IDENTIFICATION OF PRE-CLINICAL CARDIOVASCULAR IMAGING PHENOTYPES RELATED TO BLOOD PRESSURE IN YOUNG ADULTS

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DEDICATIONS

For my mum, dad, and siblings with all my love

ABBREVIATIONS

2D	Two-dimensional
ABP	Ambulatory blood pressure
AI	Artificial intelligence
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CO	Cardiac output
cPCA	contrasted Principal Component Analysis
CPET	Cardiopulmonary Exercise Testing
cTI	contrastive Trajectory inference
DBP	Diastolic blood pressure
EDV	End diastolic volume
ESV	End systolic volume
HTN	Hypertension
IVS	Interventricular septum
LA	Left atrium
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVID	Left ventricular internal diameter
LVM	Left ventricular mass
MAP	Mean arterial pressure
MST	Minimum Spanning Tree
MVPA	Moderate to Vigorous Physical Activity
PVR	Peripheral vascular resistance
PW	Posterior wall
RA	Right atrium
RMSD	Root Mean Squared Deviation
RPE	Rate of perceived exertion
RV	Right ventricle
RWT	Relative wall thickness
SBP	Systolic blood pressure
SV	Stroke volume
TAPSE	Tricuspid annulus plane systolic excursion
TSR	Trimmed scores regression
VAT	Ventilatory anaerobic threshold
VPA	Vigorous Physical Activity

ABSTRACT

IDENTIFICATION OF PRE-CLINICAL CARDIOVASCULAR IMAGING PHENOTYPES RELATED TO BLOOD PRESSURE IN YOUNG ADULTS

THESIS PRESENTED FOR THE DEGREE DOCTOR OF PHILOSOPHY IN CARDIOVASCULAR MEDICINE AT THE UNIVERSITY OF OXFORD

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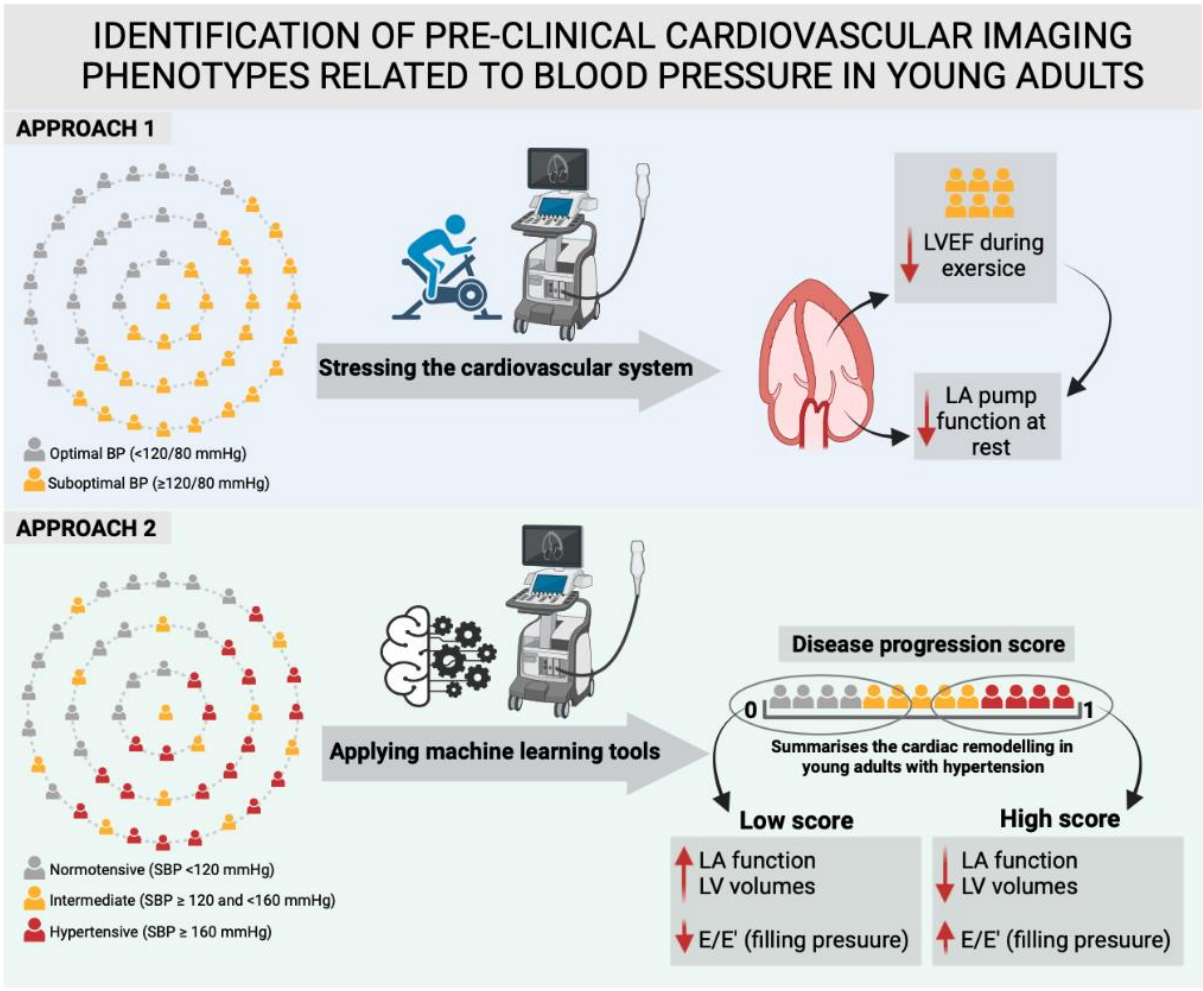
Hypertension prevalence in young adults is rising and is associated with an increased risk of stroke and cardiovascular disease in later life. However, hypertension management guidelines for patients below the age of 40 years remain conservative as their absolute risk of imminent vascular events is low. Additionally, due to the relatively short duration of exposure to hypertension, traditional measures of target organ damage such as left ventricular hypertrophy are often normal. In this thesis, I sought to identify pre-clinical cardiovascular phenotypes associated with blood pressure elevation in young adults, which might be of value for monitoring disease progression in young people.

A cohort of young participants aged 18 to 40 years with a range of blood pressure measures were recruited through clinical studies conducted at the Cardiovascular Clinical Research Facility for multi-dimensional assessment of cardiovascular health. Detailed cardiac structure and function assessment was performed using a range of imaging modalities including resting and stress echocardiography imaging. First, I established that participants

with suboptimal blood pressure (≥120/80 mmHg) have novel changes in cardiovascular remodelling identifiable with echocardiography. Specifically, I identified a reduction in left ventricular systolic function during physical exercise, which was associated with altered left atrial pump function at rest. Then, I studied whether it was possible to combine multiple echocardiographic measures using a contrastive trajectory inference machine learning model to describe the progression of cardiovascular remodelling in young adults with hypertension, and place participants on a pseudo-temporal trajectory of disease, with a corresponding score, from health (zero) to disease (one). I demonstrated feasibility of this approach and the practicality of summarising this disease progression as a single score. Finally, I demonstrated that longer duration of treatment was associated with higher score and was consistent with an established modifiable cardiovascular risk score and fitness levels. Therefore, I have demonstrated that there are progressive changes in cardiac structure and function, identifiable with echocardiography, in young adults with suboptimal blood pressure. Further work is now needed to determine whether these measures could be used clinically to better manage blood pressure in younger patients.

GRAPHICAL ABSTRACT



THE IMPACT OF COVID-19

Disruptions secondary to the Covid-19 pandemic have mildly affected the work of this thesis. Due to the suspension of the non-Covid-19 clinical research studies running in the John Radcliffe Hospital in 2020, the planned recruitment target was not achieved for the HyperEcho study (Hypertension management in young adults personalised by echocardiography and clinical outcome). More participants from this study were needed for the development of a disease progression model of hypertension in young adults. The model was then developed based on the available data combined with previous datasets and has demonstrated sufficient levels of stability and validity.

LIST OF PUBLICATIONS

Original Manuscripts Published During DPhil

Alsharqi M, Huckstep OJ, Lapidaire W, Williamson W, Mohamed A, Tan CMJ, Kitt J, Burchert H, Telles F, Dawes H, Foster C, Lewandowski AJ, Leeson P. Left atrial strain predicts cardiovascular response to exercise in young adults with suboptimal blood pressure. Echocardiography. 2021 Aug;38(8):1319-1326.

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1. INTRODUCTION

1.1. Hypertension in young adults

Hypertension complications account for more than nine million deaths globally, with half of these deaths due to cardiovascular diseases [1]. The prevalence of hypertension in young adults is increasing. At least one in 17 adults below the age of 40 in the UK [2], which equates to more than 20 million adults in the USA aged between 20 and 44 years, have hypertension [3]. Epidemiological studies indicate that cumulative exposure to uncontrolled blood pressure levels during young adulthood significantly increases the risk of early stroke and cardiovascular disease [4-9].

Hypertension is diagnosed using average clinic brachial blood pressure measures and/or 24-hour blood pressure monitoring to evaluate the blood pressure variability [10, 11]. For all adults aged from 16 years [10], the severity of hypertension is classified based on seated clinical systolic and diastolic blood pressure measures [10, 11]. Blood pressure measures of < 120 mmHg for systolic blood pressure and < 80 mmHg for diastolic blood pressure are classified as optimal blood pressure levels [10]. Stage 1 hypertension is defined as elevated systolic blood pressure measures of ≥ 140 mmHg and/or diastolic blood pressure measures ≥ 90 mmHg by the UK National Institute for Health and Care Excellence (NICE) and the European Society of Hypertension (ESH) guidelines [10, 12], while the latest American Heart Association (AHA) guidelines lowered the thresholds of stage 1 as ≥ 130 mmHg for systolic blood pressure or diastolic blood pressure of ≥ 80 mmHg [11]. Table 1.1 demonstrates the classes of hypertension with the differences among the three guidelines. The discrepancy in the definition of stage 1 hypertension was introduced following the results of a systematic review based on ten studies with a mean follow-up period ranged from two to eight years [13]. The systematic review reported that lowering systolic blood pressure target to < 130 mmHg was associated with reduced risk of stroke and adverse cardiovascular events [13]. However,

the majority of participants included in these studies were older hypertensives with the mean age ranged from 36 to 77 years, and only a small single study has the inclusion criteria of participants below the age of 50 years [14, 15].

Hypertension is underdiagnosed in younger populations [16], potentially due to the lower levels of interaction with health services during adulthood and the lack of clinical symptoms [16, 17]. In this thesis, young adulthood is defined as age 18 to 40 years old. Since this is the period when people may complete their education, seek for opportunities, enter the workforce, set financial goals, establish networks, and create a family [18, 19], health behaviours that shape a life-long trajectory of wellbeing may be formed at this time [20, 21]. However, even when hypertension is diagnosed in young adulthood, poor adherence due to busy personal and professional lives leads to failure to achieve optimal blood pressure control [22, 23].

Table 1.1. Blood pressure classification

Category (ESC/ESH)[10]	**Category (NICE)[12]**	**Category (ACC/AHA)[11]**	**Systolic (mmHg)**		**Diastolic (mmHg)**
Optimal		**Normal**	< 120	And	< 80
Normal		**Elevated**	120-129	And/or	80-84*
High normal		**Stage 1**	130-139	And/or	85-89
Grade I HTN	**Stage 1**	**Stage 2**	140-159	And/or	90-99
Grade II HTN	**Stage 2**		160-179	And/or	100-109
Grade III HTN	**Stage 3**		≥ 180	And/or	≥ 110
Isolated systolic HTN			≥ 140	And	< 90

ESC/ESH, European Society of Cardiology/European Society of Hypertension
ACC/AHA, American College of Cardiology/American Heart Association
* < 80 in the Elevated category for AHA/ACC
HTN, Hypertension

1.2. Pathophysiology of hypertension in young adults

The mechanisms of hypertension have been broadly studied in the last two decades [24]. However, areas of uncertainty about the pathophysiology of hypertension remain due to the complex nature of the disease, particularly in younger patients [25, 26]. Most hypertensive patients have no clear identifiable cause of hypertension, with only two to five percent of the patients being presented with a secondary cause of blood pressure elevation [24]. Several underlying conditions are identified as secondary causes of hypertension, including but not limited to renovascular diseases, pheochromocytoma, or single-gene mutations [10, 11, 27]. Although these conditions are rare, screening for secondary causes is recommended for younger hypertensives presented with severe hypertension (> 180/110 mmHg), drug resistant hypertension, or non-dipping status on ambulatory blood pressure monitoring [10]. Early identification and treatment of secondary conditions, for patients below the age of 40 years, is associated with better blood pressure control [28].

Physiological mechanisms to maintain normal blood pressure levels are dependent on the balance between the peripheral vascular resistance and cardiac output (Box 1.1) [24, 29]. This means elevation in mean arterial blood pressure can be due to an increase in cardiac output, an increase in peripheral vascular resistance, or a combination of both [25, 29]. The cardiac output is a product of left ventricular stroke volume and heart rate, while the peripheral vascular resistance is dominated by small arterioles (vessel diameter 30 to 330 μm) [29, 30].

In younger patients with early stages of hypertension, peripheral vascular resistance is often normal at rest, and the increase in blood pressure levels is attributable

to increased cardiac output [25, 29]. A longitudinal study with 20 years of follow-up in hypertensive young adults reported that hemodynamic patterns of patients changed from increased cardiac output and normal peripheral resistance at baseline to reduced cardiac output and increase vascular resistance at 10- and 20-year follow-up [31]. In patients with several years of hypertension, the increase in peripheral vascular resistance is more evident and cardiac output is typically reduced during exercise, mainly due to a failure to increase the stroke volume in response to exercise [29]. Despite the normal cardiac output and function at rest, several studies suggest that abnormal cardiac performance in response to exercise contributes to elevated blood pressure levels, particularly in patients with concentric left ventricular hypertrophy [32-34]. With aging, the increase in peripheral vascular resistance and stiffness augments the pressure load imposed on the left ventricle, which leads to increased ventricular wall thickness and induces impairment of ventricular relaxation [24, 25].

$$\mathbf{MAP = CO \times PVR}$$

MAP = mean arterial pressure
CO = cardiac output = stroke volume × heart rate
PVR = peripheral vascular resistance

Box 1.1. The equation that demonstrates the relationship between mean arterial pressure, cardiac output, and total peripheral vascular resistance.

1.3. Cardiovascular risk factors assessment in young adults with hypertension

Blood pressure elevation in adulthood may also be influenced by environmental and other factors occurring many years earlier [35]. The lifetime trajectory of blood pressure levels could be affected during the perinatal period. This was supported by several recent studies demonstrating that offspring of hypertensive pregnancies have higher blood pressure levels [36, 37], young adults born prematurely have higher rates of anti-hypertensive medication prescriptions [38, 39], and adults born of low weight or prematurely show early cardiovascular alterations during adulthood [40-43].

Other risk factors that could influence blood pressure levels during young adulthood have been explored thoroughly in several large studies. These factors include components of physical fitness, diet, smoking, and alcohol consumption. Epidemiological studies have illustrated an inverse relationship between physical fitness and blood pressure levels [44]. Physical fitness attenuates the elevation of blood pressure with age and help to prevent the development of hypertension [11]. In young adults, higher physical activity and fitness levels are associated with a reduction in cardiovascular risks and delay the onset of hypertension [45, 46]. Diet-related factors including excess sodium intake, insufficient potassium intake, and obesity have a direct relationship with increased blood pressure levels [10, 11]. Increased body mass index at a young age is independently associated with future risk of hypertension [47] , while weight loss is related to lowering blood pressure levels and reduced the risk of hypertension development [48, 49]. Excessive sodium consumption increases blood pressure levels [50, 51], and is independently associated with increased risk of cardiovascular disease and stroke [52]. In addition to these lifestyle modifiable risk factors, other comorbidities such

as high cholesterol levels and diabetes increase the risk of the onset of hypertension [53], and are strongly associated with adverse cardiovascular events when combined with hypertension [10, 11, 26]. Risk factors in young adults and their relationship with hypertension are summarised in Table 1.2.

Table 1.2. Association between risk factors and blood pressure levels in young adults

Risk factor category	Impact on blood pressure in young adults
Obesity	↑ waist circumference → ↑ incidence of raised blood pressure over ten years [54] ↑ body mass index (BMI) → ↑ incidence of raised blood pressure before the age of 40 years [55-57]
Diet	↑ 24-hour sodium excretion → ↑ systolic blood pressure (aged 20 – 59 years) [58] ↓ sodium consumption → ↓ systolic blood pressure levels (aged ≤ 45 years) [59] ↑ meat consumption → ↑ incidence of raised blood pressure over 15 years [60] ↑ plant-food consumption → ↓ incidence of raised blood pressure over 15 years [60]
Blood glucose and lipid profile	↑ blood glucose levels → ↑ incidence of raised blood pressure (mean age 40 ± 10 years) [61] ↑ fasting insulin levels → ↑ incidence of raised blood pressure over 20 years (aged 20 – 30 years) [62] ↑ serum triglycerides → ↑ incidence of raised blood pressure before the age of 40 years [55] ↑ serum total cholesterol → ↑ incidence of raised blood pressure (mean age 40 ± 10 years) [61]
Physical activity, mental health, and social factors	↑ physical activity levels → ↓ incidence of raised blood pressure over 15 years [63] ↑ depression levels → ↑ incidence of raised blood pressure over five years [64] ↓ socioeconomic status → ↑ incidence of raised blood pressure over ten years [65]

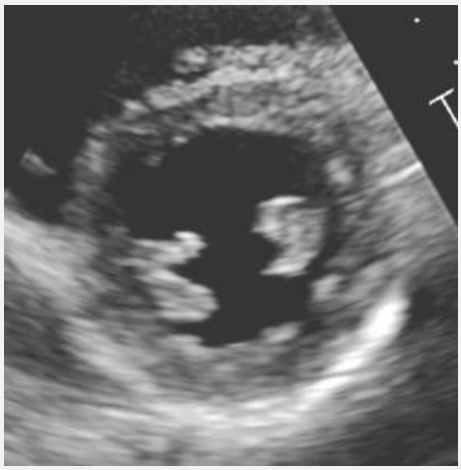
Although each risk factor is independently associated with elevated blood pressure, assessments using multiple cardiovascular risk factors provide better estimation and prediction of future adverse events [66, 67]. The three hypertension management guidelines, the British, European, and American, recommend the use of 10-year cardiovascular risk assessment prediction models to support the decision making for the initiation of anti-hypertension treatment [10-12]. Risk prediction models, such as the Framingham risk score, the Systematic COronary Risk Evaluation (SCORE) system, and the QRISK score, incorporate several risk factors for 10-year risk prediction models based on large datasets [10-12, 66].

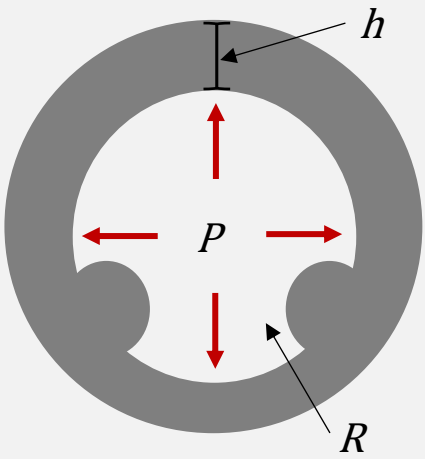
The risk-based approach for treatment initiation is supported by two meta-analyses focussed on the reduction of cardiovascular risk in middle-aged and older patients [68, 69]. Other authors, however, have reported the lack of validity and overestimation of the risk when using these risk scores, particularly in young patients [70, 71]. Despite the substantial increase of the lifetime risk of cardiovascular disease in hypertensive patients, in younger patients the absolute 10-year risk is often low [26]. In addition, these scores were validated on data derived from patients aged above 40 years, which may be less applicable to younger populations [10, 11]. In the UK, the preferred risk assessment tool is the QRISK score, which was validated on data derived on a population of 35 to 74 years of age [72]. However, the latest version (QRISK3) has been extended to include people of 25 to 84 years old [73].

1.4. Cardiovascular remodelling in hypertension

In response to elevated blood pressure, cardiac structure and function adapt in a wide spectrum of interconnected manifestations of cardiac chambers [29, 74]. According to Laplace's law, increased blood pressure exerts additional pressure load on a cardiac

chamber wall by increasing the wall tension, as illustrated in Figure 1.1 [29]. The increase in wall stress can be normalised by an increase in wall thickness or a reduction in the chamber cavity size, or both [29]. Therefore, a chronic increase in left ventricular pressure overload leads to ventricular hypertrophy, which may progressively lead to heart failure and an increased risk of developing arrhythmias, most commonly atrial fibrillation [75, 76]. However, with the growing evidence of cardiac functional and structural alterations in patients with hypertension, subclinical patterns of remodelling can be identified early, and optimal management may revert or delay the progress of cardiac remodelling [29, 74].





Laplace's Law

$$Wall\ stress\ (\sigma) = \frac{wall\ tension\ (T)}{wall\ thickness\ (h)}$$

$$T = pressure\ (P) \times\ cavity\ radius\ (R)$$

Figure 1.1. The relationship between wall stress, pressure, and cavity radius (Laplace's Law).

Several non-invasive diagnostic tools are used to evaluate cardiovascular remodelling in hypertensive patients, including electrocardiography (ECG) and echocardiography. This thesis focuses on the use of echocardiography imaging for cardiovascular assessment in hypertension. Echocardiography is an essential imaging modality in the diagnosis and management of hypertensive patients. The European guidelines recommend performing echocardiography for identifying left ventricular hypertrophy or underlying causes of hypertension, particularly in younger patients [10]. Echocardiography permits real-time imaging of the heart allowing detailed assessment for each chamber with immediate detection of structural and functional alterations.

In the following sections, I provide an overview of the structural and functional adaptation mechanisms of the left atrium, left ventricle, and the right heart in separate sections, but with emphasising the interrelated manifestations in hypertension.

1.4.1. Left atrial remodelling in hypertension

Alterations on left atrial structure and function in response to elevated blood pressure are closely related to left ventricular remodelling but can also exist independently [77-79]. Left atrial enlargement and functional abnormalities are common findings in early-onset hypertension, even in the absence of left ventricular hypertrophy [80, 81]. Several studies reported that left atrial structural and functional changes have been proven to provide diagnostic and prognostic values for a wide variety of clinical outcomes [82-84]. Increased left atrial volumes and reduced emptying function were associated with higher risk of atrial fibrillation and cardiovascular disease in asymptomatic populations [85, 86]. These findings are extended into young adulthood, as results showed that elevated blood pressure

levels were associated with increased left atrial size and the increase in left atrial size was related to greater risk of cardiovascular disease in young adults [77, 87].

Normal left atrial structure can be divided into four components: a pulmonary venous component, a lateral appendage, an inferior vestibular component surrounding the mitral valve, and a prominent body that shares the inter-atrial septum with the right atrium [88]. Compared to the left ventricle, the left atrial wall is relatively thin and smooth, whereas the appendage is rough with pectinate muscles [88]. Normal left atrial function consists of three distinct phases throughout the cardiac cycle that modulate left ventricular filling [89, 90]. During ventricular systole, the left atrium acts as a reservoir by receiving the oxygenated blood from the pulmonary veins, and this reservoir phase is highly driven by left atrial compliance, left ventricular longitudinal deformation, and right ventricular systolic pressure transmitted through the pulmonary venous flow [89-91]. When the mitral valve opens during early ventricular diastole, the left atrium passively transfers the blood to the left ventricle, and this phase represents the conduit function [89, 90]. Left atrial conduit is influenced by left ventricular relaxation, compliance, and early diastolic pressure [89, 90]. Left atrial booster pump function occurs during late ventricular diastole when the left atrium actively contracts to empty the blood into the left ventricle before the mitral valve closure [89]. This phase is modulated by intrinsic left atrial preload and contractility, as well as left ventricular compliance and end diastolic pressure [89, 92]. The left atrial function contributes to left ventricular filling by 40% during the reservoir phase, 35% in the conduit phase, and 25% by the booster pump phase [93, 94].

Left atrial adaptations in response to elevated blood pressure can occur alone or in combination with left ventricular alterations [74]. Left atrial myocardial

stiffness and fibrosis eventually progress with chronic hypertension, influencing left atrial contributions to left ventricular filling [95]. As the pressure load increases, left atrial cavity size increases to compensate the increase in wall tension, which progressively leads to left atrial systolic dysfunction and dilatation causing arrhythmias [96, 97]. Increased pressure load may also cause a temporary enhancement of left atrial booster pump function to maintain adequate ventricular filling in early stages of hypertension [74, 88]. When the disease progresses further, left atrial stiffness increases and compliance decreases, gradually leading to impairment of left atrial contractility [88]. Based on the stage of hypertension, a temporary augmentation of the pump function might be found during earlier stages, and impairment of the three left atrial phases can be found at a later stage of hypertension [88, 98]. The impairment of all left atrial phasic function is associated with left ventricular hypertrophy in hypertension [88]. When hypertension is combined with other comorbidities, such as diabetes, left atrial phasic impairment can be found even before left atrial enlargement or left ventricular hypertrophy [99]. Eshoo et. al, suggested that the impairment of left atrial reservoir and conduit function could be a predictor of adverse cardiovascular events in hypertensive patients [100].

