<td>12</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Statin Rx (no)</td>
<td>12</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Beta Blocker Rx (no)</td>
<td>12</td>
<td>24</td>
<td>0.99</td>
</tr>
<tr>
<td>Calcium Channel Blocker Rx (no)</td>
<td>1</td>
<td>4</td>
<td>0.85</td>
</tr>
<tr>
<td>Ivabradine Rx (no)</td>
<td>0</td>
<td>2</td>
<td>0.89</td>
</tr>
<tr>
<td>Salbutamol Rx (no)</td>
<td>1</td>
<td>1</td>
<td>0.96</td>
</tr>
<tr>
<td>Procedures implanting ZES (no)</td>
<td>2</td>
<td>9</td>
<td>0.94</td>
</tr>
<tr>
<td>Procedures Implanting BES (no)</td>
<td>3</td>
<td>1</td>
<td>0.45</td>
</tr>
<tr>
<td>Procedures Implanting EES (no)</td>
<td>7</td>
<td>15</td>
<td>0.87</td>
</tr>
<tr>
<td>Stents Implanted (no)</td>
<td>1.7</td>
<td>1.9</td>
<td>0.91</td>
</tr>
<tr>
<td>LMS PCI (no)</td>
<td>3</td>
<td>1</td>
<td>0.70</td>
</tr>
<tr>
<td>LAD PCI (no)</td>
<td>10</td>
<td>20</td>
<td>0.91</td>
</tr>
<tr>
<td>LCx PCI (no)</td>
<td>9</td>
<td>10</td>
<td>0.74</td>
</tr>
<tr>
<td>RCA PCI (no)</td>
<td>10</td>
<td>23</td>
<td>0.89</td>
</tr>
<tr>
<td>CABG (no)</td>
<td>1</td>
<td>1</td>
<td>0.73</td>
</tr>
<tr>
<td>other surgical intervention (valve surgery/pericardectomy (no)</td>
<td>1</td>
<td>2</td>
<td>0.80</td>
</tr>
<tr>
<td>TAVI (no)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6. Baseline demographics

Figure 16. Effect of cardiac rehabilitation on HRR10-20. P values stated are between rehab and no rehab groups.
Table 7. Mean HRR\textsubscript{10-20} ± 95% confidence intervals in relation to rehabilitation status and time. P values refer to comparisons between groups who completed rehabilitation versus those who did not complete rehabilitation at each time point.

<table>
<thead>
<tr>
<th>time point</th>
<th>no rehabilitation</th>
<th>completed rehabilitation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 0</td>
<td>-4.09±2.02</td>
<td>-3.53±2.54</td>
<td>0.78</td>
</tr>
<tr>
<td>week 6</td>
<td>1.85±0.77</td>
<td>-5.74±1.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>week 12</td>
<td>4.05±1.28</td>
<td>-6.33±2.32</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 8. Effect of progression through cardiac rehabilitation

<table>
<thead>
<tr>
<th>change in HRR\textsubscript{10-20} through cardiac rehabilitation</th>
<th>change in mean HRR\textsubscript{10-20}</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>time point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>week 0 to 6</td>
<td>-2.21</td>
<td>0.18</td>
</tr>
<tr>
<td>week 6 to 12</td>
<td>-0.6</td>
<td>0.58</td>
</tr>
<tr>
<td>week 0 to 12</td>
<td>-2.81</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Table 9. Activity level as determined by IPAQ through 3 time points. P values reflect differences between those who completed rehabilitation and those who did not.