1.4.2. Left ventricular remodelling in hypertension

Raised blood pressure levels are associated with a spectrum of structural and functional alterations in the left ventricle [101]. The pattern of remodelling could reflect the severity of hypertension and differences in age and haemodynamics [101, 102]. Left ventricular hypertrophy, impaired myocardial shortening, and impaired relaxation are the common findings in early-onset hypertension [103]. As hypertension

progresses, left ventricular dilatation and systolic dysfunction may develop, leading to heart failure, coronary artery disease, and conduction abnormalities [104]. Early identification of left ventricular structural and functional abnormalities in patients with hypertension has important prognostic value with a better survival rate [104-106]. The contribution of left ventricular remodelling patterns to the risk of cardiovascular disease is complex and not completely understood [74]. Several studies have reported that combined components of left ventricular remodelling using novel indices have incremental prognostic value for clinical outcomes, beyond single remodelling components [107-109]. An example of these indices is the left ventricular global function index, which incorporates multiple components of left ventricular volumes and has shown to be an independent predictor of heart failure and cardiovascular disease incidents [107, 108].

Left ventricular structural and functional alterations can be assessed using echocardiography imaging methods, including two- and three-dimensional imaging, Doppler velocities, and speckle tracking analysis. Structural changes can be quantified by measuring left ventricular wall thickness, the cavity dimensions and volumes, and left ventricular mass [110]. Because the mass and volumes vary with body size, indexed values to body surface area have been used to assess left ventricular hypertrophy in echocardiography [111]. Based on left ventricular mass index and relative wall thickness, left ventricular geometry can be classified into normal geometry (normal mass and thickness), concentric remodelling (normal mass with increased thickness), concentric hypertrophy (increased mass and thickness), and eccentric hypertrophy (increased mass with normal thickness) [112]. Hypertension has been associated with concentric remodelling hypertrophy during early stages and progresses to concentric and eccentric hypertrophy [29, 113]. With

chronic hypertension, a temporal, bidirectional transition between concentric and eccentric left ventricular hypertrophy has been found [113, 114]. Left ventricular hypertrophy has shown to predict a poor prognosis with three-fold increased risk independent of blood pressure levels [29, 115]. However, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study demonstrated that after one year of anti-hypertensive treatment, the prevalence of both concentric and eccentric hypertrophy was reduced [116]. Thus, the regression of left ventricular hypertrophy with pharmacological therapy provides protection from cardiovascular mortality and death beyond the reduction in blood pressure levels [117].

Chronic left ventricular hypertrophy promotes fibrosis and myocardial stiffness, leading to impaired left ventricular relaxation and raised left ventricular filling pressure, which causes diastolic dysfunction [118, 119]. Impaired relaxation happens when the left ventricular pressure during the isovolumetric relaxation time (the period from aortic valve closure and mitral valve opening) is high and requires more time to reduce below the left atrial pressure, allowing mitral valve opening. Then, once the mitral valve is open, left ventricular filling is prolonged, leaving more blood in the atrium by the end of the passive filling phase (left atrial conduit phase). This prolongation results in an increased atrial contraction force to maintain adequate filling. These mechanics can be captured by obtaining the mitral inflow waves and measuring the velocity and duration of early (E wave) and late (A wave) ventricular filling waves (Figure 1.2 A) using Doppler echocardiography imaging. In patients with hypertension, studies demonstrated that the velocity of the E wave is reduced and its duration is prolonged with increased A wave velocity, resulting in reduced E/A ratio (Figure 1.2 B) [29]. As the impairment of relaxation progresses with further increase in left ventricular filling pressure, the left ventricular

compliance is decreased mainly due to interstitial stiffness and fibrosis. When the left ventricle becomes stiffer, left atrial pressure increases resulting in a greater pressure gradient in early diastole (when the mitral valve opens). This leads to an increase of E wave velocity and shorter duration due to the reduction of left ventricular compliance that causes the left ventricular and atrial pressures to equalise earlier (Figure 1.2 C) [29, 74]. As diastolic function deteriorates, left ventricular filling pressure becomes abnormally high, leading to pulmonary congestion, and heart failure symptoms may develop in the presence of normal left ventricular ejection fraction [120, 121].

Left ventricular systolic dysfunction appears at a late stage of hypertension when looking at traditional measures such as left ventricular ejection fraction [104]. However, thanks to the advancement of speckle tracking echocardiography analysis, global and regional left ventricular systolic function can be assessed providing incremental diagnostic and prognostic value beyond the ejection fraction measures [104, 110, 122]. Longitudinal strain is used to assess left ventricular systolic shortening of the myocardium, while the circumferential strain is to measure the cross-sectional radial function and left ventricular torsion between the base and the apex of the left ventricle [123, 124]. Several studies have demonstrated that hypertension is associated with reduced left ventricular longitudinal strain that also associates with impaired left atrial strain [125, 126]. Similarly, in young adults, Kishi S et al. reported that impairment of left ventricular longitudinal and circumferential strain was associated with cumulative blood pressure in early adulthood [118].

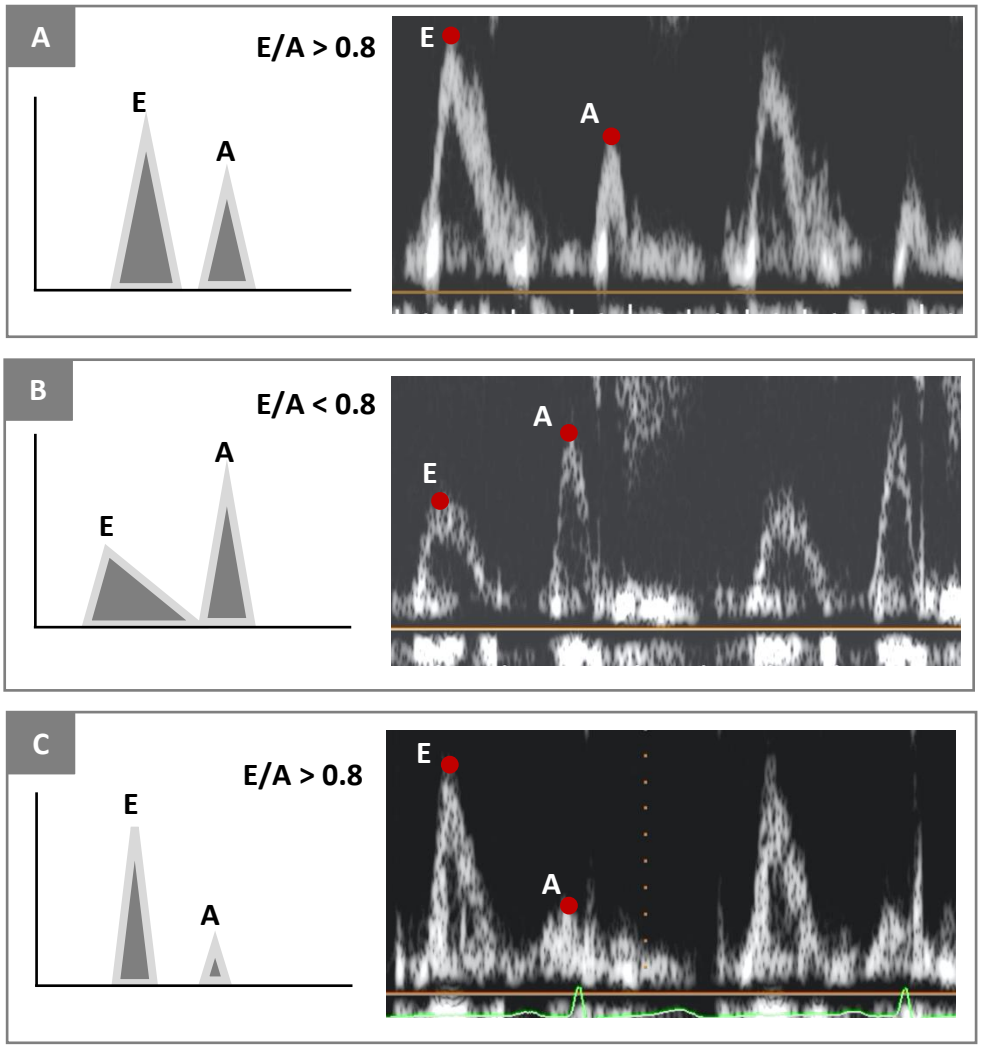


Figure 1.2. Mitral valve inflow trace using Doppler echocardiography.

Mitral valve inflow trace using Doppler echocardiography in a subject with normal diastolic function (A), subject with hypertension and impaired relaxation (B), and subject with hypertension and more severe diastolic dysfunction with elevated left atrial pressure (C).

1.4.3. Right heart remodelling in hypertension

The right heart term is referred to the right ventricle and right atrium. The right ventricle is a thin wall chamber compared to the left ventricle, and can be viewed as a triangular shaped from the apical four-chamber view or in a crescent shape from the parasternal short axis view [127]. The right ventricle pumps the blood to the pulmonary system and its function is highly modulated by the venous preload,

afterload, and the transmitted forces from the left ventricle through the interventricular septum [128]. The right atrium is connected with the right ventricle by the tricuspid valve and its main role is to facilitate right ventricular filling. Similar to the left atrium, the right atrial acts as a reservoir for systemic venous return during ventricular systole, a passive conduit transferring blood to the right ventricle during early diastole, and an active pump in late diastole [129].

There is limited evidence in the literature about the impact of hypertension on the right heart. The occurrence of right atrial and ventricular remodelling, however, may not be rare in response to elevated blood pressure [74]. A few studies have provided evidence about abnormal changes in right atrial and ventricular structure and function associated with high blood pressure [130, 131]. Karaye et al. demonstrated that the tricuspid annular plane systolic excursion was reduced to less than 15 mm in 33% of patients with hypertensive heart disease [132]. Similarly in the right atrium, a small study of 114 participants showed that hypertension was associated with right atrial enlargement and impaired systolic strain [133]. Although the mechanisms behind right heart alterations in hypertension are still not completely understood, researchers proposed that the impairment of systolic and diastolic right ventricular function with increasing systolic blood pressure was accompanied by interventricular septum remodelling [134]. Right ventricular alterations in hypertension have also shown to develop in parallel with left ventricular changes [135-137]. Similarly, impairment of right atrial mechanics in hypertension was associated with higher left ventricular mass and right ventricular hypertrophy [138-140]. With respect to the prognostic value of right heart remodelling with elevated blood pressure, right ventricular hypertrophy was independently associated with an increased risk of heart failure, atrial fibrillation, and

cardiovascular death [141, 142]. Figure 1.3 provides an illustration of the normal and increased right ventricular wall thickness. Right atrial remodelling also has prognostic significance for clinical outcomes, but there is insufficient data available to determine the independent influence of hypertension on right atrial structure and function [143-145].

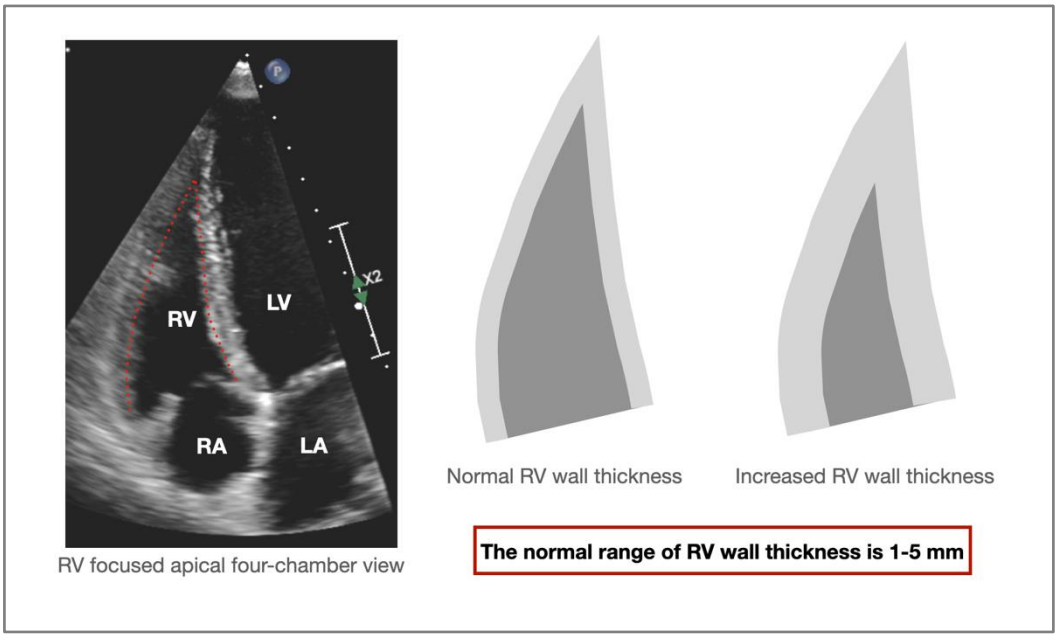


Figure 1.3. Right ventricular hypertrophy in hypertension.

Normal and increased right ventricular wall thickness viewed from the right ventricular focused apical four-chamber view. The mean value of normal wall thickness is 3 ± 1 mm with a range of 1-5 mm [110].
RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium.

1.4.4. Cardiovascular response to physical exercise in patients with hypertension

Although high blood pressure is associated with a broad spectrum of cardiovascular remodelling, the patterns of remodelling may not be observed at rest, particularly in recently diagnosed patients with mild hypertension. Exercise testing

is a physiological stress that can elicit subtle cardiovascular alterations secondary to elevated blood pressure which may not be present at rest. Exercise testing with echocardiography imaging has been widely performed to guide the diagnosis and management for a variety of clinical pathologies including ischemic and valvular heart disease [146].

A prior study, using exercise radionuclide ventriculography for non-invasive assessment of coronary atherosclerosis in hypertensive patients with chest pain, found that symptomatic patients had reduced left ventricular ejection fraction in response to exercise compared to a normotensive group [33]. The reduction in the ejection fraction during exercise was believed to be due to coexisting cardiac abnormalities such as ischemic heart disease and left ventricular hypertrophy [33]. However, Douglas et al. found a similar response to exercise on asymptomatic patients with mild to moderate hypertension and no clinical evidence of ischemic heart disease or ventricular hypertrophy [147]. Findings from two other studies also support the association between increased blood pressure and exercise-induced systolic dysfunction [34, 148]. Exercise-induced systolic dysfunction was marked in older hypertensives [34, 147, 148], and associated with impaired diastolic filling [149]. In younger hypertensives, there is a paucity of studies that describe left ventricular systolic function during exercise testing. A recent study has provided evidence on impaired systolic function at 40% and 60% of peak exercise intensity in young adults born prematurely and had higher blood pressures compared to adults born at term [150]. Abnormal systolic function in response to exercise was also associated to subnormal left ventricular mid-wall fractional shortening at rest in asymptomatic hypertensive patients [151]. This finding has prognostic significance in predicting

cardiovascular risk in hypertensive patients independent of age, blood pressure measures, or left ventricular hypertrophy [151, 152].

1.5. Current limitations of the hypertension management in young adults

Optimal blood pressure control is to maintain blood pressure levels below 120 mmHg and 80 mmHg for systolic and diastolic blood pressure, respectively [10, 11]. This can be achieved by pharmacological and/or non-pharmacological interventions [10, 11]. Both approaches have shown a beneficial effect in lowering blood pressure measures and reducing the risk of cardiovascular, cerebrovascular, and renal events [10, 11]. Non-pharmacological interventions, such as adhering to regular physical activity, weight reduction, and diet modifications, are usually prescribed for patients with mild hypertension [11]. This lifestyle modification approach helps to prevent or delay the need of pharmacological intervention [10], but pharmacological treatment is recommended in patients with more severe hypertension, especially those with high risk of cardiovascular disease [10, 11]. Randomised clinical trials have demonstrated that a reduction of ten mmHg in systolic blood pressure or five mmHg in diastolic blood pressure is associated with a 20% reduction of adverse cardiovascular events [10]. However, these studies were carried out on from older, high risk patients [10]. Current data on the management of hypertension and prevention of cardiovascular disease have been established from populations over 40 years of age [10]. Younger hypertensives below the age of 40 years are known to have different pathophysiological responses to high blood pressure, mainly due to the relatively shorter exposure of the disease [153]. According to the latest European and American guidelines of hypertension prevention

and management, there is a gap in the evidence for whether to start anti-hypertensive medication in young patients with stage I hypertension [10, 11]. This is due to the lack of longitudinal clinical studies with sufficient follow-up duration [10, 11, 18].

1.5.1. Non-pharmacological interventions

Based on the current recommendations for hypertension management in patients below the age of 40 years, patients are encouraged to implement lifestyle modifications as the first line of blood pressure control in the absence of end organ disease or secondary causes of hypertension [10, 11]. Although lifestyle modifications, such as performing regular aerobic exercise, have shown a beneficial impact on controlling blood pressure, exercise interventions have varying degrees of success in younger populations [46]. A heterogeneous blood pressure response to exercise has been observed in young patients with hypertension [46]. This response could be related to a variety of factors including the intensity of exercise, the level of adherence and compliance to exercise sessions, or subclinical cardiovascular abnormalities [46, 154].

A meta-analysis reported that supervised aerobic exercise sessions, higher exercise intensity, and longer intervention sessions were associated with larger reduction in both systolic and diastolic blood pressure values [46]. Increasing exercise intensity could elicit subclinical cardiovascular remodelling patterns that are usually preserved at rest [150]. Young adults with a history of premature birth had higher systolic and diastolic blood pressure measures compared to full-term born adults and had lower left ventricular ejection fraction in response to physical exercise [150]. These findings could partially explain the heterogenous blood pressure response to physical exercise in young adults. In the Oxford Cardiovascular Clinical Research Facility, we carried out a randomised clinical trial to assess the effect of supervised aerobic exercise

interventions on blood pressure levels in young adults [155]. We found that moderate to high intensity exercise interventions for 16 weeks did not significantly lower systolic or diastolic blood pressure, despite the significant increase in cardiovascular fitness. These findings are under revision for publication.

1.5.2. Pharmacological interventions

The effect of the pharmacological approach, on the other hand, in lowering blood pressure measures in young patients has been understudied due to the lack of sufficient long-term data [10, 11, 18]. The American guidelines recommend starting pharmacological treatment for patients with stage I hypertension (systolic blood pressure 130–139 mmHg or diastolic blood pressure 80–89 mmHg) with estimated 10-year cardiovascular risk of ≥ 10% [11]. In patients with stage II hypertension (systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHg), anti-hypertensive treatment is recommended regardless of the cardiovascular risk score [11]. However, in the UK, NICE guidelines recommend initiating pharmacological therapy for patients with systolic blood pressure of 140 to 159 mmHg or diastolic blood pressure of 90 to 99 mmHg with evidence of existing target organ damage, or a QRISK score of > 10% in those free of cardiovascular disease [12]. The European guidelines highlight the lack of evidence for the effect of anti-hypertension therapy in younger patients but suggest the initiation of treatment to avoid harm consequences of the long-term sustained elevation of blood pressure [10].

Despite differences in threshold levels for treatment initiation among the guidelines, the recommendation of starting treatment has been established from randomised clinical trials carried out in older and high-risk populations [10, 11]. A retrospective study on a large cohort of low-risk patients with mild hypertension was

conducted to assess the benefits and harms of initiating anti-hypertensive medication during a median follow-up period of six years [156]. The results showed that early initiation of anti-hypertensive treatment in low-risk patients was associated with higher risk of adverse events [156]. Furthermore, the adherence level of anti-hypertension medication regimen in younger patients is poor [157], which could be due to the lack of clinical symptoms and awareness of cardiovascular risks [18]. The non-adherence level was the highest among patients aged between 18 and 34 years old [157]. On a large-scale study, from a nationwide health insurance database, in young hypertensives aged between 20 to 44 years with anti-hypertension treatment, researchers found that poor adherence was associated with increased risk of adverse cardiovascular events on later life [158].

1.6. The potential role of artificial intelligence in the diagnosis and management of young adults with hypertension

Although artificial intelligence has been around since the 1950s, its first applications in medicine were only reported in the last three decades [159]. Recently, there has been an exponential growth of interest in using artificial intelligence and machine learning techniques to assist in medical diagnosis and personalised management. Such techniques have the ability to integrate big data and facilitate automated assessments of large datasets rapidly. In the last few years, innovative diagnostic and decision-making applications have been developed using artificial intelligence tools for a variety of conditions including cancer, cardiovascular, and neurodegenerative disease. In hypertension, blood pressure control rate remains unsatisfactory worldwide despite the

wide availability of anti-hypertension treatments [160]. Having addressed the limitations of hypertension management in young adults and the complexity of the disease architecture in the previous sections, advances of artificial intelligence applications may help to overcome these limitations. The definitions of commonly used artificial intelligence techniques and their potential applications in hypertension are provided in the following sections.

1.6.1. Terminology and techniques

Artificial intelligence is a broad term of computational systems that allow for performing tasks that would usually require levels of human intelligence (Figure 1.4) [161]. A subfield of artificial intelligence is machine learning, which provides automated detection and analysis of large complex data, such as echocardiography features.

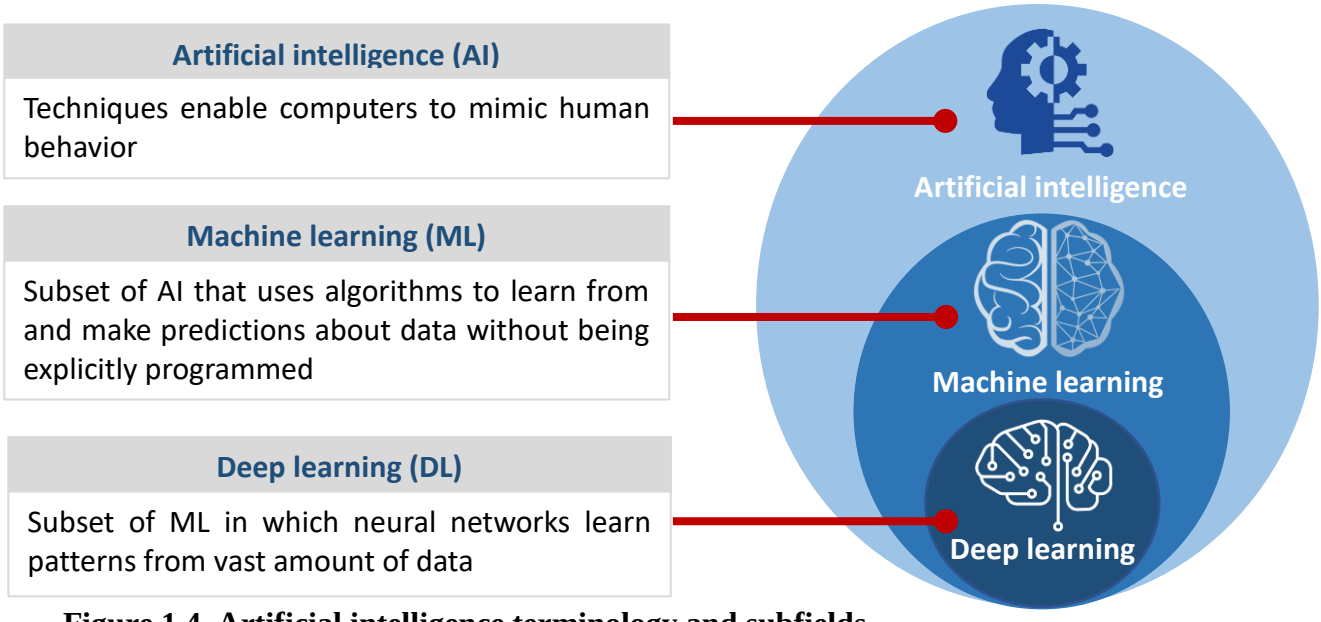


Figure 1.4. Artificial intelligence terminology and subfields.

Machine learning can be classified into three categories: supervised learning, unsupervised learning, and reinforcement learning (Figure 1.5). In supervised machine learning, algorithms are applied to data with existing labels of outcomes or diagnosis. The supervised algorithms learn underlying patterns within the data and compare them with the given labels for disease prediction or classification modelling. These algorithms can be as simple as regression analysis to identify linear associations, or more sophisticated tools such as support vector machines and random forests for non-linear prediction models. Convolutional neural network (deep learning) is another form of supervised learning using multi-layered classification networks (Figure 1.6 A) [161, 162]. Such supervised tools have been applied on echocardiography data to differentiate between pathologies with similar presentation such as constrictive pericarditis and restrictive cardiomyopathy [163].

Unsupervised learning techniques, in contrast, learn from unlabelled input data and create different groups based on the similarities of underlying potential patterns. The principal component analysis is a relatively simple unsupervised method. It identifies features with the most variation in a dataset using dimensionality reduction tools. Clustering analysis algorithms, including partitioning or grid-based algorithms, are another form of unsupervised learning (Figure 1.6 B) [162, 164]. These unsupervised methods have been extensively applied on echocardiography data to study interpatient similarities in cardiac structure and function [165], and cluster large cohorts into more homogenous subgroups [166]. Reinforcement learning has rarely been applied in echocardiography clinical applications since it is based on interactions with an environment and learning by a trial-and-error approach [167]. These machine learning methods are not mutually exclusive and can be integrated together to create a more powerful tool [168, 169]. The method of integrating different algorithms to identify the

approach with the best performance is known as “ensemble machine learning” [170]. An integrated algorithm of supervised and unsupervised tools has been applied to map cardiac phenotypes in patients with heart failure using echocardiography data [171] .

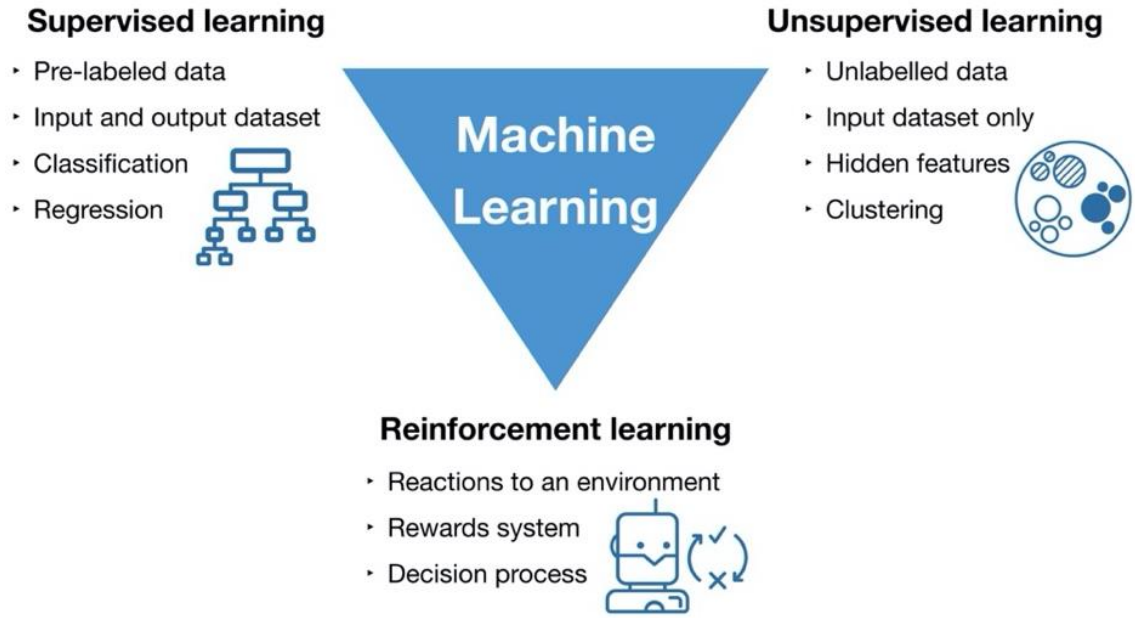


Figure 1.5. The difference between machine learning tools.

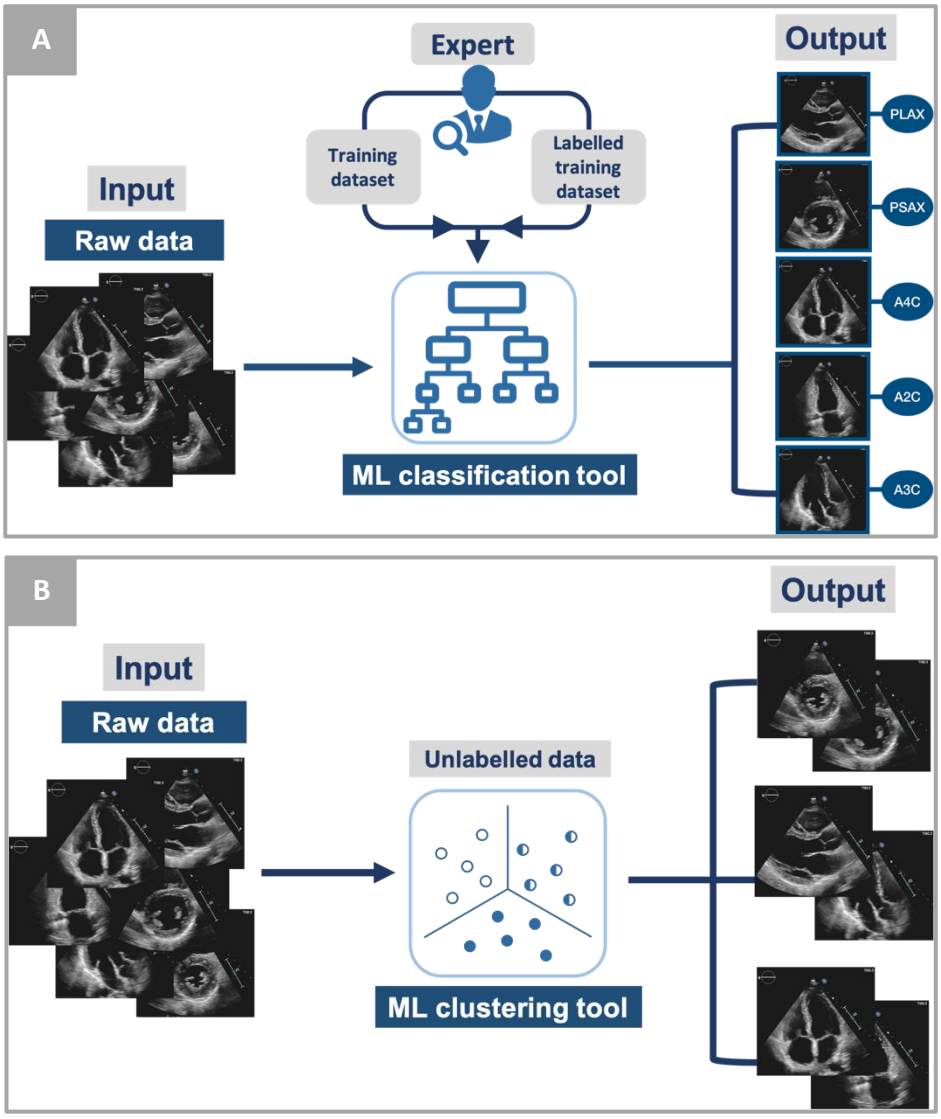


Figure 1.6. An illustration of supervised and unsupervised learning algorithms.

Panel A illustrates a supervised classifier algorithm to assign echocardiography images into pre-labelled classes. Panel B shows an unsupervised clustering algorithm to group echocardiography images based on similarities.
ML, machine learning

1.6.2. Machine learning applications in patients with hypertension

While machine learning tools can classify a patient's diagnosis or predict outcomes, new strategies for hypertension diagnosis and management have emerged [172, 173]. For example, applications of remote blood pressure monitoring and supports [174-176], big data prediction models for the incidence and complications of hypertension [177-179], and testing the effectiveness of treatment for personalised management [180, 181]. In addition to these applications, a surge of interest and research in the use of machine learning in medical imaging to support diagnostic and management decisions only started recently [182]. Researchers have shown that applying machine learning algorithms in echocardiography data combined with clinical data provides incremental prognostic value of clinical outcomes beyond traditional measures [183, 184].

In patients with hypertension, applications of novel machine learning algorithms on echocardiography features have provided comprehensive understanding of the interrelated cardiac alterations. Using unsupervised learning methods, Katz et al. have combined the effect of 47 clinical, laboratory, and echocardiography features to classify 1273 patients with hypertension into distinct subgroups [185]. This resulted in two distinct clusters of hypertensive patients with markedly different clinical characteristics and cardiac mechanics [185]. Authors suggested that these clusters may have different responses to targeted therapy for the prevention of heart failure [185]. Similarly, other studies supported the use of unsupervised machine learning tools to cluster patients based on cardiac function similarities by integrating multiple echocardiography features [165, 186, 187]. Furthermore, in a prior study, ensemble machine learning algorithm was applied for automated differentiation between physiological and pathological left ventricular hypertrophy [188]. This algorithm has shown 96%

sensitivity and 77% specificity for discrimination between athletes left ventricular hypertrophy and pathological hypertrophy [188]. As the left atrial, left ventricular, and right heart remodelling in hypertension is highly inter-connected, a learning algorithm model could be used to better understand the pathophysiological interplay in young adults with hypertension. In this thesis, I focused on applying machine learning tools for the identification of pathological patterns in patients with hypertension using high-dimensional clinical and echocardiography data.

1.7. Thesis aims and hypotheses

Currently, there is insufficient evidence about the cardiovascular pathophysiological alterations in response to high blood pressure and its treatment in younger populations to be able to guide treatment decisions. Therefore, the aim of this thesis was to identify novel subclinical cardiovascular imaging phenotypes that may be of clinical value to monitor blood pressure management in young adults. Firstly, I explored whether individual novel cardiac measures identified with echocardiography either at rest or in response to stress could provide information on early cardiac changes related to blood pressures. Then I studied whether combining measures using machine learning tools could provide more comprehensive summaries of phenotypic changes related to hypertension.

To address the first objective, I investigated whether young adults with hypertension have abnormal myocardial response to physical exercise, and whether this response could be predicted from resting echocardiography. Specifically, I hypothesised that:

1. Young adults with suboptimal blood pressure (≥ 120/80 mmHg) will have reduced left ventricular ejection fraction in response to physical exercise.

2. Left atrial phasic function at rest will be associated with the adverse cardiac response to physical exercise in young adults with suboptimal blood pressure.

To address the second objective, I aimed to develop a disease progression model by applying a novel machine learning algorithm on cross-sectional echocardiography data of young adults with a range of blood pressure. The aim of the model development was to combine the effect of multiple clinical and echocardiography data, to place participants on a trajectory from health to disease assigned with a disease progression score, to identify important parameters relevant to the disease progression of hypertension in young adults, and to study the dynamic changes of individual parameters over the course of the disease progression. My specific hypotheses were:

3. A disease progression model of hypertension in young adults will be developed from cross-sectional echocardiography datasets using a semi-supervised machine learning algorithm.
4. The model outcomes will be associated with different clinical stages of hypertension, be consistent with an established modifiable cardiovascular risk score and alter in response to a 16-week exercise intervention.

2. STUDY POPULATION

2.1. Overview

The work of this thesis is based on several clinical studies focused on the cardiovascular assessment of young adults with elevated blood pressure, conducted in CCRF at the John Radcliffe Hospital. Two completed studies were included in this work: The Young Adult Cardiovascular Health sTudy (YACHT), and the Trial of Exercise to Prevent Hypertension in young Adults (TEPHRA), as well as an ongoing study: Hypertension management in Young adults Personalised by Echocardiography and Clinical Outcomes (HyperEcho). All studies are ethically approved and conducted following the same standardised protocol for clinical investigations, data collection, and data analysis. For the purpose of this thesis, the three datasets were merged to generate a single large dataset of young adults with a range of blood pressure measurements.

This chapter provides details about the design of each study, inclusion and exclusion criteria, and recruitment procedures, with identification of participant selection criteria for each hypothesis.

2.2. Young Adult Cardiovascular Health sTudy (YACHT)

The YACHT study was an observational case-control study, started in August 2014 and completed in May 2016. The aim of this study was to better understand how birth histories could influence cardiovascular health and blood pressure levels by investigating cardiovascular structure, function, and physical exercise response in full-term born (≥ 37 weeks), prematurely born (< 37 weeks), and hypertensive young adults aged 18 to 40 years. The study was approved by the

South Central Berkshire Research Ethics Committee (Reference 14/SC/0275), and registered on the www.clinicaltrials.gov (NCT02103231) database. The study was supported by funding from British Heart Foundation (BHF).

2.2.1. Study recruitment

Participants' eligibility for this study was based on the following inclusion and exclusion criteria:

Inclusion criteria:

- Participant is willing and able to give informed consent for participation in the study.
- Male or female, aged 18 to 40 years.
- Verifiable history of preterm birth or full-term birth.
- Able (in the investigator's opinion) and willing to comply with all study requirements.
- Participant is freely able to access the John Radcliffe Hospital for study visits.

Exclusion criteria:

- Aged < 18 years > 40 years.
- Unwilling or unable to give informed consent for participation in the study.
- Pregnant or lactating during the course of the study.
- Any significant disease or disorder which, in the opinion of the investigator, might influence the participant's ability to participate in the study.
- Contraindication to Magnetic Resonance Imaging.

The study was completed with 149 young adults recruited including 63 participants with a history of premature birth and 86 full term born participants.

2.2.2. Study procedures

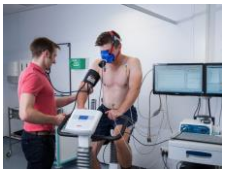
Eligible participants underwent several study procedures including detailed blood pressure measures (clinical measures at rest and during exercise, and 24-hour ambulatory blood pressure monitor), transthoracic echocardiography imaging (at rest and during exercise), magnetic resonance imaging (for the heart, brain, and liver), cardiopulmonary exercise testing, molecular and cell biology assessment, and lifestyle and physical activity questionnaires. All study measures are illustrated in Figure 2.1.

2.2.3. Personal contribution

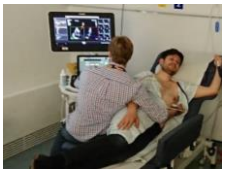
The study recruitment, data collection, and analysis were all completed before I joined the Cardiovascular Clinical Research Facility. However, I performed an additional echocardiography image analysis for a subgroup of the study participants to generate the necessary data for my analysis.

Study Measures

Blood pressure measures
Resting, exercise, and 24h ABP monitor

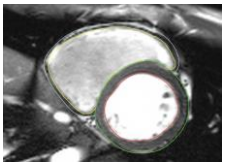


Cardiopulmonary exercise testing (CPET)
Peak exercise test and spirometry



Echocardiography
Resting, and exercise

Molecular and cell biology
Pre and post exercise blood samples



Magnetic resonance imaging (MRI)
Cardiac, brain, and liver

Lifestyle and physical activity questionnaires

Figure 2.1. An illustration of YACHT study measures.

2.3. Trial of Exercise to Prevent HypeRtension in young Adults (TEPHRA)

TEPHRA study was a single centre, two-arm, and parallel randomised controlled (1:1) trial, started on June 2016 and completed in January 2020. The aim of this trial was to assess the effect of physical exercise on lowering blood pressure measures in young adults (aged 18 to 35 years) with elevated blood pressure and to investigate the influence of premature birth on blood pressure levels and the exercise response. TEPHRA was approved by the Oxford B Research Ethics Committee (Reference 16/SC/0016) and registered on the www.clinicaltrials.gov (NCT02723552) database. The study was supported by funding from Wellcome Trust, British Heart Foundation, the Oxford BHF Centre for Research Excellence, and National Institute for Health Research (NIHR) Oxford Biomedical Research Centre.

2.3.1. Study recruitment

Potential participants were approached through online advertising on social media (Facebook, Instagram, and Twitter), invitation from hospital birth registers and GP records, and invitation from previous participation in research studies. Participants' eligibility for this trial was based on the following criteria:

Inclusion Criteria:

- Participant is willing and able to give informed consent for participation in the study.
- Male or female aged from 18 to 35 years old.
- Verified birth history: preterm birth (< 37 weeks) or full-term birth (> 37 weeks).

- Ability to access and use computer/internet.
- Willing to complete duration of intervention, follow-up and attend study visits at the John Radcliffe Hospital.
- 24-hour awake ABP greater than 115/75 mmHg.
- Able (in the investigator's opinion) and willing to comply with all study requirements.

Exclusion Criteria:

- Clinic blood pressure greater than 159 mmHg systolic and/or 99 mmHg diastolic at initial screening.
- 24-hour awake ABP greater than 150 mmHg systolic and/or 95 mmHg diastolic.
- Clinic blood pressure greater than 140 mmHg systolic and/or 90 mmHg diastolic plus evidence of end organ damage secondary to hypertension.
- Pregnancy.
- Simultaneous participation in another human or clinical randomised trial (if there was any possibility of compromising health, safety, or well-being, or any possible compromise of study data).
- Unable to walk briskly on the flat for 15 minutes.
- Those maintaining levels of cardiovascular fitness and activity at or above the levels required for the intervention arm.
- Unable to attend the regular supervised exercise sessions.
- Use of beta-blockers such as atenolol or equivalent.
- Body mass index > 35 kg/m^2.
- Major contra-indications to exercise participation.
- Evidence of cardiomyopathy.

- Evidence of inherited cardiac conduction abnormalities.
- Evidence of congenital heart disease or significant chronic disease relevant to cardiovascular status.

A total of 203 young adults were recruited in this trial with 102 randomised to the exercise arm (in which 75 were full term born participants and 27 were born prematurely), and 101 to the control arm (74 born at full term and 27 born prematurely).

2.3.2. Study procedures

The trial was designed to begin with a screening visit to assess participants' eligibility for the trial that was followed with a baseline study visit (visit 1) for detailed assessment of cardiovascular structure and function. After completing visit 1, participants were randomised (1:1) to either a 16-week exercise intervention arm or control arm. Participants randomised to the exercise intervention arm were provided with a gym membership at Brookes Sport to complete three supervised aerobic exercise sessions (60 minutes each) per week and for 16 weeks. Participants from outside Oxford completed their exercise sessions at their own gym with remote supervision. The control arm participants were advised to maintain their usual physical activity levels. After 16 weeks of randomisation, all participants attended their second assessment visit (visit 2) for a follow-up cardiovascular assessment, and after 52 weeks from visit 1 participants attended their final follow-up visit. The TEPHRA visits flow is illustrated in Figure 2.2.

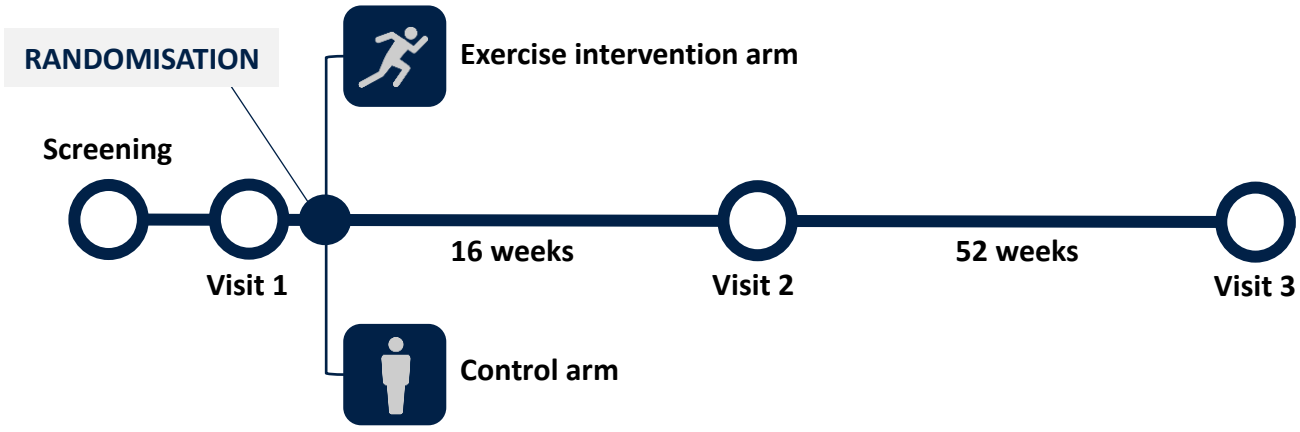


Figure 2.2. TEPHRA study visits flow.

During visit 1, all participants completed a set of study measures including: detailed blood pressure measures (clinical measures at rest and during exercise, and 24-hour ambulatory blood pressure monitor); transthoracic echocardiography imaging (at rest and during exercise); magnetic resonance imaging (MRI) (for the heart, brain, and liver); cardiopulmonary exercise testing; molecular and cell biology assessment; microvascular assessment (retinal imaging and capillaroscopy); physical examination (body composition, ECG, and physical activity monitor); and lifestyle and physical activity questionnaires. All measures were repeated during the second study visit (visit 2). In visit 3 only blood pressure measures, echocardiography assessment, and cardiopulmonary exercise testing were performed. Study investigators who were not involved in the exercise intervention were blinded until after completion of final data analysis. All study measures are shown in Figure 2.3.

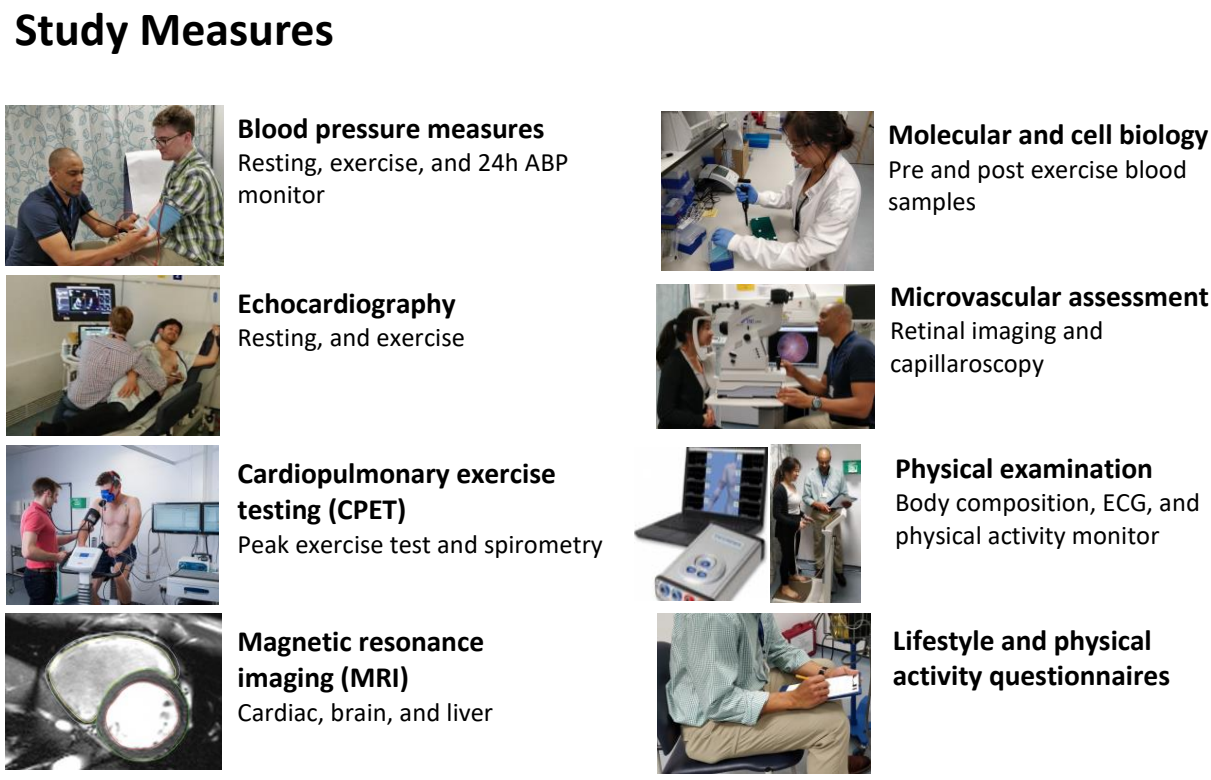


Figure 2.3. An illustration on TEPHRA study measures.

2.3.3. Personal contribution

Although trial design, recruitment and data collection started before my DPhil, I contributed to all aspects of trial management, recruitment, data collection and analysis from the start of my DPhil.

Recruitment: As part of the TEPHRA team, I worked to advertise the study and target potential participants to reach our target recruitment. I contacted potential participants to answer their queries, arrange for their screening visits, and assessed their eligibility during the visit.

Study visits and data collection: TEPHRA study visits include several procedures and required at least two investigators to plan and run a study visit. I worked on planning and running study visits, and performed all study

procedures except for the MRI and blood sample collection. When I joined the team, we developed a stress echocardiography protocol that could be applied during the cardiopulmonary exercise test protocol. I was responsible for the echocardiography data collection at rest and during exercise. I helped training the clinical research assistants at CCRF to master echocardiography image acquisition and analysis.