<table>
<thead>
<tr>
<th>Time interval</th>
<th>IPAQ</th>
<th>Rehab</th>
<th>No rehab</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sedentary (%)</td>
<td>57.5</td>
<td>55.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>moderate (%)</td>
<td>37.5</td>
<td>38.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vigorous (%)</td>
<td>5</td>
<td>5.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MET-min/week</td>
<td>1140.25± 383</td>
<td>1160.56± 659</td>
<td>0.96</td>
</tr>
<tr>
<td>week 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sedentary (%)</td>
<td>0</td>
<td>55.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>moderate (%)</td>
<td>20</td>
<td>38.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vigorous (%)</td>
<td>80</td>
<td>5.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MET-min/week</td>
<td>3922.5± 346</td>
<td>1268.33± 645</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>week 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>sedentary (%)</td>
<td>0</td>
<td>55.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>moderate (%)</td>
<td>15</td>
<td>38.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vigorous (%)</td>
<td>85</td>
<td>5.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MET-min/week</td>
<td>4037.5± 296</td>
<td>1236.11± 649</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 10. Correlation of activity level and autonomic function in the rehabilitation group

<table>
<thead>
<tr>
<th>Time Period</th>
<th>MET-min/week</th>
<th>HRR&lt;sub&gt;10-20&lt;/sub&gt;</th>
<th>r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 0</td>
<td>1140.25</td>
<td>-3.53</td>
<td>0.11</td>
<td>0.41</td>
</tr>
<tr>
<td>week 6</td>
<td>3922.5</td>
<td>-5.74</td>
<td>-0.42</td>
<td>0.006</td>
</tr>
<tr>
<td>week 12</td>
<td>4037.5</td>
<td>-6.33</td>
<td>-0.32</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Table 11. Relationship of change in autonomic function with change in activity level

<table>
<thead>
<tr>
<th>Interval</th>
<th>change in HRR&lt;sub&gt;10-20&lt;/sub&gt;</th>
<th>change in MET-min/week</th>
<th>r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>week 0 to 6</td>
<td>-2.21</td>
<td>2782.25</td>
<td>0.63</td>
<td>0.0007</td>
</tr>
<tr>
<td>week 6 to 12</td>
<td>-0.6</td>
<td>115</td>
<td>0.32</td>
<td>0.12</td>
</tr>
<tr>
<td>week 0 to 12</td>
<td>-2.81</td>
<td>2897.25</td>
<td>0.68</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
4.4: DISCUSSION

Participation in cardiac rehabilitation is known to improve survival in patients with coronary artery disease [162, 176]. This study shows a significant correlation between completing cardiac rehabilitation and improved autonomic function as measured with HRR\textsubscript{10-20} in a population of patients with IHD who predominantly underwent PCI. This improvement in autonomic function may be explained by the improved activity levels also seen through the study period. This augmentation of autonomic function following cardiac rehabilitation gives credence to both the use of cardiac rehabilitation to potentially improve prognosis. The findings of this pilot study also raise the possibility of using autonomic function parameters, specifically HRR\textsubscript{10-20}, as a potentially ‘modifiable factor’ to assess the response to cardiac rehab, which might assist with risk-modelling and prediction of the risk of future vascular events in individual patients with IHD.

The group which did not complete rehabilitation was demonstrated to have a deterioration in autonomic function over time. The pathophysiology leading to this deterioration may be that through maintaining poor physical activity, there is a further loss of sensitivity of the autonomic system to respond to stimuli. We did observe that through increasing physical activity levels as demonstrated through improving MET-min/week, autonomic function improved in our group which completed rehabilitation.

Limitations include that this was not a randomised study: all patients were initially referred to the cardiac rehabilitation programme, indicating that there may be a selection bias. The main control group were self-selected patients who did not wish to participate in the programme, again potentially creating a selection bias. All of these patients initially underwent assessment by a cardiac rehabilitation specialist nurse on initial in-patient referral, and attended for a baseline educational session with basic lifestyle advice including smoking cessation, weight loss and medication adherence. Following this educational session, they thereafter decided to not proceed with the physical activity component of the rehabilitation. However, both groups’ baseline characteristics were comparable, including potential confounders. A further limitation is the limited sample size which may have led to a type II error in some of our subgroup analyses.

Additionally, this investigation was performed as a case-control analysis, showing significant correlation between measured parameters, but this cannot prove or disprove causation.
Error may have crept into the analysis given the signal average index ratings fluctuating within the separate measurements; however, given that each waveform was individually scrutinized for significant issues, this potential limitation has been minimised.