Data processing and analysis: I created the echocardiography dataset structure, and together with DPhil candidates Dr Afifah Mohamed, and Dr Jamie Kitt, interpreted all echocardiography images obtained from the three study visits at rest, including conventional and speckle tracking analysis. I also interpreted all exercise echocardiography images. I reviewed and cleaned the completed echocardiography dataset and uploaded it onto Castor platform.

2.4. Hypertension management in Young adults Personalised by Echocardiography and clinical Outcome (HyperEcho)

The HyperEcho study is a multi-centre longitudinal observational study, started in October 2018 and still ongoing with an expected completion to be in 2028. The aim of the HyperEcho study is to improve and personalise the management of young adults with hypertension aged 18 to 40 years. The study has been conducted to investigate whether baseline transthoracic echocardiography imaging along with routine clinical data collected in the hypertension clinic can improve risk stratification for cardiovascular disease in young adults with hypertension. The study has been approved by the South West – Frenchay Research Ethics Committee (Reference 18/SW/0188) and registered on the www.clinicaltrials.gov (NCT03762499) database. The study is supported with funding from the NIHR Oxford Biomedical Research Centre, the Saudi Arabian Cultural Bureau, and Oxford Cardiovascular Clinical Research Facility.

2.4.1. Study recruitment

Participants are characterised as hypertensive patients aged between 18 to 40 years old and referred to the hypertension clinic to manage their blood pressure. Potential participants have been approached from the outpatient hypertension clinics of NHS trusts within England.

Inclusion Criteria:

- Participant is willing and able to give informed consent for participation in the study.
- Male or female, aged 18 - 40 years (at the time of their appointment at the hypertension clinic).
- Referred for a Hypertension Clinic in England.

Exclusion Criteria:

- Unable or unwilling to give valid consent for participation in the study.

At the time of writing this thesis, 250 adults aged 18 to 40 years old have been recruited from six recruiting sites within England, with our aim to recruit 750 participants.

The actively recruiting sites are illustrated in Figure 2.4 as follows:

- Oxford University Hospitals (OUH)
- George Eliot Hospital
- High Wycombe hospital
- Broomfield Hospital
- Nottingham University Hospital
- London North West University Healthcare NHS trust

Figure 2.4. HyperEcho sites map.

2.4.2. Study procedures

The study includes a single study visit that has been carried out during the planned routine visit of potential participants to the hypertension clinics of NHS trusts within England. Potential participants have been asked to consent for the use of their clinical data that have been collected in the hypertension clinic, including: clinic blood pressure measures; 24-hour blood pressure monitoring reports; ECG; blood samples; body fat composition; medical history; referral letters; and echocardiography reports, if available. If the echocardiography scan was not performed as part of the clinical service, a research echocardiography scan has been performed for Oxford participants only. In addition to this, all participants have been asked to consent to further review of their clinical data and medical notes once every year for the follow-up data collection and up to ten years after the baseline visit. The baseline study visit and follow-up data collection flow is demonstrated in Figure 2.5.

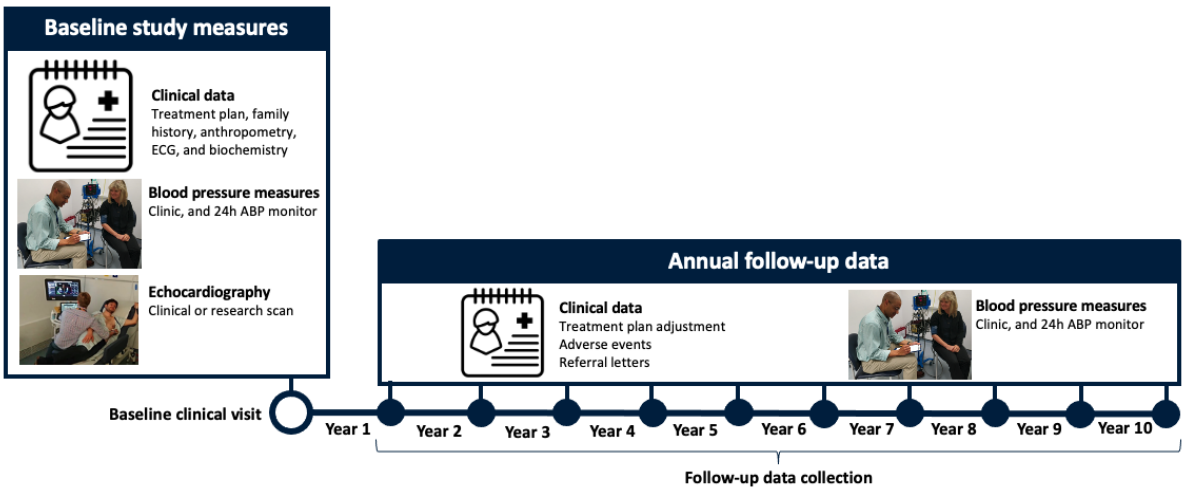


Figure 2.5. HyperEcho study data collection flow at the baseline study visit and annual follow-ups.

2.4.3. Personal contribution

Ethical approval and amendments: From the start of my DPhil, I started designing the study and preparing the study protocol, participant information leaflets, consent forms, invitation letters and all required documents to obtain the ethical approval with the study Chief Investigator Professor Paul Leeson and the assistant clinical research coordinator Dr Katja Pfafferott. The study was ethically approved in October 2018 and the recruitment was initiated immediately. I managed to amend the study to include eight external study sites, and with the help of the clinical research assistant Annabelle McCourt, we initiated the study on five external sites, and they are actively recruiting at the time of writing this thesis. During COVID-19, the study activities were paused. With the help of the study governance team (Philippa Kemp and Dr Hanan Lamlum), we have successfully resumed the study recruitment remotely to maintain patients' and healthcare providers' safety.

Study recruitment: I identified all potential participants at OUH through the Electronic Patients Record (EPR) system and created a securely stored log file with details of all participants that received invitation letters. I met and recruited the majority of participants (90%) at OUH, performing the research echocardiography scan when required. When there was an abnormal or unexpected finding, I arranged for a consultation with the clinical care team.

Data collection: I created the electronic data collection platform via Castor and generated a unique identification number for each participant (i.e., 0X001, 0X002) with a specific identification number for each study site (i.e., 01H00X,

02H00X). The research teams from external sites were all invited to input their data in this platform. I trained Gunes Thaygaraja and Jo Sawyer, cardiovascular research data coordinators, to assist with the study data input with regular data monitoring sessions to maintain data entry completeness.

Data processing and analysis: Echocardiography image processing, analysis and reporting were completed by me immediately after scanning the participants following the latest British Society of Echocardiography guidelines [189]. I reviewed all echocardiography images and reports including the OUH NHS and external sites scans and reports. For the purpose of this thesis, I processed and analysed blood pressure measures, anthropometric data, echocardiography imaging data, and medical history data.

2.5. Merged database

To achieve the aims of this thesis, a database of young adults who participated in the above three clinical studies at CCRF was created. Data processing and cleaning was carried out for each dataset separately. The three datasets were then merged, after which another round of outlier detection was performed. Included study measures and their similarities between studies are shown in Table 2.1. The database includes young adults aged between 18 to 40 years old who completed detailed clinical blood pressure assessment and baseline transthoracic echocardiography phenotyping. Participants with a history of premature birth were excluded from this database.

Table 2.1. The database included study measures and similarities between the three studies

Datasets / Study measures	YACHT	TEPHRA	HyperEcho
Anthropometry	✓	✓	✓
Blood pressure assessment	✓	✓	✓
Ambulatory monitoring devices:			
• 24-Hour blood pressure monitoring	✓	✓	✓
• Physical activity monitoring	✓	✓	
Resting echocardiography	✓	✓	✓
Cardiac magnetic resonance imaging	✓	✓	
Cardiopulmonary exercise test	✓	✓	
• Stress echocardiography	✓	✓	
Blood samples and biochemistry	✓	✓	✓

2.6. Participants selection for each hypothesis

To test each hypothesis of this thesis, specific criteria for participant selection were applied as follows:

2.6.1. Hypotheses 1 and 2 selection criteria and characteristics

Young adults aged 18 to 40 years and born full-term who had undergone detailed assessment of clinical blood pressure profiles at rest and during exercise, anthropometry, transthoracic echocardiography imaging at rest, cardiopulmonary exercise testing with stress echocardiography imaging, and who were not already on anti-hypertensive medication, were identified to test hypotheses 1 and 2. Based on resting clinical systolic and diastolic blood pressure measurements, participants were classified into suboptimal blood pressure group and optimal blood pressure group with frequency matching between groups for age, sex, and bodyweight. The suboptimal blood pressure group includes participants with blood pressure measured between 120/80 mmHg and 159/100 mmHg, and those with blood pressure measured less than 120/80 mmHg were classified in the optimal blood pressure group. A total of 127 young adults (59 with optimal blood pressure and 68 with suboptimal blood pressure) were identified who fulfilled the selection criteria and had adequate quality of echocardiography images during exercise.

2.6.2. Hypothesis 3 selection criteria and characteristics

A larger cohort of young adults aged between 18 to 40 years old with a range of blood pressure measurements was identified to test hypothesis 3. All participants with detailed assessment of blood pressure profiles, anthropometry, and baseline transthoracic echocardiography imaging were included. Participants with more than 30% of missing data were excluded. A total of 411 young adults were identified to develop the disease progression model of young adults with hypertension. Based on clinical systolic blood pressure measurements and for the model development tool requirements, participants were classified into three categories:

- **Target:** Participants with systolic blood pressure ≥ 160 mmHg (n=33).
- **Background:** Participants with systolic blood pressure < 120 mmHg and not on anti-hypertensive medication (n=111).
- **Intermediate:** Participants with systolic blood pressure ≥ 120 mmHg and < 160 mmHg (n=267).

2.6.3. Hypothesis 4 selection criteria and characteristics

Hypothesis 4 consists of three questions in which the participants were identified from the cohort included to test hypothesis 3.

For the first question, to classify participants based on their clinical stages of hypertension, only those who have referral and treatment information were included. A total of 396 participants were included, and a group of 15 participants,

who referred to the hypertension clinic and had no treatment information, were excluded. Based on these data, participants were classified into four stages of clinical hypertension as follows:

A. No referral to a hypertension clinic with no pharmacological treatment (n=246).
B. Referred to a clinic but with no pharmacological treatment (n=24).
C. Referred with less than two years of pharmacological treatment (n=70).
D. Referred with more than two years of pharmacological treatment (n=56).

The second question was to compare the disease progression score with an established modifiable cardiovascular risk score. A subgroup of hypothesis 3 cohort who completed the clinical procedures required to calculate the modifiable cardiovascular risk score were included (n= 179). Details on the score calculation are provided in Chapter 3 section 3.10.

For the third question, to test the effect of a 16-week exercise intervention on the disease progression score, participants who were involved in hypothesis 3, randomised to the exercise intervention arm or control arm, and who completed visit 2 in TEPHRA were included. A total of 126 young adults were identified, with 60 of them randomised to the exercise intervention and 66 to the control arm.

3. METHODS AND MATERIALS

3.1. Overview

This chapter describes the methods and materials utilised in this thesis. I present the details of the clinical investigations and methods of data collection, processing, and analysis with a description of the statistical tools employed.

3.2. Anthropometry

Participants had their height and weight measured by standing on an integrated height and weight measurements station (Seca, Birmingham, United Kingdom) with footwear removal and wearing only light clothing. Height and weight were measured to the nearest centimetre and 0.1 kg, respectively. Body mass index (BMI) was calculated for all participants using the standard formula:

$$BMI\ (kg/m^2) = \frac{Weight\ (kg)}{Height\ (m)^2}$$

Body surface area (BSA) was also calculated using the Mosteller formula:

$$BSA\ (m^2) = \sqrt{\frac{[Height\ (cm) * Weight\ (kg)]}{3600}}$$

3.3. Blood pressure profiles

Resting blood pressure measurements were obtained using a digital blood pressure monitor (GE Dinamap V100, GE Healthcare, Chalfont St. Giles, United Kingdom). After five minutes of rest in a seated position, three consecutive blood

pressure readings on the left arm were recorded with a minute between each measurement. The average of the last two measurements was included in the analysis.

3.4. Ambulatory monitoring devices

All participants were fitted with an ambulatory 24-hour blood pressure monitoring device and wrist worn activity monitor by a trained study investigator at the end of their study visit. There is a detailed description below for each device procedure.

3.4.1. 24-Hour ambulatory blood pressure monitoring

Participants were fitted with a 24-Hour ambulatory blood pressure monitoring device (TM-2430, A&D Instruments, Abingdon, United Kingdom). Based on participants' arm circumference, correct bladder cuff size was chosen. The monitoring device settings were adjusted to obtain automatic blood pressure readings throughout the 24 hours (every 30 minutes during the daytime and hourly from 11.00 pm to 7.00 am). To ensure accurate blood pressure recordings, participants were instructed to remain still during blood pressure measurements, record their awake and sleep time in a diary sheet, and record any physical activity that may affect blood pressure readings (i.e., cycling or running). In CCRF, trained investigators downloaded measurements using Doctor Pro 2 or Doctor Pro 3 software for Windows (A&D Company Limited, Tokyo Japan), and stored a hard copy of the readings.

3.4.2. Physical activity monitoring

Participants were also fitted with Axivity AX3 wrist-worn (Axivity Ltd, Newcastle, UK), tri-axial accelerometers. These were worn for nine days by participants and then posted back to the study team. Physical activity information was extracted from raw sensor data using the same analysis pipeline as used for UK Biobank participants [190]. The first seven complete days of wear data were analysed. Hours spent between 100 and 400 milligravities (mg) activity intensity were classed as Moderate to Vigorous Physical Activity (MVPA) (i.e., walking, leisurely cycling) time and hours spent above 400 mg were classed as Vigorous Physical Activity (VPA) (i.e., jogging, running, active sport).

3.5. Echocardiography imaging

A comprehensive 2D and 3D echocardiography scan was performed for each participant using a Philips EPIC 7C, Philips iE33 echocardiography ultrasound machine (Philips Healthcare, Surrey, United Kingdom). Image acquisition was performed in the left lateral decubitus position and following the British Society of Echocardiography standards for image acquisition and optimisation. Conventional image analysis was completed offline using Philips IntelliSpace Cardiovascular (ISCV) 2.1 (Philips Healthcare Informatics, Belfast, Ireland), and TomTec Image Arena 4.6 (Chicago, IL, United States) software was used to perform 2D left ventricular and left atrial speckle tracking analysis. Cardiac structure, function, and deformation analysis was performed as follows:

3.5.1. Cardiac structure assessment (2D echocardiography)

Cardiac chambers quantification was performed according to the latest published guidelines for chamber assessment in echocardiography [110, 189].

3.5.1.1. Left ventricular assessment

Left ventricular linear dimensions were measured from the 2D parasternal long axis view. During end diastole (at the beginning of QRS complex), the left ventricular outflow tract dimension, interventricular septum, and inferolateral wall thickness were measured, as well as the left ventricular internal diameter (the largest left ventricular dimension). The smallest left ventricular internal dimeter at end systole (at the end of T wave) was also measured. Measurements are shown in Figure 3.1. Left ventricular relative wall thickness (RWT) ratio was calculated using the following formula:

$$RWT = \frac{2 * \ Inferolateral\ wall\ thickness\ (cm)}{Left\ ventricular\ diastolic\ dimeter\ (cm)}$$

Left ventricular mass (LVM) was also estimated from left ventricular dimensions using Devereux formula:

$$LVM\ (g) = 0.8 * 1.04[(LVIDd + PW + IVS)^3 - (LVIDd)^3] + 0.6\ g)$$

$LVIDd: left\ ventricular\ internal\ diameter\ during\ diastole\ (cm)$

$PW: posterior\ wall\ or\ inferolateral\ wall\ thickness\ (cm)$

$IVS: interventricular\ septum\ thickness\ (cm)$

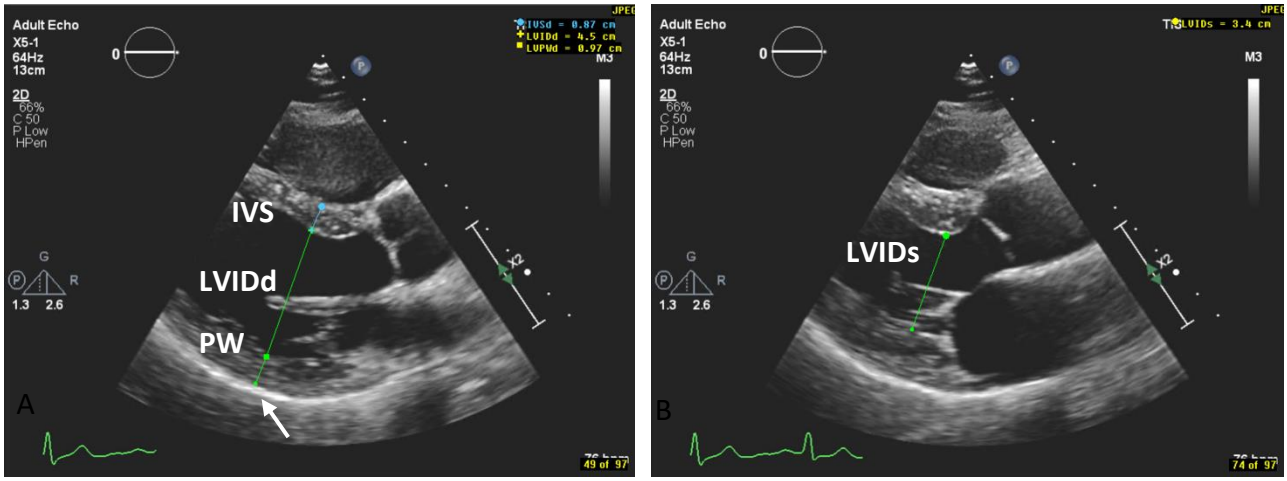


Figure 3.1. Left ventricular linear measurements.

Left ventricular linear dimensions measured from the two-dimensional parasternal long axis view at end diastole (A) and end systole (B). Dimensions were measured perpendicular to the left ventricular long axis starting from the IVS myocardial wall, through the cavity, and to the bright pericardial border (arrow).
IVS, interventricular septum; LVIDd, left ventricular internal diameter diastole; PW, posterior wall or inferolateral wall; LVIDs, left ventricular internal diameter systole.

Biplane left ventricular volume measurements were obtained from apical four- and two-chamber views using the method of disks. End diastolic volume was calculated by tracing the left ventricular endocardial border during end diastole (largest cavity) in both views. At the same cardiac beat, endocardial border tracing was also performed during end systole (smallest cavity) in the two apical views, to allow biplane stroke volume, ejection fraction, and cardiac output calculation. Left ventricular volumetric measurements are illustrated in Figure 3.2.

Left ventricular stroke volume was calculated using the below formula:

$$Stroke\ volume\ (ml) = End\ diastolic\ volume\ (ml) - End\ systolic\ volume\ (ml)$$

Left ventricular ejection fraction was estimated using the biplane modified Simpson's method as follows:

$$Ejection\ fraction\ (\%) = \frac{Stroke\ volume\ (ml)}{End\ diastolic\ volume\ (ml)} * 100$$

Cardiac output was calculated using the following formula:

$$Cardiac\ output\ (ml/minutes) = Stroke\ volume\ (ml) * Heart\ rate\ (beats/minutes)$$

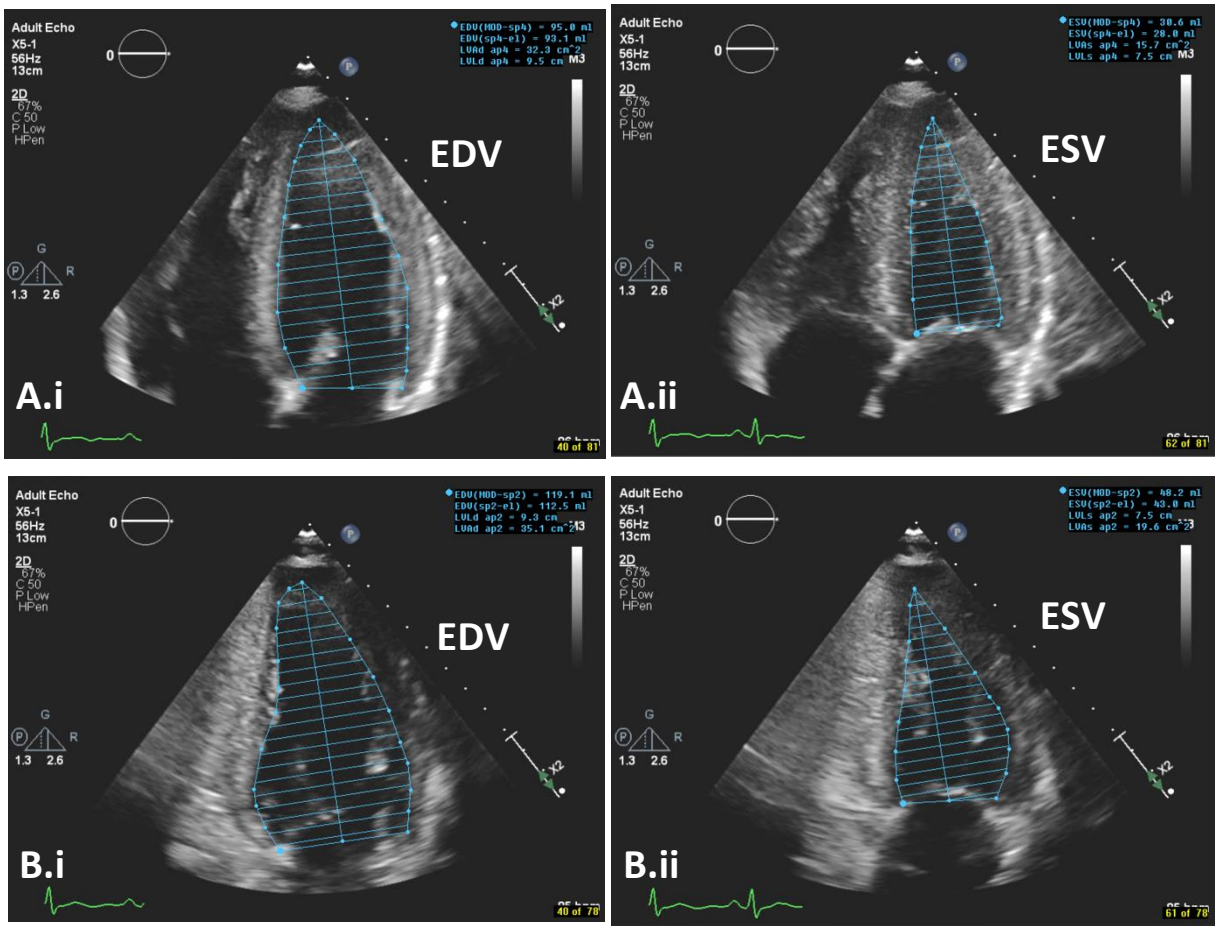


Figure 3.2. Left ventricular volumetric measurements.

Biplane left ventricular volumes were measured from the two-dimensional apical four-chamber (A) and two-chamber views (B) at end diastole (i) and end systole (ii). Left ventricular endocardial borders were traced at the largest and smallest cavities to calculate volumes using modified Simpson's method.
EDV, end diastolic volume; ESV, end systolic volume.

3.5.1.2. Right ventricular assessment

Right ventricular linear dimensions were measured from the apical four-chamber right ventricular focused view. Right ventricular dimensions including the base, mid and length were all measured from the same frame during end diastole. The tricuspid annulus plane systolic excursion (TAPSE) was measured from an M-Mode plane obtained with a cursor aligned parallel with the right ventricular free wall and through the lateral tricuspid annulus. Assessment of the right ventricle is demonstrated in Figure 3.3.

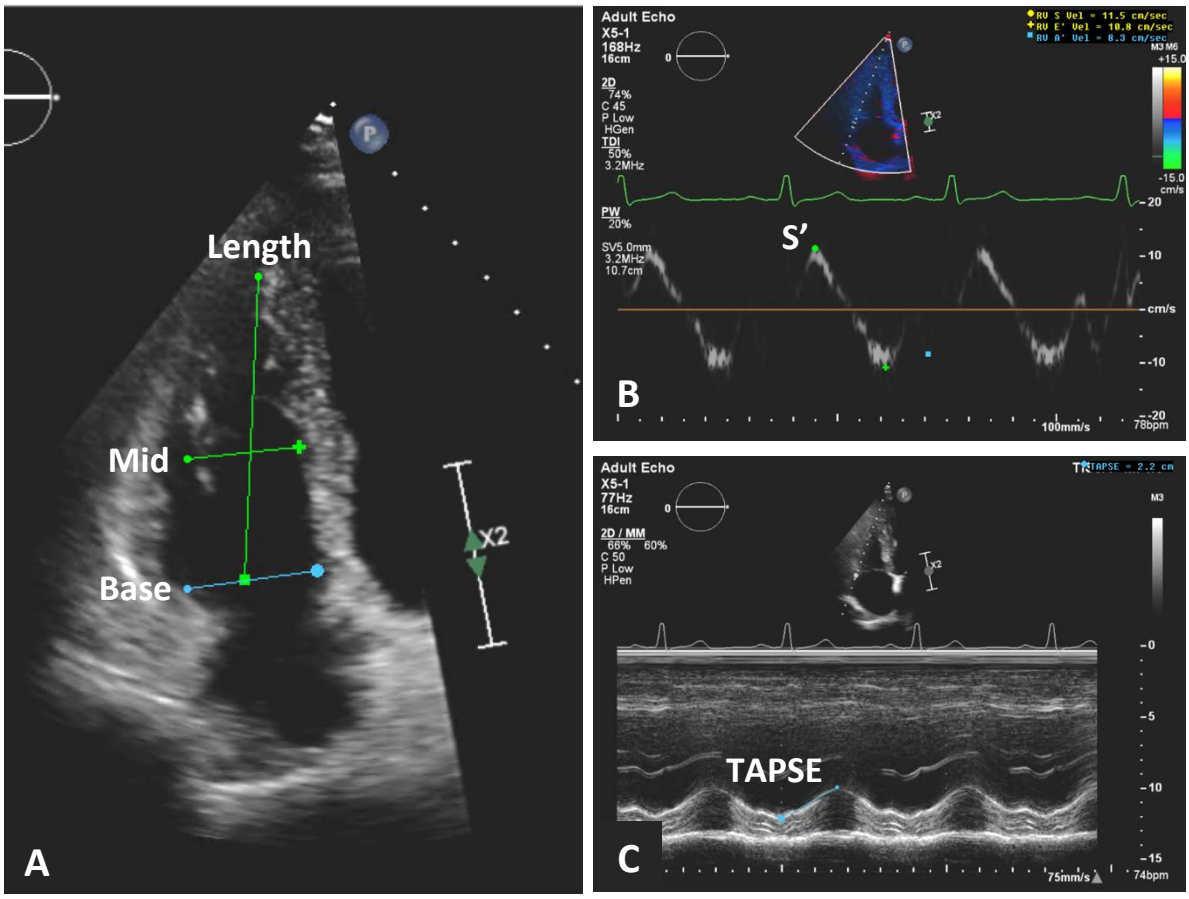


Figure 3.3. Right ventricular assessment.

Right ventricular structure and function were assessed from the right ventricular focused apical four-chamber view. Right ventricular base, mid, and length dimensions were obtained at end diastole from the two-dimensional plane (A). Wall motion velocity during systole S' was measured using tissue Doppler imaging (B). Using M-mode (C), tricuspid annulus plane systolic excursion (TAPSE) was measured as a slope from beginning of systole peaking to end systole.

3.5.1.3. Atrial assessment

Left atrial volume was estimated using the biplane method of disks by tracing the left atrial endocardial border in apical four- and two-chamber views at end systole. The same method was used to estimate right atrial volume, but a single plane measurement was obtained only from the apical four-chamber view. Figure 3.4 illustrates the volume assessment for both atria.

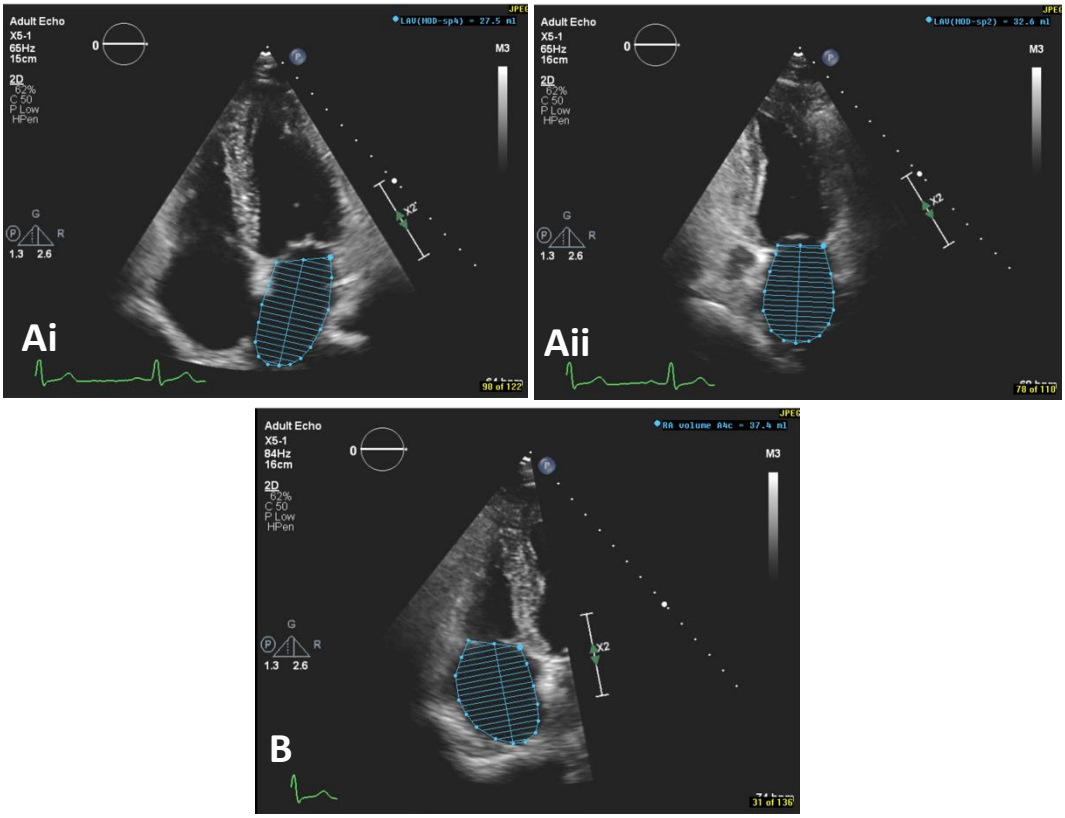


Figure 3.4. Left and right atrial volumes.

Left atrial volume was measured by tracing the endocardial borders of the left atrium at end systole from apical four- (Ai) and two- (Aii) chamber views for the biplane assessment. Right atrial volume was measured using the same method but on a single plane from apical four-chamber view (B).

3.5.2. Cardiac function assessment (Doppler velocities)

Doppler velocities of intracardiac blood and myocardial tissues were obtained and measured following the European Association of Cardiovascular Imaging (EACVI) recent diastolic function [191] and valvular assessment guidelines [192]. From apical four-chamber view, four mm sample volume was positioned at the tip of mitral valve leaflets to obtain a trans-mitral flow trace and E and A velocities were measured at end expiration, and E/A ratio was calculated. At the same view, a smaller sample volume was placed at the lateral and septal mitral annulus considering the best alignment between the ultrasound beam and annular motion. S', E', and A' velocities were measured for both annulus and averaged. The mitral valve E to E' ratio was calculated using lateral, septal, and averaged E' velocity. Right ventricular S' velocity was also measured from apical four-chamber view by placing the sample volume at the lateral tricuspid annulus. Cardiac time intervals such as the isovolumic relaxation time, isovolumic contraction time, and the ejection time were all measured from the septal tissue Doppler trace.

Aortic valve peak velocity was measured from continuous wave Doppler through the valvular flow obtained from apical five chamber view. A pulsed wave Doppler sample volume was placed below the aortic valve to measure the left ventricular outflow tract velocity time integral. Pulmonary valve velocities were also measured from the parasternal short axis view at the level of the great vessels. The peak velocity was measured from the continuous wave Doppler trace, and the acceleration time was estimated from the pulsed wave Doppler trace as the time interval from the onset of the wave to its peak. Tricuspid valve regurgitation velocity was measured when available from parasternal right ventricular inflow

view, parasternal short axis view, and apical four-chamber view using continuous wave Doppler. The highest velocity was considered. Illustrations of Doppler velocities assessment is shown in Figure 3.5.

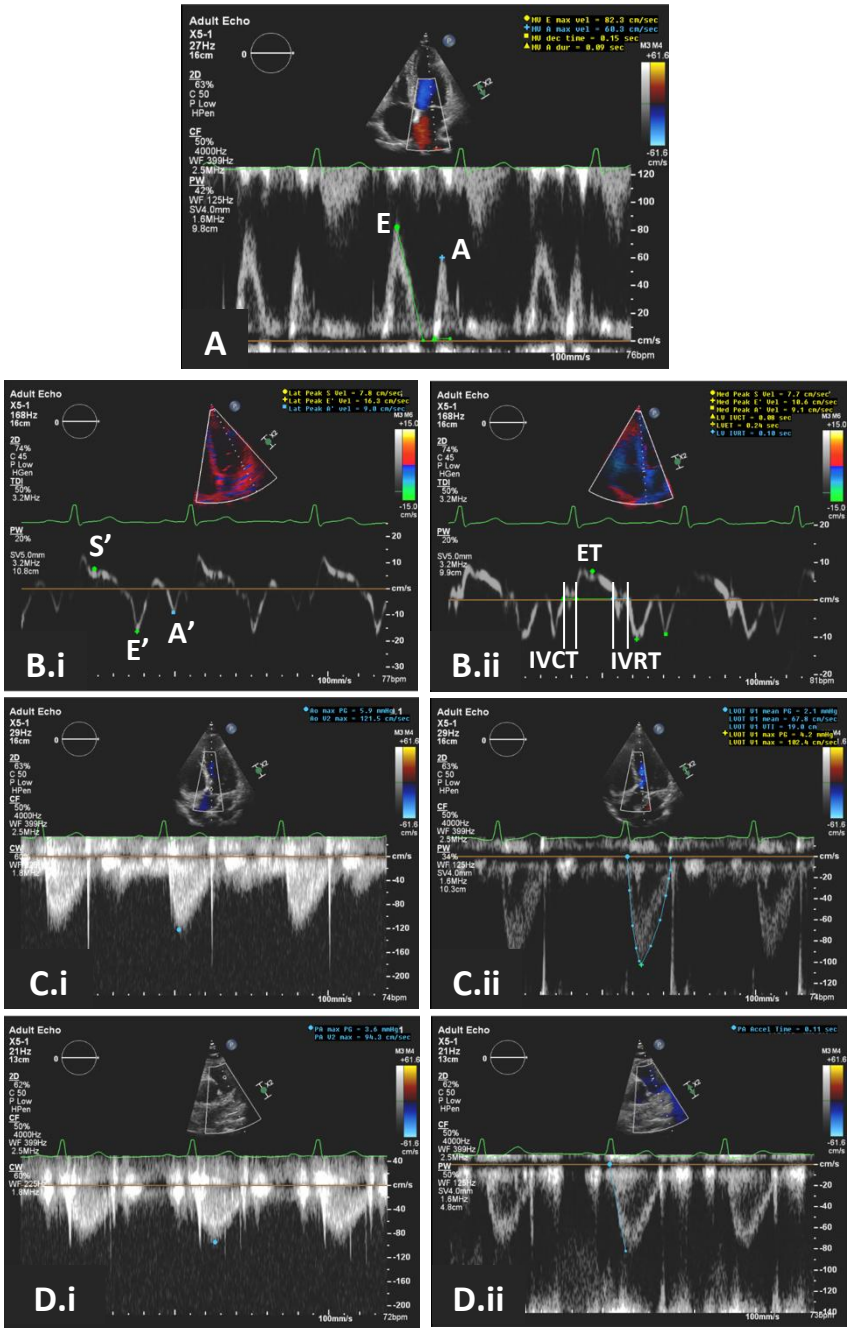


Figure 3.5. Doppler velocities assessment.

By using pulsed wave Doppler, mitral valve inflow was obtained from the apical four-chamber view, and peak E and A velocities were measured as shown in panel (A). Tissue Doppler imaging was applied on the lateral (B.i) and septal (B.ii) walls, and S', E', and A' velocities were measured. From the septal wall trace, time intervals including isovolumetric contraction time (IVCT), ejection time (ET), and isovolumetric relaxation time (IVRT) were calculated. Aortic peak velocity was measured from continuous wave Doppler trace placed through the aortic flow in apical five chamber view (C.i), and the outflow tract velocity time integral was measured from the pulsed wave trace as illustrated in (C.ii). Panel D illustrate pulmonary valve peak velocity (D.i) and pulmonary acceleration time (D.ii).

3.5.3. Cardiac deformation assessment (Speckle tracking analysis)

Focused left ventricular views were obtained from apical four-, two-, and three-chamber views with a similar heart rate and frame rate for the deformation analysis. Speckle tracking analysis of the left ventricle was performed by tracing left ventricular endocardial borders at the end diastole and end systole frames for each view (Figure 3.6). Peak global and segmental longitudinal strain values were obtained for each view separately as well as the global triplane values. The global triplane longitudinal strain was used in this thesis analyses as the left ventricular longitudinal strain.

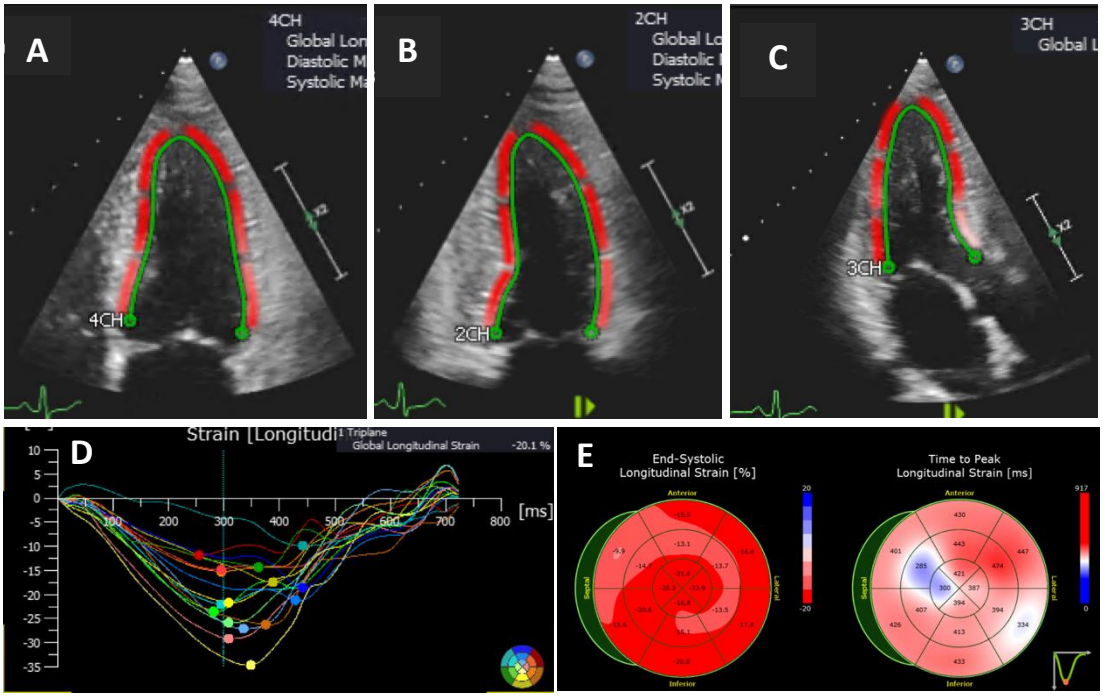


Figure 3.6. Left ventricular longitudinal strain assessment.

Left ventricular longitudinal strain was obtained by tracing the endocardial borders from the apical four- (A), two- (B), and three- (C) chamber views. Segmental and global strain values were recorded as shown in the strain traces in (D) and in the bull's eye plots (E).

Speckle tracking analysis of the left atrium was performed by tracing the endocardial borders in apical four- and two-chamber views to allow for biplane assessment. Measurements from both views were then averaged. Peak atrial longitudinal strain (PALS), peak atrial contraction strain (PACS), and the difference between PALS and PACS were measured (Figure 3.7). These three parameters reflect the left atrial reservoir, booster pump, and conduit function, respectively. Left atrial analysis was performed using TomTec Image Arena 4.6 (Chicago, IL, United States) software with the QRS complex used as a reference point for the measurement in accordance with the latest EACVI recommendations [193].

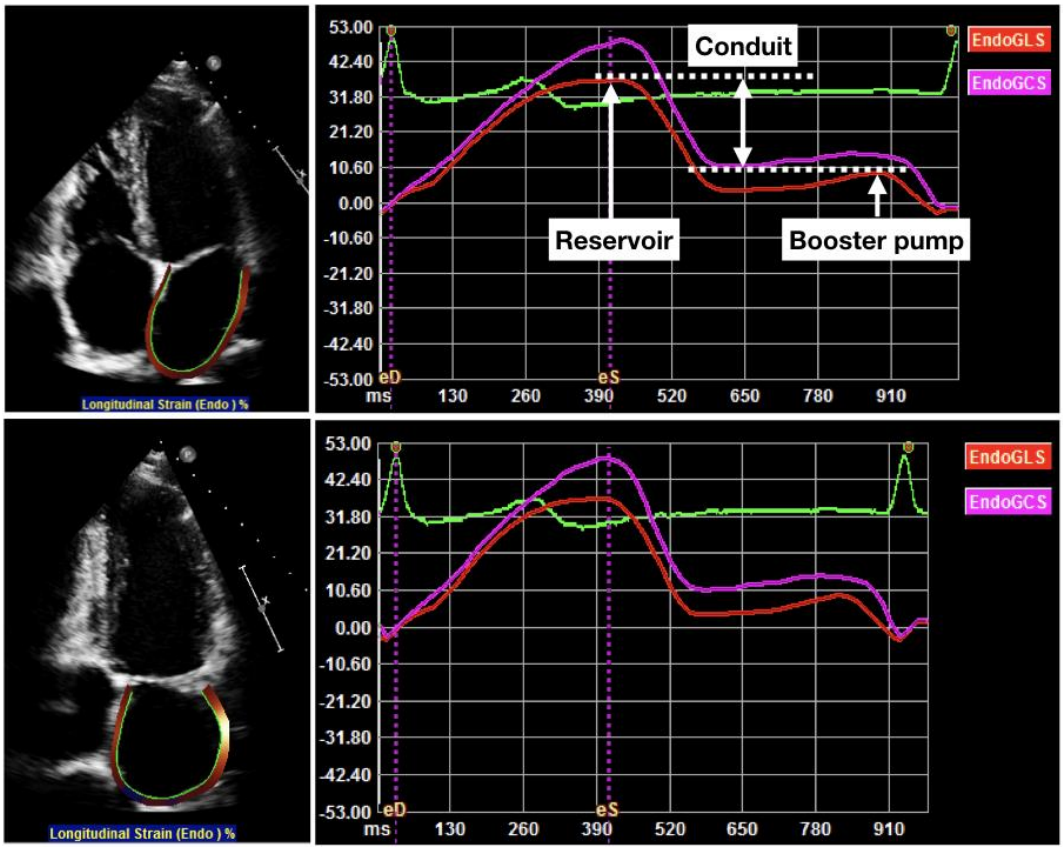


Figure 3.7. Left atrial longitudinal strain assessment.

Left atrial longitudinal strain was obtained by tracing the endocardial borders from the apical four- (A) and two- (B) chamber views. The highest peak after the QRS was identified as peak atrial longitudinal strain (PALS) and represents the reservoir function. The next peak which occurs at the time of the P wave was measured as peak atrial contraction strain (PACS) and reflects the booster pump function. The difference between PALS and PACS was measured to estimate the conduit function. Values were obtained from both views and averaged for biplane measurements.

3.6. Cardiovascular magnetic resonance imaging

Cardiovascular magnetic resonance imaging was performed at rest for YACHT and TEPHRA participants using 3.0-Tesla (3T TIM Trio, Siemens Medical Solutions, Germany). Images were retrospectively ECG gated with a three-lead precordial ECG.

3.6.1. Left ventricular mass and volumes

Left ventricular images were acquired at a steady state free precession (SSFP) during breath hold at end expiration with the following sequence parameters: echo time 1.48 ms, echo spacing 3.4 ms, temporal resolution 47.04 ms, flip angle 50°, slice thickness 8.0 mm, and inter-slice gap 2.0 mm. Image analysis was performed offline using CVI42 (Circle Cardiovascular Imaging Inc., Calgary, Canada). Left ventricular volumes were estimated from the entire short axis stack by manual contouring of endocardial and epicardial borders at end diastole (the largest cavity), and end systole (the smallest cavity) frames. The sum of the ventricular areas in the stack was calculated to estimate left ventricular end diastolic and end systolic volume. The difference between the end diastolic and end systolic volumes was measured as the stroke volume, and the ejection fraction was estimated by dividing the stroke volume by the end diastolic volume. The sum of myocardial area in the stack was multiplied by the specific gravity of myocardium per cm^3 (1.05 g/cm^3) to calculate the left ventricular mass.

3.7. Cardiopulmonary exercise testing (CPET) with stress echocardiography

A peak cardiopulmonary exercise test was completed for YACHT and TEPHRA participants during their baseline study visit. The test was conducted following a validated protocol on a seated stationary cycle ergometer (Ergoline GmbH, Bitz, Germany) with instructions to maintain a rate of 60 rotations per minutes throughout the test. Ventilation variables and respiratory gases were recorded using a computer-based system (Metalyzer 3B, Cortex Biophysik, Leipzig, Germany). Perceived exertion rate was collected every two minutes using the standard Borg scale. Every three minutes, a blood pressure measurement was taken by a manual mercury sphygmomanometer (Accoson Freestyle, Essex, United Kingdom). The test was continuously monitored by a trained investigator, and prior to the procedure participants were encouraged to reach their maximum exercise intensity.

3.7.1. Stress echocardiography

Echocardiography imaging was obtained on the upright cycle position at 40%, 60%, and 80% of peak exercise intensity for YACHT participants, and at 60% of peak intensity for TEPHRA participants. In YACHT, the exercise intensities were identified prior to the stress echocardiography imaging using a CPET. In TEPHRA, timing of image acquisition was planned to coincide with moderate workload based on an exercise heart rate zone coinciding with 60% Heart Rate Reserve, calculated taking into account sex, age and resting heart rate, consistent with guidelines for planning moderate exercise workload training [194]. Precise workload at time of image acquisition was assessed after completion of the stress

echocardiography CPET. Apical four-chamber images were acquired using the same ultrasound machines used for resting echocardiography. Left ventricular ejection fraction was estimated using the method of disks (modified Simpson's method) and the global longitudinal strain was calculated using speckle tracking echocardiography analysis as an average of all left ventricular segments in apical four-chamber view. All measurements were performed offline using ISCV 2.1 (Philips Healthcare Informatics, Belfast, Ireland), and TomTec Image Arena 4.6 (Chicago, IL, United States) software.

3.8. Blood sample collection and biochemistry analysis

Fasting blood samples (8-12 hours fasting) were collected before and after the cardiopulmonary exercise test for YACHT and TEPHRA participants. Sample analysis was carried out at the Oxford John Radcliffe Hospital Biochemistry Laboratory. HyperEcho participants had a single blood sample collection as part of their NHS clinical service during their clinical visit. All participants had glucose levels and lipid profiling including low density lipoprotein (LDL), high density lipoprotein (HDL), total lipoprotein cholesterol, and triglycerides.

3.9. Exercise intervention compliance

Participants who were randomised to the exercise intervention arm in TEPHRA were asked to complete three aerobic training sessions per week, aiming for 60 minutes exercise at 60-80% peak heart rate measured at baseline. Participants were encouraged to attend supervised sessions at the gym offered by the study team at Brookes Sport for

16 weeks. Remote exercise intervention was also considered for participants from outside Oxford. Participants were provided with a wrist-worn heart rate and activity monitor (Fitbit Charge HR) and encouraged to wear daily with a goal of 10,000 steps per day. On completion of 16 weeks of training, participants received a 60-minute motivational coaching session. The coaching session explored confidence and motivation to maintain regular physical activity and encouraged participants to identify personalised strategies to achieve their goals and maintain cardiovascular fitness until 52-week follow-up. To track physical activity in the intervention group, records were kept of sessions attended and activity from the wrist-worn activity monitor tracked using the Fitabase data management platform (Fitabase, San Diego, USA). Participants in the control group were sign-posted to educational materials produced by the British Heart Foundation explaining hypertension, hypertension prevention and recommended lifestyle behaviours to maintain heart health. The target intervention exposure was three aerobic sessions per week, completed on separate days, for 16 weeks, with a compliance threshold set at 80%; equivalent to ≥ 39 independent aerobic exposures with no greater than two weeks between exposures. The intervention compliance was assessed using the following protocols:

- **Compliance per Protocol 1:** 80% attendance at supervised sessions.
- **Compliance per Protocol 2:** 80% attendance at supervised sessions merged with the number of active days.
- **High Dose Exposure in 16 weeks:** 80% attendance at supervised sessions, or MVPA-VPA greater than three hours per week (if evidence of wear time five times per week), or 10,000 steps per day every day averaged over wear time (if evidence of wear time five times per week).