Conclusions

The data support the hypothesis that completion of cardiac rehabilitation is associated with improved autonomic function determined by HRR_{10-20}. This association has not previously been described and requires further study to elucidate physiological and pathophysiological cause.

Future research may allow the further elucidation of how rehabilitation and increased activity augments autonomic function, with other autonomic indices being measured, such as through cardiopulmonary exercise testing. Additionally, the use of HRR_{10-20} as a modifiable risk index may be applied to other modalities, such as in post-operative patients, or following structural cardiac interventions, such as TAVI.
CHAPTER FIVE:

CONCLUSIONS
5.1: CONCLUSIONS

The use of orthostatic challenge to measure autonomic function has up until this point primarily been used in the assessment of falls and syncope. Through this research, we have established that the use of HRR_{10-20} allows autonomic function to be assessed to detect a difference in autonomic tone between those who have had complete revascularisation versus those who did not. Additionally, we have identified a reliable measure of autonomic function in HRR_{10-20} which can be modified through a rehabilitation programme. Both arms of the research project allow us to say that in a real-world clinical setting, assessment of HRR_{10-20} as an autonomic marker can potentially provide relevant clinical information.

These innovative pilot data are hypothesis generating and will prompt future research in this niche area of vascular medicine.

The physiology behind the homeostatic control of HR is increasingly well understood. Beyond the previously described role of autonomic variables in risk stratification, it may be possible following future research to use physiological parameters such as HRR_{10-20} as surrogate markers of disease progression and measures of treatment success or regression.

5.2: IMPLICATIONS FOR FUTURE RESEARCH

Further research into using HRR_{10-20} should be performed to answer the questions arising from this work. The underlying pathophysiology responsible for the correlation between autonomic function and revascularisation status should be further explored; autonomic function could be assessed prior to revascularisation and after revascularisation, perhaps with cardiac MRI or invasive assessment of underlying ischaemic myocardium with fractional flow reserve or similar intracoronary physiological measurements.

Additionally, the manner in which autonomic function could be affected by surgical revascularisation should be explored. These assessments could be performed as part of a randomised control trial, with the control group comprising patients on optimal medical therapy, which recently has been shown to be as efficacious as revascularisation in certain circumstances [177]. Autonomic function has now been demonstrated to correlate with revascularisation status, and given that previous research has demonstrated that revascularisation status correlates with mortality, autonomic function could potentially be used to determine procedural success in future research.
The use of HRR\textsubscript{10-20} as an index to assess autonomic function may also be applied to other modalities beyond coronary artery disease, such as patients undergoing structural cardiac intervention (including TAVI).

Further research on the impact of structured rehabilitation exercise on autonomic function in cardiac pathologies is also warranted. This project demonstrated a correlation between completing rehabilitation and maintenance of autonomic function over a strict time period. This could be assessed further with a longer follow-up period, and with assessment of exercise capacity during rehabilitation using a more accurate measurement, such as exercise-stress test measured VO2-max.

Through our observations, we have raised questions which can be assessed in future research: does autonomic function correlate with increasing complexity of coronary artery disease? Is myocardial ischaemia the driving factor behind autonomic dysregulation? Does revascularisation improve autonomic function? Does percutaneous versus surgical revascularisation make a difference? How does physical activity modulate autonomic function in patients with cardiac disease? Can autonomic function be used as an endpoint in clinical research on revascularisation and rehabilitation success? These questions need to be assessed in future research studies in this field and may allow autonomic function to be used as a marker of procedural success in the future.


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APPENDIX
INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE
(October 2002)

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health-related physical activity.

Background on IPAQ
The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ
Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation
Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ
International collaboration on IPAQ is on-going and an international Physical Activity Prevalence Study is in progress. For further information see the IPAQ website.

More Information
INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous and moderate activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?
   
   [ ] Yes
   
   [ ] No → **Skip to PART 2: TRANSPORTATION**

The next questions are about all the physical activity you did in the last 7 days as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, heavy construction, or climbing up stairs as part of your work? Think about only those physical activities that you did for at least 10 minutes at a time.
   