- **Maintained Dose Exposure up to 52 weeks:** Evidence that maintained activity between 16 and 52 weeks, wear time greater than three hours per week, and steps average 8,000 or greater than 150 minutes MVPA per day.

3.10. Calculation of lifetime risk of cardiovascular disease

Cardiovascular risk score was calculated for all YACHT and TEPHRA participants based on eight modifiable risk factors (one point awarded to the healthier category for each factor) following the below criteria:

1. Body mass index less than 25 kg/m^2.
2. Highest tertile of cardiovascular fitness and/or physical activity.
3. Alcohol consumption of less than eight drinks per week.
4. Non-smoker for more than six months.
5. Blood pressure on awake ambulatory monitoring lower than 130/80 mmHg.
6. A non-hypertensive diastolic response to exercise (peak diastolic blood pressure less than 90 mmHg).
7. Total cholesterol level lower than 200 mg/dL.
8. Fasting glucose level lower than 100 mg/dL.

This score criteria were adapted from established cardiovascular risk scores to include dynamic exercise blood pressure response [195].

3.11. Statistical analysis

Statistical analysis was performed using R software Version (4.0.2). Shapiro-Wilk test and visual assessment were used to assess for normality. Comparison between two groups for continuous variables was performed using two-sided, independent samples Student t-tests for normally distributed data and Mann-Whitney for non-normally distributed data. For categorical variables, comparison between two groups was performed using Chi-squared test. Results are reported as mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. Pearson correlation analysis was performed to identify relevant relationships between resting echocardiography parameters and cardiovascular response to physical exercise. Multivariable linear regression modelling was then carried out to study continuous associations between resting echocardiography phenotypes and both during exercise and post exercise intervention measurements adjusted for potential covariables such as, age, sex, body mass index, and mean arterial blood pressure [196-198]. A p value of ≤ 0.05 and a 95% confidence interval not crossing zero were used to determine statistical significance.

The disease progression model development was performed using MATLAB R2019b programming environment (Mathworks Inc., Natick, MA, USA) by applying a contrastive Principal Component Analysis (cPCA) algorithm, a non-linear semi-supervised machine learning tool. This tool identifies low-dimensional unique patterns in the target group relative to the background group and generate unique pseudotimes scores to order participants from zero to one. Details about the model development and testing its validity and stability are described in the statistical analysis section in Chapter 6, section 6.3.3.

4. IMPAIRED CARDIAC RESPONSE TO PHYSICAL EXERCISE USING ECHOCARDIOGRAPHY IN YOUNG ADULTS WITH SUBOPTIMAL BLOOD PRESSURE

4.1. ABSTRACT

Aims: Young adults with elevated blood pressure have a heterogenous response to exercise interventions. Presence of subclinical cardiac remodelling might be an underlying mechanism accounting for the heterogenous response. In this chapter, I aimed to investigate the left ventricular function at rest and during physical exercise in young adults with suboptimal blood pressure.

Methods: One hundred and twenty-seven young adults aged 18 to 40 years who had undergone detailed clinical and cardiovascular phenotyping, including blood pressure measurements, resting echocardiography, and cardiopulmonary exercise testing combined with echocardiography were included in this analysis. Left ventricular ejection fraction (LVEF) and global longitudinal strain during exercise were measured from an apical four-chamber view. Cardiac measures at rest and myocardial response during moderate physical exercise were compared between participants with suboptimal blood pressure ≥ 120/80mmHg (n=68) and those with optimal blood pressure < 120/80mmHg (n=59) using independent samples Student t-tests.

Results: Participants with suboptimal blood pressure had higher left ventricular mass (p=0.031) and reduced mitral valve E velocity (p=0.02) compared to those with optimal blood pressure. During exercise, the suboptimal blood pressure group had higher left ventricular end diastolic and systolic volumes (p=0.001, and p=0.001 respectively) and reduced LVEF (p=0.001) compared to the optimal blood pressure group.

Conclusion: Young adults with suboptimal blood pressure demonstrate a reduction in their submaximal LVEF during physical exercise. Reduced LVEF response may influence workload perception during exercise, which could adversely influence training adherence in young adults with hypertension.

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4.2. INTRODUCTION

Higher risk of stroke and cardiovascular disease have shown to be associated with poor control of blood pressure levels in young hypertensives [4, 199]. Although exercise interventions to manage blood pressure are promoted, there have been no studies to demonstrate they are effective in lowering blood pressure early during young adulthood [10]. Recent studies reported that the degree of successful blood pressure control in young hypertensives with exercise interventions varies [200], and long-term benefits are often not sustained [46]. At the same time, there is limited evidence to support routine use of anti-hypertensive medication in all young adults with hypertension and, indeed, long-term medication may carry risks [11, 201]. Therefore, the guidelines recommend additional biomarkers, specifically left ventricular hypertrophy (LVH) or evidence of end-organ damage, to risk stratify patients for treatment [10, 11]. LVH and fibrosis in hypertension develop as a result of an increase in left ventricular afterload and wall stress, with sustained elevation of blood pressure over years [34, 202]. However, the relatively shorter duration of disease exposure in younger hypertensives means that the gross changes in left ventricular morphology required to reach criteria for diagnosis of LVH are not often observed [33, 147]. Whether alternative biomarkers of clinically relevant remodelling are present in younger hypertensives remains unclear.

Introducing physiological stress has been used clinically to elicit subclinical signs of cardiac remodelling [103, 194]. Prior studies reported that an abnormal response of left ventricular systolic function during physical exercise [34, 147, 202] reflects as a consequential functional impact of myocardial fibrosis and increased left ventricular loading in hypertension [10, 11, 201]. This finding has been observed in older patients with hypertension and symptoms of chest pain [33]. Although this

abnormal response was initially believed to be due to coexisting coronary artery disease [33], it was also found in older asymptomatic patients with moderate hypertension and no evidence of coronary artery disease [147]. Whether similar response of left ventricular systolic dysfunction during exercise can be found in young adults with hypertension is unknown. In this chapter, I hypothesised that young adults with suboptimal blood pressure (≥ 120/80 mmHg) have reduced left ventricular ejection fraction in response to physical exercise compared to normotensives.

4.3. METHODS

4.3.1. Study population

This chapter includes young participants aged between 18 to 40 years old, who underwent detailed assessment of blood pressure measures, resting echocardiography imaging, and cardiopulmonary exercise testing combined with stress echocardiography imaging. Details of this cohort and how participants were recruited are provided in Chapter 2, section 2.6.1. Participants with inadequate echocardiographic image quality during exercise, and those on antihypertensive medication were excluded.

4.3.2. Study measures

All participants completed the following cardiovascular assessments, which are described in detail in Chapter 3 (Methods and materials):

- Anthropometry (section 3.2).
- Blood pressure profiles (section 3.3).
- Physical activity monitoring (section 3.4.2).
- Echocardiography imaging (section 3.5).
    - Cardiac structure assessment (2D echocardiography)
        - Left ventricular assessment
        - Right ventricular assessment
        - Atrial assessment
    - Cardiac function assessment (Doppler velocities)
    - Cardiac deformation assessment (speckle tracking echocardiography)

- Cardiopulmonary exercise testing (CPET) (section 3.7).
    - Stress echocardiography

4.3.3. Statistical analysis

To examine blood pressure-related differences, participants were classified in a suboptimal blood pressure group (systolic and/or diastolic blood pressure ≥ 120/80 mmHg) and compared to an age, sex, and frequency-matched optimal blood pressure group (systolic and/or diastolic blood pressure < 120/80 mmHg). Statistical analyses were performed using R software Version (4.0.2). Shapiro-Wilk test and visual assessment were used to assess for normality. Comparisons between-group were performed using independent samples Student t-tests for normally distributed data and Mann-Whitney and Kruskal-Wallis tests for non-normally distributed data. Intraclass correlation coefficient analysis was performed to test the inter- and intra- operator variability for the left ventricular parameters during exercise in which the parameters were re-assessed twice for ten randomly selected scans. First by a second operator, and then the same parameters were measured again by the first operator. A *p*-value of ≤0.05 was used to indicate statistical significance.

The sample size was calculated based on a previously reported standard deviation of left ventricular ejection fraction (8.6%) during exercise in young adults [150]. A sample size of 100 participants, with 50 participants in each group, allowed a 5% difference in ejection fraction to be identified between groups with 85% power at alpha = 0.05. As this was a retrospective study, all participants who met the inclusion criteria were included.

4.4. RESULTS

4.4.1. Baseline clinical characteristics

One hundred and twenty-seven young adults (59 with optimal blood pressure and 68 with suboptimal blood pressure) who fulfilled the selection criteria were identified. Participants on antihypertensive medication (n=6), and those with inadequate echocardiographic image quality during exercise (n=19) were excluded. Resting brachial systolic and diastolic clinic blood pressure were 130 ± 9 mmHg and 79 ± 9 mmHg in the suboptimal blood pressure group, and in the optimal blood pressure group 113 ± 9 mmHg and 67 ± 6 mmHg. The daily physical activity levels were similar in both groups. Baseline clinical characteristics are provided in Table 4.1.

Table 4.1. Baseline clinical characteristics

	Optimal BP n=59	**Suboptimal BP n=68**	**P value**
Age	25.61 ± 4.3	26.56 ± 4.6	0.241
Male n (%)	28 (47.5)	38 (55.9)	0.086
Height (cm)	173.04 ± 8.9	172.5 ± 9.4	0.776
Weight (kg)	69.9 ± 10.6	72.6 ± 10.2	0.152
Body mass index (kg/m^2)	23.28 ± 2.48	24.42 ± 3.4	0.036
Body surface area (m^2)	1.83 ± 0.17	1.86 ± 0.16	0.290
Systolic blood pressure (mmHg)	113.6 ± 8.8	130.6 ± 8.8	**<0.0001**
Diastolic blood pressure (mmHg)	67.3 ± 5.8	79.3 ± 9.2	**<0.0001**
Mean arterial blood pressure (mmHg)	82.7 ± 4.4	96.4 ± 8.2	**<0.0001**
VPA (hour/week)	0.8 ± 1.1	0.7 ± 1.1	0.417

Data are expressed as mean ± standard deviation, and percentages (%) were appropriate.
BP, blood pressure; MVPA, moderate vigorous physical activity; VPA, vigorous physical activity.

4.4.2. Resting echocardiography

Echocardiography results at rest are presented in Table 4.2. Resting echocardiography measures demonstrated similar left ventricular dimensions, volumes, and ejection fractions between groups, but greater left ventricular mass index in those with suboptimal blood pressure (70.2 ± 14.5 g/m^2) compared to those with optimal blood pressure (64.06 ± 14.8 g/m^2, p=0.021). However, no participants exceeded clinical thresholds for left ventricular hypertrophy (115 g/m^2 in males, 95 g/m^2 females) [110]. In addition, in the suboptimal blood pressure group, mean mitral valve E wave velocity was lower (p=0.02) compared to the optimal blood pressure group. Left ventricular global longitudinal strain was similar between groups.

Table 4.2. Resting echocardiography parameters

	Optimal BP n=59	Suboptimal BP n=68	P value
RESTING LEFT VENTRICULAR STRUCTURE			
Heart rate (bpm)	59.4 ± 10.2	63.4 ± 11.8	0.050
Interventricular septum (cm)	0.86 ± 0.15	0.82 ± 0.17	0.185
LV internal dimension diastole (cm)	4.76 ± 0.46	4.76 ± 0.4	0.979
Posterior wall thickness (cm)	0.86 ± 0.16	0.89 ± 0.14	0.236
LV internal dimension systole (cm)	3.16 ± 0.39	3.18 ± 0.38	0.721
LV mass (g)	118.5 ± 33.2	131.4 ± 32.2	**0.031**
LV mass index (g/m^2)	64.06 ± 14.8	70.2 ± 14.5	**0.021**
Relative wall thickness	0.36 ± 0.06	0.38 ± 0.06	0.240
LV biplane end diastolic volume (ml)	99.3 ± 25.8	100.6 ± 23.7	0.767
LV biplane end systolic volume (ml)	53.9 ± 11.6	53.7 ± 10.3	0.898
RESTING LEFT VENTRICULAR FUNCTION			
LV biplane ejection fraction (%)	63.1 ± 4.9	63.1 ± 5.08	0.946
LV stroke volume (ml)	61.47 ± 15.2	63.52 ± 15.4	0.455
Cardiac output (L/min)	3.61 ± 9.8	4.006 ± 1.04	**0.034**
LV global longitudinal strain (%)	-21.4 ± 3.04	-21.25 ± 2.4	0.737
Mitral valve E velocity (cm/s)	85.1 ± 15.6	78.6 ± 14.09	**0.020**
Mitral valve A velocity (cm/s)	48.3 ± 12.2	48.6 ± 11.3	0.918
Average E' velocity (cm/s)	14.6 ± 2.3	13.9 ± 2.5	0.092
RESTING LEFT ATRIAL STRUCTURE			
LA volume (ml)	36.6 ± 10.1	38.4 ± 11.5	0.342
LA volume index (ml/m^2)	20.07 ± 5.3	20.6 ± 5.8	0.562
RESTING RIGHT VENTRICULAR FUNCTION			
TAPSE (cm)	2.2 ± 0.36	2.1 ± 0.32	0.702
RV S' velocity (cm/s)	12.4 ± 2.06	12.7 ± 1.5	0.380

Data are expressed as mean ± standard deviation.
BP, blood pressure; LV, left ventricle; LA, left atrium; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle

4.4.3. Physical exercise blood pressure, echocardiography, and fitness

Between group comparisons of blood pressure levels, echocardiographic characteristics, and respiratory measures during moderate exercise load are presented in Table 4.3. Mean left ventricular ejection fraction was reduced in participants with suboptimal blood pressure compared to participants with optimal blood pressure (p=0.001) during moderate exercise. The ejection fraction was reduced in the suboptimal group throughout the exercise test, when measured at 40%, 60%, and 80% of peak exercise intensity (Figure 4.1), despite no between group differences in ejection fraction at rest. Differences in left ventricular ejection fraction during moderate exercise intensity compared with resting measures are shown in Figure 4.2. Greater left ventricular end diastolic and systolic volumes were also found (p=0.001, and p=0.001, respectively) in those with suboptimal blood pressure. There was no between-group difference in left ventricular deformation during physical exercise. Peak VO2 and ventilatory anaerobic threshold (VAT) were similar between groups. Inter-operator agreement coefficients for left ventricular end diastolic volume, end systolic volume and ejection fraction were 0.999, 0.996, and 0.984, respectively, while the intra-operator agreement coefficients for the same parameters were 1, 0.999, and 0.996, respectively.

Table 4.3. Clinical and echocardiography parameters during moderate exercise intensity

	Optimal BP n=59	Suboptimal BP n=68	*P* value
EXERCISE MEASURES			
Exercise intensity (%)	57.5 ± 10.2	57.9 ± 8.2	0.793
Systolic blood pressure (mmHg)	151.2 ± 16.9	166.7 ± 22.3	**<0.0001**
Diastolic blood pressure (mmHg)	77.04 ± 9.5	79.1 ± 14.9	0.401
Mean arterial blood pressure (mmHg)	101.8 ± 9.6	108.3 ± 12.05	**0.003**
EXERCISE CARDIAC FUNCTION			
Heart rate (bpm)	144.3 ± 11.8	146.9 ± 9.3	0.209
LV ejection fraction (%)	77.6 ± 4.1	74.4 ± 5.2	**0.001**
LV end diastolic volume (ml)	64.8 ± 26.07	80.8 ± 23.7	**0.001**
LV end diastolic volume index (ml/m^2)	35.7 ± 14.07	43.1 ± 11.2	**0.003**
LV end systolic volume (ml)	16.5 ± 6.9	21.3 ± 7.2	**0.001**
LV end systolic volume index (ml/m^2)	9.11 ± 3.7	11.3 ± 3.6	**0.002**
LV global longitudinal strain (%)	-23.9 ± 1.9	-23.8 ± 2.6	0.867
EXERCISE RESPIRATORY FUNCTION			
Peak VO2 (ml/min/kg)	38.5 ± 8.6	37.4 ± 8.8	0.481
VAT (ml/min/kg)	22.1 ± 6.04	20.8 ± 6.6	0.235
VE/VCO2 $_{Peak}$	31.6 ± 5.1	31.6 ± 4.9	0.941
RER $_{Peak}$	1.2 ± 0.07	1.2 ± 0.06	0.545
RPE $_{VAT}$	10.9 ± 2.6	10.6 ± 2.6	0.563

Data are expressed as mean ± standard deviation.
BP, blood pressure; LV, left ventricle; bpm, beat per minute; VAT, ventilatory anaerobic threshold; VE/VCO2, ventilatory equivalent of carbon dioxide; RER, respiratory exchange ratio; RPE, rate of perceived exertion

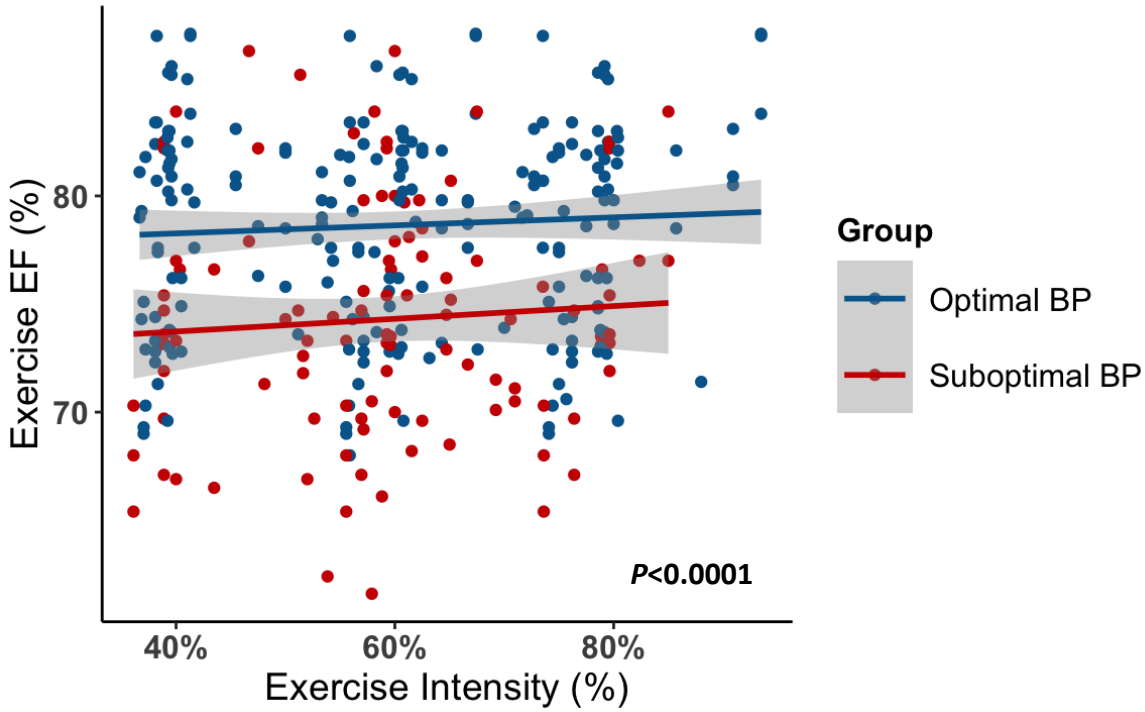

Figure 4.1. Left ventricular ejection fraction measured at 40%, 60%, and 80% of the peak exercise intensity.

Left ventricular ejection fraction throughout the exercise test measured at 40%, 60%, and 80% of peak exercise intensity and its difference between participants with suboptimal (red) and optimal (blue) blood pressure levels. The ejection fraction measures were consistently reduced at 40%, 60%, and 80% of peak exercise intensity in participants with suboptimal blood pressure compared to those in the optimal blood pressure group.

BP, blood pressure.

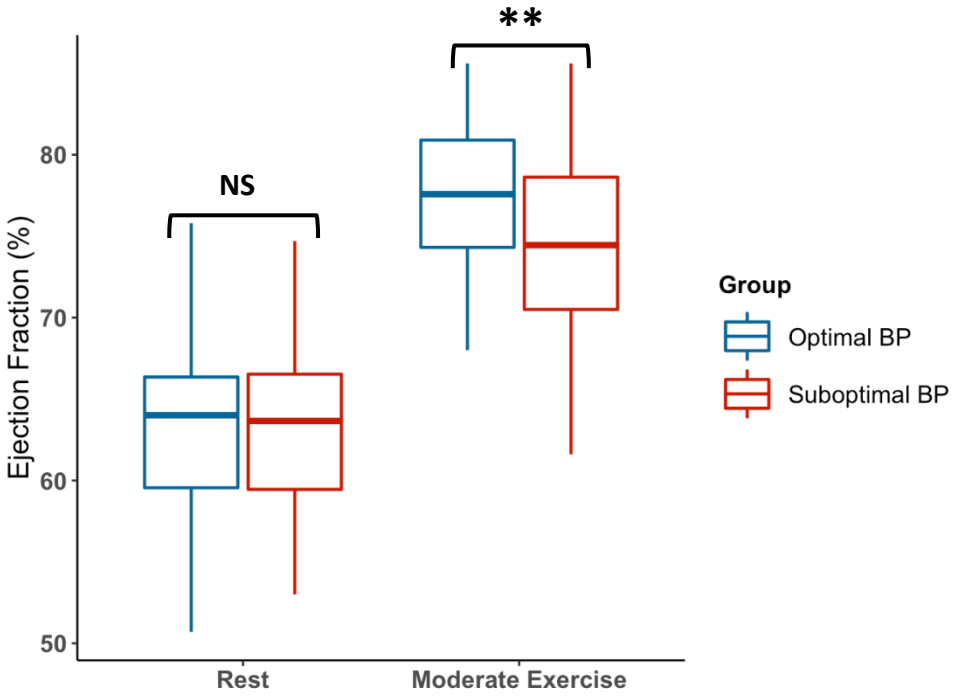

Figure 4.2. A comparison of the left ventricular ejection fraction measured at rest and moderate exercise between the suboptimal and optimal blood pressure groups.

Differences in left ventricular ejection fraction during moderate exercise load between participants with suboptimal and optimal blood pressure levels. Mean left ventricular ejection fraction was similar between groups at rest, but during moderate exercise intensity, participants with suboptimal blood pressure (red) had lower ejection fraction response than the optimal blood pressure group (blue) (p=0.001).

BP, blood pressure

****** Denotes $p < 0.01$

^{NS} Denotes $p > 0.05$

4.5. DISCUSSION AND CONCLUSION

In this chapter, we investigated the left ventricular response during moderate physical exercise and how it differs between young adults with optimal and suboptimal blood pressure. Although there was no significant difference in left ventricular ejection fraction at rest, participants with suboptimal blood pressure (≥ 120/80 mmHg) had lower left ventricular ejection fraction during moderate physical exercise when compared to those with optimal blood pressure (< 120/80 mmHg). In addition, the suboptimal blood pressure group had higher left ventricular volumes compared with the optimal blood pressure group during exercise.

Previous studies reported that abnormal left ventricular performance to physical exercise was found in symptomatic older patients with hypertension [34, 147, 149]. Exercise induced systolic dysfunction was associated with the presence of coronary artery disease or left ventricular concentric hypertrophy [33, 34]. However, reduced left ventricular ejection fraction in response to physical exercise was also found in asymptomatic older hypertensive patients with mild to moderate hypertension and no evidence of existing ventricular hypertrophy or cardiac disease [147, 148]. Miller et al. demonstrated that when compared to normotensives, hypertensive patients who had lower left ventricular ejection fraction response, also had greater end systolic volume during exercise [147]. The results in this chapter extend these findings to a younger cohort, with lower average levels of clinical blood pressure, suggesting this change in the left ventricle in response to physical exercise may be an early indicator of heart failure in individuals with raised blood pressure.

In the course of hypertension, increased blood pressure leads to a hyperkinetic state of ventricular systolic function, as a result of the compensatory hypertrophy at rest, progressing further to ventricular failure when remained uncontrolled [203]. With the

chronic increase in afterload, left ventricular function at rest may appear normal, while the ventricular reserve is limited during exercise [33, 203]. The inability to increase left ventricular ejection fraction during exercise could be a forewarning sign of a decompensation state [33]. A blunted ejection fraction response during exercise may occur due to abnormal coronary reserve, left ventricular hypertrophy, impaired intrinsic myocardial contractility, or increased peripheral vascular resistance [203-206], but this seems unlikely in asymptomatic young hypertensives. Previous studies showed that exercise-induced systolic dysfunction was marked in older patients with chronic hypertension [34, 147]. This finding was associated with impaired fractional shortening in hypertensive patients which could predict mortality and morbidity independent of the presence of left ventricular hypertrophy, age, and blood pressure [151]. Further studies are needed to determine whether this reduced left ventricular performance during exercise can be reverted by anti-hypertensive medication.

In the suboptimal blood pressure group in this cohort, the mean left ventricular ejection fraction during exercise (74 ± 5%) is relatively high compared to what was reported in prior studies. The findings from previous studies were established from older populations with a mean age around 50 years [33, 34, 147, 148] and it is known that left ventricular ejection fraction could be influenced by age. Younis et al., demonstrated the effect of age on left ventricular response during upright physical exercise, and found that exercise ejection fraction reduces with age [207]. The young men group (mean age 23 ± 2) included in their study had a mean ejection fraction of 80 ± 4% during exercise which is consistent with my findings [207]. Further, a recent study in young adults with a history of preterm birth and had higher systolic and diastolic blood pressure compared to a matched control group (term born adults), also had impaired left ventricular function in response to upright exercise [150]. The mean ejection fraction during exercise

for those with high blood pressure was reported at 71.9 ± 8.7 % at 60% of peak exercise intensity [150]. Authors suggested that this impaired ventricular response to exercise could explain the increased risk of heart failure in those with a history of preterm birth [150]. Whether life-style modification and exercise interventions can beneficially alter cardiac function and morphology remain unknown and require further research.

According to the European and NICE hypertension management guidelines, patients below the age of 40 years with stage I hypertension and no evidence of end-organ damage (i.e., left ventricular hypertrophy), exercise intervention and life-style modification should be the first line of treatment [10, 12]. A recent meta-analysis reported that supervised exercise interventions are effective in lowering blood pressure levels, but there is insufficient data about the long-term benefits in younger patients [46]. A heterogenous response to exercise interventions in controlling blood pressure was observed in young adults which could be due to the level of exercise intensity and adherence, or subclinical cardiac remodelling [46]. The reduction in left ventricular ejection fraction during exercise could influence the workload perception and therefore, adversely influence the training adherence. The findings of this chapter provide an insight of an early sign of cardiac remodelling from the earliest stages of hypertension. Thus, early identification of the reduced left ventricular response to physical exercise may help personalise the clinically prescribed exercise interventions for longer sustained benefit.

4.5.1. Study limitations

Firstly, this work is a case-control study using retrospective data to understand pathophysiological mechanisms. Although participant selection was not dependent on the echocardiographic parameters, repeated studies in clinical

populations are required to replicate the results. Secondly, a relatively large number of participants were excluded from the analysis because the frame rates required for assessment of left ventricular ejection fraction and global longitudinal strain could not always be acquired due to the increase in heart and breathing rate during moderate exercise. This potentially could bias the study population to those with higher levels of fitness (with relatively lower heart rate and breathing rate during moderate exercise workload), which might lead to an underestimation in differences between groups. Finally, resting echocardiography images were performed in the lateral decubitus position, while the exercise images were obtained on the upright cycle position. The upright cycle ergometry method was selected for the stress echocardiography to minimise torso movement during image acquisition. However, this means a comparison between baseline and exercise left ventricular measures may not be accurate and could be confound by the change in posture [208].

4.5.2. Conclusion

This chapter shows that young adults with suboptimal blood pressure have physiological differences in their submaximal left ventricular ejection fraction response to physical exercise compared to normotensive peers. Whether this abnormal left ventricular response to physical exercise is associated with subclinical cardiovascular remodelling at rest is unknown.

5. PREDICTION OF IMPAIRED CARDIOVASCULAR RESPONSE TO PHYSICAL EXERCISE FROM RESTING ECHOCRDIOGRAPHY IMAGING IN YOUNG ADULTS WITH SUBOPTIMAL BLOOD PRESSURE

5.1. ABSTRACT

Aims: To investigate whether the reduced left ventricular response during physical exercise in young adults with suboptimal blood pressure (≥ 120/80mmHg) can be predicted from changes in left atrial function at rest.

Methods: One hundred and twenty-seven adults aged 18 to 40 years who completed clinical blood pressure measurements, resting echocardiography, and cardiopulmonary exercise testing combined with echocardiography, were included in this analysis. Left atrial phasic function was measured by conventional and speckle tracking echocardiography from baseline apical four- and two-chamber views and compared between participants with suboptimal systolic or diastolic blood pressure ≥ 120/80mmHg (n=68) and optimal blood pressure < 120/80mmHg (n=59) using independent samples Student t-tests. Multivariable linear regression modelling was performed to study the continuous association between resting echocardiographic features and left ventricular volumes and ejection fraction in response to exercise adjusted for potential confounders. The sensitivity and specificity were also calculated at multiple cut-off values.

Results: Resting left ventricular mass and left atrial contraction strain were correlated with left ventricular ejection fraction during exercise (r=-0.21, p=0.028, and r=0.25, p=0.009, respectively). When adjusted for age, sex, body mass index and mean arterial pressure in the regression model, left atrial booster pump function at rest was the only predictor of left ventricular ejection fraction (β=0.29, p=0.011) during exercise. The sensitivity and specificity of the prediction model, using a cut-off value at 9% for left atrial pump strain at rest and 75% for left ventricular ejection fraction during exercise, were calculated at 64.5% and 71.4%, respectively.

Conclusion: Reduced left ventricular systolic function during exercise in young adults with suboptimal blood pressure can be predicted by their left atrial booster pump function at rest. Echocardiographic measures of left atrial function may provide an early marker of functionally relevant, subclinical, cardiac remodelling in young adults with hypertension.

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5.2. INTRODUCTION

Young adults with sustained elevation in blood pressure are at increased risk of cardiovascular disease and stroke in later life [4-6]. Due to the relatively shorter exposure of hypertension in younger patients, signs of end organ damage and other risk stratification biomarkers are often not observed. Therefore, young patients remain untreated and the opportunity to intervene early in the disease process is missed. In the previous chapter, I found that young adults with suboptimal blood pressure (≥ 120/80 mmHg) had a reduced left ventricular ejection fraction during moderate physical exercise (60% of peak exercise intensity). Exercise induced systolic dysfunction has also been found in older hypertensives [33, 34, 147] , in whom it was associated with underlying diastolic filling abnormalities [149].

Subclinical alterations of left ventricular diastolic mechanics could be explained by associated left atrial remodelling and resulting changes in phasic function [209, 210]. Changes in left atrial structure and function in response to blood pressure elevation are closely linked to left ventricular remodelling [77-79]. Left atrial booster pump phase, in particular, contributes to left ventricular filling by 25% [93, 94], and is known to vary with left ventricular compliance and end diastolic pressure [89, 92, 210]. Using speckle tracking echocardiography, left atrial phasic function has been shown to be altered in older hypertensive patients [88, 98], even before the presence of ventricular structural abnormalities [99]. Recent studies have reported that left atrial strain indices may provide additional information in the assessment of diastolic function beyond traditional measures such as the E/e' ratio [85, 211, 212]. Measuring the E velocity through the mitral valve inflow, or the e' velocity which represents the annular tissue velocity at a single sample volume [191], may not reflect the intrinsic left atrial properties and stiffness. Therefore, estimating left atrial

reservoir, conduit, and booster pump function using peak and contraction longitudinal strain have shown to provide incremental assessment of early left atrial remodelling [99] particularly in patients with hypertension [209, 212].

Exercise testing may not be always feasible, predicting the adverse left ventricular response during exercise from resting echocardiography parameters could help to identify an early diagnostic biomarker in young adults. I hypothesised that abnormal left ventricular-atrial coupling becomes evident early in the development of hypertension and is therefore identifiable in young adults with advancing hypertensive disease [151]. In the previous chapter, I showed that the left ventricular response during exercise was reduced in young participants with suboptimal blood pressure. In this chapter, I tested whether this response can be predicted by changes in left atrial function at rest.

5.3. METHODS

5.3.1. Study population

The study cohort selected for this chapter is the same cohort studied in the previous chapter. Detailed description is available in Chapter 4, section 4.3.1. Study population.

5.3.2. Study measures

The same study measures described in Chapter 4 (section 4.3.2. Study measures) were used in this chapter. In addition to these study measures, left atrial speckle tracking analysis of resting echocardiography images was performed as described previously in Chapter 3, section 3.5.3. Cardiac deformation assessment (Speckle tracking analysis).

5.3.3. Statistical analysis

Statistical analyses were performed using R software Version (4.0.2). Shapiro-Wilk test and visual assessment were used to assess for normality. The same criteria used in Chapter 4 to classify participants into suboptimal blood pressure and optimal blood pressure groups were applied. Between-group comparisons for resting left atrial deformation parameters were performed using two-tailed independent samples Student t-tests for normally distributed data and Mann-Whitney and Kruskal-Wallis tests for non-normally distributed data. Correlation analysis between resting echocardiography features and left ventricular response to physical exercise was tested using Pearson correlation

test and was applied to the cohort as a whole. Multivariable linear regression modelling was performed to study the continuous association between resting echocardiographic features and left ventricular response during exercise adjusted for potential confounders (age, sex, body mass index, and mean arterial blood pressure) [196-198]. To avoid over adjustment, echocardiography parameters included in the regression model were not indexed to body surface area. A *p*-value of ≤ 0.05 was used to indicate statistical significance. The sensitivity and specificity of the prediction model were studied to identify the best cut-off values of left atrial contraction at rest and left ventricular ejection fraction during exercise in this cohort. Multiple cut-off values were tested to select the optimal value with the highest sensitivity and specificity.

5.4. RESULTS

5.4.1. Clinical and imaging characteristics at baseline and during exercise

Baseline clinical characteristics of the 172 participants (59 with optimal blood pressure and 68 with suboptimal blood pressure) are shown in Table 4.1 in Chapter 4. Resting echocardiography features with group comparisons are also illustrated in Chapter 4 in Table 4.2. Left atrial speckle tracking parameters at rest including left atrial peak longitudinal strain (reservoir function), left atrial peak contraction strain (booster pump function), and the difference between them (conduit function) are demonstrated in Table 5.1 in this chapter. Participants with suboptimal blood pressure had lower mean reservoir (p=0.17), conduit (p=0.163), and pump function (p=0.827) compared to the optimal blood pressure group, but this was not statistically significant. Between group comparisons of clinical and imaging characteristics during moderate physical exercise (60% of peak exercise intensity) are illustrated in Table 4.3 in Chapter 4.

Table 5.1. Resting left atrial deformation

	Optimal BP n=59	**Suboptimal BP n=68**	***P* value**
LA Reservoir strain (%)	40.7 ± 6.9	38.9 ± 7.2	0.170
LA Conduit strain (%)	31.6 ± 6.6	29.9 ± 6.4	0.163
LA Pump strain (%)	9.1 ± 3.9	8.9 ± 4.4	0.827

Data are expressed as mean ± standard deviation.
BP, blood pressure; LA, left atrium.

5.4.2. Correlation analysis of the cardiac response to physical exercise and resting echocardiography parameters

Pearson correlation coefficients for resting echocardiography features and left ventricular response during moderate exercise intensity are presented in Table 5.2. Resting left ventricular mass was negatively correlated with left ventricular ejection fraction during exercise (r=-0.21, p=0.028), and was positively correlated with left ventricular systolic and diastolic volumes during exercise (r=0.48, p<0.0001, and r=0.49, p<0.0001, respectively) (Figure 5.1). Left atrial booster pump function at rest was also correlated with left ventricular ejection fraction (r=0.25, p=0.009) and systolic volume (r=-0.29, p=0.002) during moderate exercise (Figure 5.1). Left ventricular and atrial volumes at rest were correlated with exercise left ventricular volumes, but not exercise ejection fraction as presented in Table 5.2. Table 5.2. also shows that there was no relationship between right ventricular function at rest and left ventricular performance during exercise in this cohort.

Table 5.2. Correlation analysis between cardiac response to physical exercise and resting echocardiography parameters

	Exercise LV EF		Exercise LV EDV		Exercise LV ESV	
	r	***P* value**	***r***	***P* value**	***r***	***P* value**
RESTING LEFT VENTRICULAR STRUCTURE						
Relative wall thickness	0.026	0.793	0.053	0.590	-0.001	0.989
LV mass (g)	**-0.214**	**0.028**	**0.487**	**<0.0001**	**0.49**	**<0.0001**
LV biplane end diastolic volume (ml)	-0.121	0.211	**0.492**	**<0.0001**	**0.514**	**<0.0001**
LV biplane end systolic volume (ml)	-0.122	0.209	**0.415**	**<0.0001**	**0.45**	**<0.0001**
RESTING LEFT VENTRICULAR FUNCTION						
LV biplane ejection fraction (%)	0.045	0.645	-0.001	0.993	-0.08	0.409
LV global longitudinal strain (%)	-0.105	0.290	-0.087	0.381	0.040	0.686
Mitral valve E velocity (cm/s)	0.033	0.740	**-0.280**	**0.004**	-0.149	0.130
Mitral valve A velocity (cm/s)	-0.052	0.602	-0.155	0.115	-0.139	0.158
Average E' velocity (cm/s)	0.117	0.240	**-0.2**	**0.044**	-0.129	0.195
RESTING LEFT ATRIAL STRUCTURE AND FUNCTION						
LA volume (ml)	-0.055	0.571	**0.465**	**<0.0001**	**0.378**	**<0.0001**
LA Reservoir strain (%)	0.107	0.276	-0.111	0.255	-0.152	0.120
LA Conduit strain (%)	-0.028	0.774	-0.075	0.444	0.009	0.924
LA Pump strain (%)	**0.251**	**0.009**	-0.079	0.421	**-0.292**	**0.002**
RESTING RIGHT VENTRICULAR FUNCTION						
TAPSE (cm)	0.136	0.186	0.167	0.104	0.053	0.608
RV S' velocity (cm/s)	0.055	0.599	0.047	0.658	-0.018	0.861

r , Pearson correlation coefficient
LV, left ventricle; EF, ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; LA, left atrium; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle

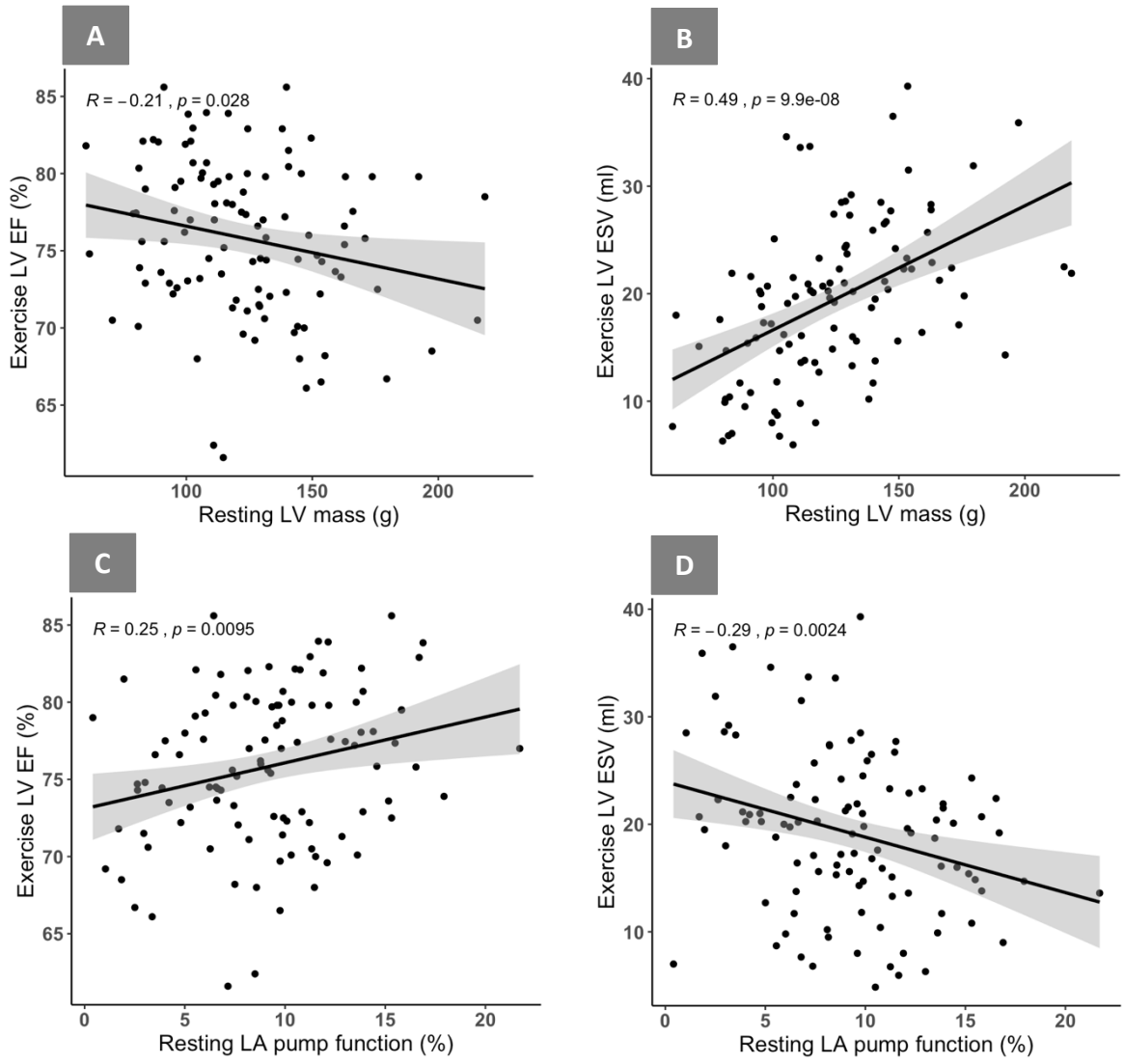


Figure 5.1. Relationships between resting and exercise echocardiography measures.

Scatter plots show the relationship of left ventricular mass and left atrial booster pump function at rest with left ventricular ejection fraction (A and C) and end systolic volume (B and D) during moderate physical exercise.

LV, left ventricle; EF, ejection fraction; ESV, end systolic volume; LA, left atrium.

5.4.3. Multivariate regression model to predict left ventricular ejection fraction during exercise

Association analysis between resting echocardiography parameters and left ventricular response during physical exercise adjusted for age, sex, body mass index and mean arterial blood pressure is presented in Table 5.3. Resting left ventricular mass was associated with left ventricular diastolic (β=0.27, *p*=0.001) and systolic (β=0.08, *p*=0.001) volumes during exercise. Left atrial biplane volume was also associated with left ventricular volumes during exercise but not with the ejection fraction as illustrated in Table 5.3. Left atrial booster pump function at rest was the only parameter associated with left ventricular ejection fraction during physical exercise (β=0.29, *p*=0.011) and was also associated with left ventricular end systolic volume (β=-0.49, *p*=0.002) when adjusted for age, sex, body mass index and mean arterial blood pressure. There was no association between daily physical activity and exercise left ventricular ejection fraction (*p*=0.542) even when adjusted for the confounders (*p*=0.722).

Table 5.3. The association between resting echocardiography parameters and left ventricular response to physical exercise adjusted for age, sex, BMI, and mean arterial blood pressure

	Exercise LV EF		Exercise LV EDV		Exercise LV ESV	
	β	***P* value**	**β**	***P* value**	**β**	***P* value**
RESTING LEFT VENTRICULAR STRUCTURE						
Relative wall thickness	12.05	0.141	-24.4	0.533	-13.5	0.241
LV mass (g)	-0.01	0.481	**0.27**	**0.001**	**0.08**	**0.001**
LV biplane end diastolic volume (ml)	-0.01	0.448	**0.48**	**<0.0001**	**0.14**	**<0.0001**
LV biplane end systolic volume (ml)	-0.05	0.281	**0.99**	**<0.0001**	**0.3**	**<0.0001**
RESTING LEFT VENTRICULAR FUNCTION						
LV biplane ejection fraction (%)	0.05	0.564	0.04	0.923	-0.09	0.484
LV global longitudinal strain (%)	-0.2	0.310	-1.001	0.278	0.009	0.974
Mitral valve E velocity (cm/s)	-0.01	0.771	-0.27	0.091	-0.03	0.470
Mitral valve A velocity (cm/s)	-0.02	0.713	-0.48	0.045	-0.1	0.111
Average E' velocity (cm/s)	0.18	0.393	-0.94	0.350	-0.25	0.401
RESTING LEFT ATRIAL STRUCTURE AND FUNCTION						
LA volume (ml)	0.01	0.748	**0.83**	**<0.0001**	**0.19**	**0.004**
LA Reservoir strain (%)	0.03	0.634	-0.1	0.729	-0.07	0.405
LA Conduit strain (%)	-0.06	0.364	0.09	0.788	0.08	0.387
LA Pump strain (%)	**0.29**	**0.011**	-0.6	0.273	**-0.49**	**0.002**
RESTING RIGHT VENTRICULAR FUNCTION						
TAPSE (cm)	1.53	0.335	12.75	0.096	1.3	0.544
RV S' velocity (cm/s)	0.08	0.777	0.79	0.562	-0.03	0.937

β , Regression coefficient
LV, left ventricle; EF, ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; LA, left atrium; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle

5.4.4. Separate correlation and regression analysis for each group

The relationship and association between resting echocardiography parameters and left ventricular response during exercise were studied separately for the suboptimal blood pressure group and the optimal blood pressure group. Table 5.4 presents the correlation and regression analysis of left atrial pump strain and left ventricular mass at rest with left ventricular ejection fraction during exercise. The association between resting left atrial pump strain and the ejection fraction during exercise remained significant in the suboptimal blood pressure group (r=0.37, p=0.003), even when adjusted for the confounders (β=0.41, p=0.015), but not in the optimal blood pressure group (β=0.06, p=0.707). There was no statistically significant association between left ventricular mass at rest and left ventricular ejection fraction during exercise in both groups. Figure 5.2 illustrates the relationship of left atrial pump strain and left ventricular mass at rest with left ventricular ejection fraction during exercise in participants with suboptimal (red) and optimal (blue) blood pressure measures.

Table 5.4. The correlation and regression* analysis of left atrial pump strain and left ventricular mass at rest with left ventricular ejection fraction during exercise for the suboptimal and optimal blood pressure group

	Exercise LV ejection fraction			
	Optimal BP n=59		Suboptimal BP n=68	
Pearson correlation	***r***	***P* value**	***r***	***P* value**
Resting LV mass (g)	-0.14	0.366	-0.13	0.306
Resting LA pump strain (%)	0.01	0.934	0.37	**0.003**
Regression analysis	***β***	***P* value**	***β***	***P* value**
Resting LV mass (g)	-0.02	0.396	-0.01	0.689
Resting LA pump strain (%)	0.06	0.707	0.41	**0.015**

r , Pearson correlation coefficient

β , Regression coefficient

LV, left ventricle; LA, left atrium

* The regression model is adjusted for age, sex, body mass index, and mean arterial blood pressure

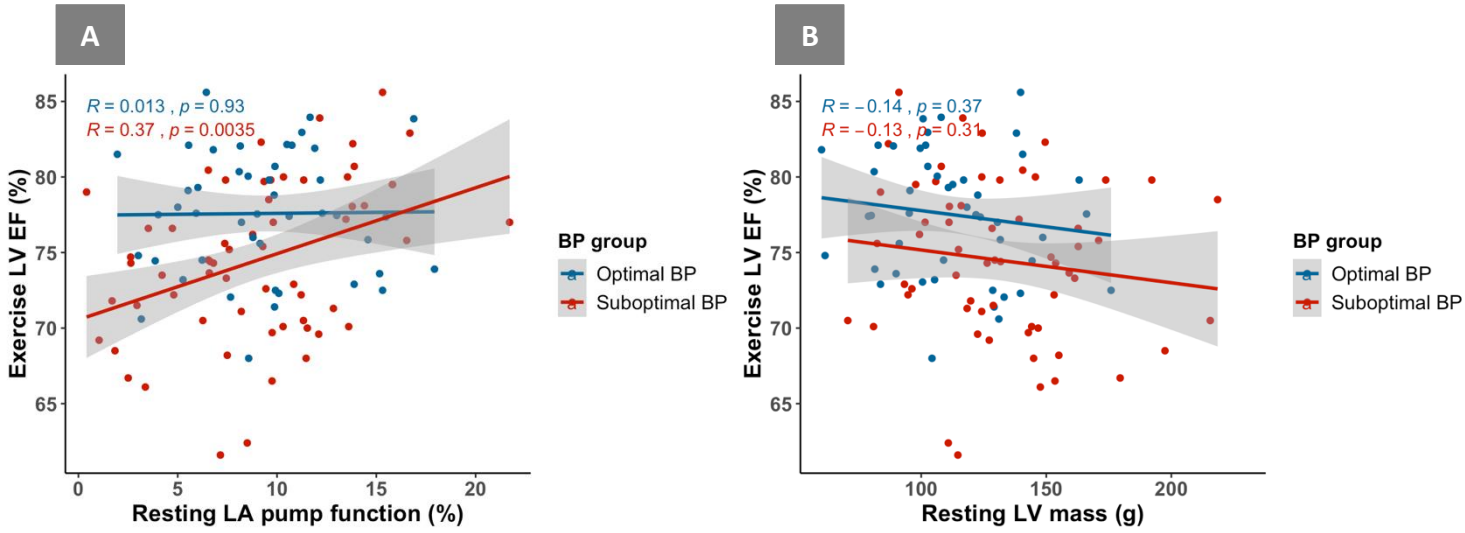


Figure 5.2. Relationships between resting and exercise echocardiography measures separated by blood pressure groups.