   ____ days per week
   
   [ ] No vigorous job-related physical activity → **Skip to question 4**

3. How much time did you usually spend on one of those days doing vigorous physical activities as part of your work?

   ____ hours per day
   ____ minutes per day

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads as part of your work? Please do not include walking.

   ____ days per week
   [ ] No moderate job-related physical activity → **Skip to question 6**

LONG LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised October 2002.
5. How much time did you usually spend on one of those days doing moderate physical activities as part of your work?

   _____ hours per day
   _____ minutes per day

6. During the last 7 days, on how many days did you walk for at least 10 minutes at a time as part of your work? Please do not count any walking you did to travel to or from work.

   _____ days per week
   [ ] No job-related walking → Skip to PART 2: TRANSPORTATION

7. How much time did you usually spend on one of those days walking as part of your work?

   _____ hours per day
   _____ minutes per day

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the last 7 days, on how many days did you travel in a motor vehicle like a train, bus, car, or tram?

   _____ days per week
   [ ] No traveling in a motor vehicle → Skip to question 10

9. How much time did you usually spend on one of those days traveling in a train, bus, car, tram, or other kind of motor vehicle?

   _____ hours per day
   _____ minutes per day

Now think only about the bicycling and walking you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the last 7 days, on how many days did you bicycle for at least 10 minutes at a time to go from place to place?

    _____ days per week
    [ ] No bicycling from place to place → Skip to question 12

LONG LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised October 2002.
11. How much time did you usually spend on one of those days to bicycle from place to place?
   ____ hours per day
   ____ minutes per day

12. During the last 7 days, on how many days did you walk for at least 10 minutes at a time to go from place to place?
   ____ days per week
   □ No walking from place to place → Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

13. How much time did you usually spend on one of those days walking from place to place?
   ____ hours per day
   ____ minutes per day

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the last 7 days in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, chopping wood, shoveling snow, or digging in the garden or yard?
   ____ days per week
   □ No vigorous activity in garden or yard → Skip to question 16

15. How much time did you usually spend on one of those days doing vigorous physical activities in the garden or yard?
   ____ hours per day
   ____ minutes per day

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate activities like carrying light loads, sweeping, washing windows, and raking in the garden or yard?
   ____ days per week
   □ No moderate activity in garden or yard → Skip to question 18

LONG LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised October 2002.
17. How much time did you usually spend on one of those days doing moderate physical activities in the garden or yard?

______ hours per day
______ minutes per day

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate activities like carrying light loads, washing windows, scrubbing floors and sweeping inside your home?

______ days per week

☐ No moderate activity inside home  

Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY

19. How much time did you usually spend on one of those days doing moderate physical activities inside your home?

______ hours per day
______ minutes per day

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the last 7 days solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the last 7 days, on how many days did you walk for at least 10 minutes at a time in your leisure time?

______ days per week

☐ No walking in leisure time  

Skip to question 22

21. How much time did you usually spend on one of those days walking in your leisure time?

______ hours per day
______ minutes per day

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do vigorous physical activities like aerobics, running, fast bicycling, or fast swimming in your leisure time?

______ days per week

☐ No vigorous activity in leisure time  

Skip to question 24

LONG LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ, Revised October 2002.
23. How much time did you usually spend on one of those days doing vigorous physical activities in your leisure time?
   _____ hours per day
   _____ minutes per day

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis in your leisure time?
   _____ days per week
   [ ] No moderate activity in leisure time
      -> *Skip to PART 5: TIME SPENT SITTING*

25. How much time did you usually spend on one of those days doing moderate physical activities in your leisure time?
   _____ hours per day
   _____ minutes per day

**PART 5: TIME SPENT SITTING**

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the last 7 days, how much time did you usually spend sitting on a weekday?
   _____ hours per day
   _____ minutes per day

27. During the last 7 days, how much time did you usually spend sitting on a weekend day?
   _____ hours per day
   _____ minutes per day

This is the end of the questionnaire, thank you for participating.