Scatter plots to illustrate the relationship of left atrial booster pump function (A) and left ventricular mass (B) at rest with left ventricular ejection fraction during moderate physical exercise in participants with suboptimal blood pressure (red) compared to those in the optimal blood pressure group (blue).

LV, left ventricle; EF, ejection fraction; LA, left atrium; BP, blood pressure.

5.4.5. Sensitivity and specificity analysis

The sensitivity and specificity of the prediction model of the exercise ejection fraction from left atrial pump strain at rest was calculated for participants with suboptimal blood pressure. The calculation was performed using multiple cut-off values as illustrated in Table 5.5. The optimal cut-off value for left atrial pump strain at rest was 9%, and 75% was selected for left ventricular ejection fraction during exercise. The sensitivity and specificity for these cut-off values were calculated at 64.5%, and 71.4%, respectively.

Table 5.5. Sensitivity and specificity analysis using multiple cut-off values of left atrial pump function at rest and left ventricular ejection fraction during exercise for the suboptimal blood pressure group

	Positive **Exercise EF < 75%**	**Negative** **Exercise EF ≥ 75%**
Positive **Resting LA pump ≤ 8%**	True positive n=18	False positive n=7
Negative **Resting LA pump > 8%**	False negative n=13	True negative n=21

Sensitivity = 18/(18+13)*100 = 58.1%
Specificity = 21/(21+7)*100 = 75%

	Positive **Exercise EF < 75% ***	**Negative** **Exercise EF ≥ 75% ***
Positive **Resting LA pump ≤ 9% ***	True positive n=20	False positive n=8
Negative **Resting LA pump > 9% ***	False negative n=11	True negative n=20

Sensitivity = 20/(20+11)*100 = 64.52%
Specificity = 20/(20+8)*100 = 71.4%

	Positive **Exercise EF < 74%**	**Negative** **Exercise EF ≥ 74%**
Positive **Resting LA pump ≤ 8%**	True positive n=13	False positive n=12
Negative **Resting LA pump > 8%**	False negative n=13	True negative n=21

Sensitivity = 13/(13+13)*100 = 50%
Specificity = 21/(21+12)*100 = 63.63%

	Positive **Exercise EF < 74%**	**Negative** **Exercise EF ≥ 74%**
Positive **Resting LA pump ≤ 9%**	True positive n=15	False positive n=13
Negative **Resting LA pump > 9%**	False negative n=11	True negative n=20

Sensitivity = 15/(15+11)*100 = 57.7%
Specificity = 20/(20+13)*100 = 60.6%

* The cut-off values selected for the best sensitivity and specificity were 9% for the left atrial contraction strain, and 75% for exercise left ventricular ejection fraction (red frame).
Participants with inadequate image quality for left atrial booster pump calculation (n=9) were excluded from this analysis.

5.5. DISCUSSION AND CONCLUSION

In this chapter, I examined whether the reduction in systolic function during exercise in participants with suboptimal blood pressure is associated with subclinical cardiovascular remodelling by studying the association between resting echocardiography parameters and left ventricular ejection fraction, end diastolic volume, and end systolic volume during physical exercise. Although left ventricular mass at rest was correlated with the left ventricular ejection fraction and volumes during exercise, there was no association with the exercise ejection fraction when adjusted for age, sex, body mass index and mean arterial blood pressure. Resting left atrial booster pump function estimated from left atrial peak contraction strain was the only independent variable associated with the reduction in left ventricular ejection fraction during exercise when adjusting for age, sex, body mass index, and mean arterial blood pressure.

Previous studies in patients with hypertension demonstrated that the impairment in left ventricular performance during exercise was associated with left ventricular hypertrophy [33, 34]. The impaired response to physical exercise was also found in patients with mild hypertension before the development of left ventricular hypertrophy [147, 148]. Using radionuclide angiography, Cuocolo et al. found that the reduction in left ventricular ejection fraction during exercise in hypertensive patients is related to abnormal diastolic filling [149]. Left ventricular diastolic filling is highly modulated by left atrial reservoir, conduit, and booster pump function [93, 94]. In clinical practice, radionuclide angiography is not easily translatable, but by using speckle tracking echocardiography, early diastolic adaptations secondary to blood pressure elevation can be identified from left atrial deformation analysis [212].

Prior studies demonstrated that in patients with hypertension all left atrial phases can be reduced due to the increase in pressure load and wall tension [88, 100]. A number of studies reported a temporary augmentation of the pump function that was found during early stages of hypertension to compensate the impairment of the reservoir and conduit function [79, 98]. Mondello et al. reported that asymptomatic patients with hypertension and normal left atrial volume, have declined left atrial reservoir and conduit function [99]. Impaired left atrial deformation was also found in hypertensive patients with no evidence of left atrial enlargement and left ventricular hypertrophy [209]. These findings suggest that left atrial strain indices using speckle tracking echocardiography can be used to identify early subclinical remodelling secondary to hypertension [98]. In this chapter, I have shown that left atrial booster pump function at rest is a predictor of functionally relevant changes in left ventricular response to exercise in this cohort of young adults. When left atrial contraction strain declines below the mean, less than 9, there is a reasonable likelihood, based on 64.5% sensitivity and 71.4% specificity, that the participants in the suboptimal blood pressure group will have a lower ejection fraction during exercise. The booster pump function is modulated by intrinsic left atrial preload and contractility, as well as left ventricular compliance and end diastolic pressure [89, 92, 210]. This may explain the association between resting left atrial contraction and left ventricular response during exercise.

In previous studies, left atrial contraction was estimated using the mitral A wave velocity which reflects the atrio-ventricular pressure difference before the closure of the mitral valve at end diastole [213]. However, the A wave velocity is volume dependent as it is a measure of the amount of blood flow from the left atrium to left ventricle during atrial contraction [213]. Thus, the impairment in left atrial intrinsic myocardial function may not be detected [213]. Interestingly, in this cohort of young adults, there was

no correlation between the mitral valve A wave velocity recorded at rest and left ventricular ejection fraction during exercise, even when adjusted for potential confounders.

Hypertension is known to induce left ventricular hypertrophy and an increase in left ventricular mass to compensate the increase in left ventricular wall stress and maintain the stroke volume [74, 214]. Past studies examining patients with hypertension have predominantly focused on left ventricular hypertrophy [118, 215], and even the hypertension management guidelines recommended to initiate anti-hypertensive medication in the presence of left ventricular hypertrophy [10-12]. The reason for this is because of that the presence of left ventricular hypertrophy in patients with hypertension was associated with poor prognosis, independent of the blood pressure level [115]. In this work, although the left ventricular mass was higher in participants with suboptimal blood pressure compared to those in the optimal blood pressure group, none of the participants exceeded the clinical threshold for left ventricular hypertrophy (115 g/m^2 in males, 95 g/m^2 females) [110]. This could explain the lack of association between left ventricular mass at rest and left ventricular response during exercise in this group of participants. Similarly with left ventricular longitudinal strain, recent evidence has indicated that left ventricular longitudinal function impairment estimated by global strain can be an early marker of systolic dysfunction in patients with hypertension [216, 217]. However, in this cohort of young adults there was no between-group difference in left ventricular strain at rest. This could reflect the short duration of hypertension in this group of young age participants with relatively early changes in blood pressure.

According to recent American and European guidelines for hypertension prevention and management, there is insufficient evidence for whether to start anti-hypertensive medication in young adults with stage I hypertension [10, 11]. Lifestyle

modifications, such as regular aerobic exercise, have been shown to be beneficial with regards to blood pressure control. However, exercise interventions to manage blood pressure in young patients vary in success with heterogeneous blood pressure response to exercise in those with hypertension [200]. This has been explained by a variety of factors including the intensity of exercise, the level of adherence to exercise sessions, or subclinical cardiovascular remodelling [46]. The results of this chapter and chapter 4 could partially explain the heterogenous response to exercise interventions in lowering blood pressure in young individuals. The subclinical left ventricular and atrial remodelling would be expected to influence the workload perception during exercise, which could adversely influence training adherence [46]. Whether either the ventricular response or left atrial remodelling is reversible with lifestyle or pharmacological blood pressure control requires further study. In clinical practice, young individuals with blood pressure of $\geq$ 120/80 mmHg, and are found to have evidence of left atrial remodelling on their resting echocardiography, may warrant more detailed evaluation and potentially more targeted intervention. However, this requires further evaluation in follow on studies and trials.

The identification of the left ventricular response to exercise could be complicated due to the need for exercise stress echocardiography. However, as resting left atrial strain appears to predict the left ventricular response during exercise, left atrial measures at rest may be a relatively simple approach for clinicians to risk-stratify young adults with hypertension.

5.5.1. Study limitations

Although there were no statistical significance in between-group differences in the left atrial reservoir, conduit, and booster function, which could be due to the small sample size in each group, the findings of this chapter were based on the regression models developed using the whole cohort to overcome the limitation of the small sample size. In addition, due to lack of validated specific left atrial software, left atrial strain assessment conducted in this chapter was performed using speckle tracking software designed for left ventricular assessment. Following the latest EACVI recommendations for left atrial strain measurements [193], manual tracing of left atrial endocardium was performed without tracing the pericardium. In addition,

5.5.2. Conclusion

In this chapter, I identified the association between resting echocardiography parameters and left ventricular response to physical exercise in young adults with mildly elevated blood pressure. Left atrial booster pump function was the only parameter associated with left ventricular ejection fraction during exercise even when adjusted for potential confounders. Subclinical left atrial remodelling appears to be an independent early marker of cardiac alterations secondary to elevated blood pressure in young adults. These findings could be clinically useful to identify young adults who require more aggressive or personalised blood pressure management.

6. MACHINE LEARNING BASED DISEASE PROGRESSION MODEL FOR YOUNG ADULTS WITH HYPERTENSION

6.1. ABSTRACT

Aims: Multiple variable models have shown to be more consistent across population than single variable prediction models. In this chapter, I introduce a novel semi-supervised machine learning method that combines the effect of multiple echocardiography features to develop a disease progression model and test its stability. In addition, I identify the important relevant echocardiography parameters.

Methods: For model development, 411 young adults (28.9 ± 5.7 years) with a range of blood pressure measures who completed a comprehensive transthoracic echocardiography scan at the CCRF were included. Participants were labelled based on the clinical brachial systolic blood pressure into three groups: Target (≥ 160 mmHg), Background (< 120 mmHg, and not on antihypertension medication), and Intermediate (≥ 120 mmHg and < 160 mmHg). A contrastive Principal Component Analysis (cPCA) algorithm was applied on 68 variables to identify low-dimensional unique patterns in the target group relative to the background group. Based on the variance similarities, participants were ordered and assigned with a score from zero (health) to one (disease). The disease progression model was tested for its stability and validity by applying a five K cross-validation test.

Results: After the contrastive dimensionality reduction of the data, 21 variables were identified with the highest contribution (more than 80%) of the model development. E/E' ratio and left atrial pump function were the highest in participants with high disease progression score, while the reservoir and conduit function were the highest in those with low score. The disease progression score was higher in the suboptimal blood pressure group who had reduced left ventricular response during exercise, compared with controls. The root mean squared deviation for the model was calculated at 0.2, which indicates a sufficient level of stability.

Conclusion: Using baseline clinical and echocardiography data from a cross-sectional dataset, we developed a disease progression model of hypertension in young adults. The model allowed us to identify the important relevant echocardiography phenotypes, and how they change throughout the disease progression in this cohort. Further validation for the model on new datasets is required.

Publication Status: The methods and results presented in this chapter have been filed for a patent application (No. 2113322.8) on 17th September 2021. A manuscript is being prepared to be submitted to The Lancet.

6.2. INTRODUCTION

Target organ damage secondary to hypertension usually occurs late in the course of uncontrolled hypertension [218]. Therefore, identification of subclinical cardiac remodelling and early management of hypertension may prevent or delay the onset of adverse events [218, 219]. Cardiac remodelling secondary to hypertension can be in the form of an increase in left ventricular wall thickness, left atrial enlargement, and/or diastolic dysfunction leading to heart failure with preserved ejection fraction [29, 74, 219]. In chronic end stages of the disease, with increased left ventricular stiffness and long-term left ventricular hypertrophy, systolic dysfunction may develop starting with regional longitudinal impairment [118] and progress to a global impairment in the form of reduced ejection fraction [29, 74, 219]. Using prediction models and follow-up data in older patients with hypertension, increased left ventricular mass assessed by echocardiography and cardiac magnetic resonance imaging [111, 114, 220], and impaired left atrial phasic function estimated by speckle tracking echocardiography [78, 85, 221] were found to be independently associated with poor prognostic outcomes.

Current guidelines in the management of hypertension and prevention of cardiovascular disease in young patients are based on data from populations over 40 years of age [10-12]. This is because of the lack of longitudinal studies in younger patients with a sufficient follow-up duration to assess the long-term treatment effect and detection of signs of target organ damage [10, 11, 18, 26]. However, younger patients often present with normal cardiac structure and function, except in severe cases [222]. This could be due to the relatively shorter duration of hypertension compared to older populations [223]. Patients below the age of 40 with hypertension may have different pathophysiological responses to high blood pressure [26]. Using current hypertension

management guidelines in young adults could therefore result in missing a critical window for early intervention.

During adulthood, between the age of 18 to 40 years, individuals may travel between countries to complete their education, enter the workforce, and start a family [18]. Since tracking young patients for five to ten years is becoming challenging [18, 26], the majority of studies in the literature about young hypertensives are designed for a cross-sectional data collection [10, 18, 26]. Cross-sectional datasets consist of data collected at a single time-point, which have traditionally been of limited use to study the disease progression later in life without the availability of follow-up data.

In the previous chapters, using a cross-sectional dataset, I identified a reduced left ventricular ejection fraction response to physical exercise in young adults with suboptimal blood pressure measures ($\geq$ 120/80 mmHg). To determine whether this adverse response during exercise can be predicted from resting echocardiography data, I investigated the association between resting echocardiography parameters and exercise outcomes. Although left ventricular mass at rest was higher in participants with suboptimal blood pressure, it was not associated with the reduced left ventricular response during exercise. Left atrial booster pump function at rest was the only independent variable associated with the reduction in exercise ejection fraction.

The use of singular variables in prediction models has shown to be inconsistent across populations [224]. A number of recent studies have shown an additional prognostic value of the combined effects of multiple echocardiography features in patients with hypertension [107, 108]. Machine learning statistical tools have the ability to integrate multi-dimensional data using supervised or unsupervised learning algorithms [161, 170]. Such algorithms have been applied to echocardiography data to classify heart failure patients with hypertension into distinct subgroups [185], and to study inter-patient

similarities in cardiac function from a cross-sectional dataset [165]. Although these applications have provided an incremental understanding of the cardiac remodelling in patients with hypertension, the cardiac pathological progress of hypertension in younger patients remains understudied and not completely understood.

To overcome the lack of longitudinal data in younger populations, an unsupervised machine learning technique that extracts temporal information from cross-sectional datasets has been developed in cancer genomics [225, 226]. This technique integrates high-dimensional cross-sectional 'snapshot' gene expression data, which allows ordering individuals based on the severity of the disease and study the dynamic biological and pathological progress [226, 227]. This tool has since been further developed into a novel contrastive trajectory inference (cTI) algorithm by Iturria-Medina et al. [228]. This algorithm provides semi-supervised identification of enriched patterns and generation of a pseudo-temporal score to order patients with Alzheimer's and Huntington's diseases relative to a comparison healthy population [229]. The pseudo-temporal scores predicted the neuropathological severity and clinical deterioration to advanced disease stages [228, 229]. In this chapter, I hypothesise that such an algorithm could be applied on a cross-sectional multi-dimensional clinical and echocardiography dataset of young adults with a range of blood pressures to study the disease progression of hypertension.

My aims of this chapter are: (i) to develop a model that combines the effect of relevant resting clinical and echocardiography features to place the participants on a trajectory from health to disease; (ii) to identify the important parameters relevant to the disease progression of hypertension in young adults, and study the changes of individual parameters (i.e. left ventricular mass) over the course of the disease

progression; and (iii) to determine whether the disease progression score is associated with the adverse cardiac response to physical exercise.

6.3. METHODS

6.3.1. Study population

The work in this chapter utilised data from a cohort of young adults aged between 18 and 40 years who completed a comprehensive transthoracic echocardiography scan at the CCRF, John Radcliffe Hospital, between 2014 and 2019. Participants with known gestational history of preterm birth were excluded from this work. Detailed description of the participant recruitment process and selection criteria are provided in Chapter 2, section 2.6.2.

6.3.2. Clinical investigations and variables

All participants had the following cardiovascular assessments, which are described in detail in Chapter 3 (Methods and materials):

- Anthropometry (section 3.2).
- Blood pressure profiles (section 3.3).
- Echocardiography imaging (section 3.5).
    - Cardiac structure assessment (2D echocardiography)
        - Left ventricular assessment
        - Right ventricular assessment
        - Atrial assessment
    - Cardiac function assessment (Doppler velocities)
    - Cardiac deformation assessment (speckle tracking echocardiography)
- Cardiac magnetic resonance (section 3.6).
    - A subgroup of the cohort underwent cardiovascular magnetic resonance imaging with left ventricular mass and volumes assessment, as described in

Chapter 3 (section 3.6.1). Left ventricular mass data were used in this chapter to study the pattern of remodelling in left ventricular mass through the course of the disease progression in this cohort of young adults.

- Cardiopulmonary exercise testing with stress echocardiography imaging
    - A subgroup of the cohort underwent cardiopulmonary exercise testing with stress echocardiography imaging, as described in Chapter 3 (section 3.7).

6.3.3. Statistical analysis

6.3.3.1. Data processing

Participants and variables with more than 30% missing data were excluded from the analysis. The remaining missing data was replaced with imputed values by using the trimmed scores regression (TSR) tool. All baseline clinical and echocardiography variables were adjusted for sex [196, 197] and included to develop the model, but without including any blood pressure measurements. Resting blood pressure measurements were used to categorise participants into three groups:

- Target (participants with systolic blood pressure ≥ 160 mmHg).
- Background (participants with systolic blood pressure < 120 mmHg, and not on antihypertension medication).
- Intermediate (participants with systolic blood pressure ≥ 120 mmHg and < 160 mmHg).

6.3.3.2. Model development

The model development was performed using MATLAB R2019b programming environment (Mathworks Inc., Natick, MA, USA). After labelling participants based on systolic blood pressure measures as target, background, and intermediate, the cTI algorithm was applied on the baseline clinical and echocardiography data to develop the model [229]. The disease progression model development consists of five main steps: (i) Data adjustment for sex using additive linear models with pair-wise interactions [230]; (ii) Feature selection using an unsupervised method by comparing participant variance and neighbourhood variance [231]; (iii) Data visualisation and exploration by applying a contrasted Principal Component Analysis (cPCA) tool to identify enriched, non-linear, low-dimensional pathological patterns in the target group relative to the background [232]; (iv) Disease progression score calculation. The score was calculated as the shortest distance value from any participant to the background centroid using the Minimum Spanning Tree (MST) [229]. Score values were standardised between zero and one. Based on these values, participants were ordered from health (low scores close to the background group) to disease (high scores close to the target group); and (v) Estimation of feature relevance to quantify the total contribution of each data feature to the obtained reduced representation space [233]. The model development process is described in steps in Figure 6.1.

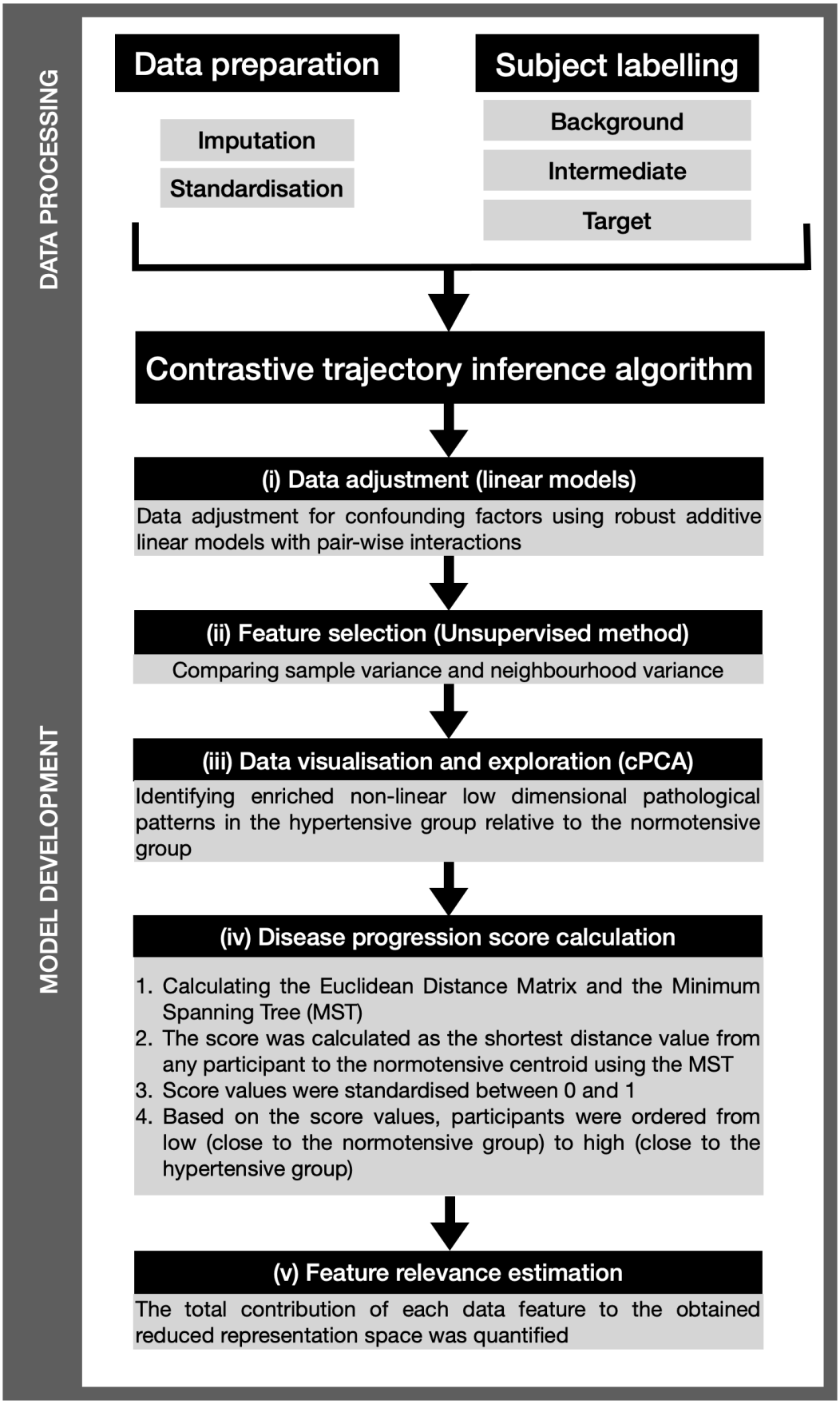


Figure 6.1. A flow chart illustrating the steps of the disease progression model development.

6.3.3.3. Model validation

To test the disease progression model robustness and stability, two criteria for the model stability and validity were applied:

i) Stability

Model stability can be defined by a robustness in the disease progression scores to removing participants from the dataset on which the model is trained. After applying the algorithm on the full dataset and obtaining disease progression scores (original) for each participant, a 5K cross-validation test was carried out. In each of the five folds, 20% of the target and background participants were held out from the dataset for testing after which the cPCA algorithm was run. The Root Mean Squared Deviation (RMSD) was then calculated by measuring the differences between repeated and original values for each fold [234]. The differences were squared, and the sum of the squared differences was divided by the number of the participants and then the square root was calculated. An RMSD value of ≥ 0.5 was considered as an indication of poor model stability. The RMSD was calculated as follows:

$$RMSD = \sqrt{\frac{\sum(x_e - x_o)^2}{n}}$$

$$x_e - The\ repeated\ value$$

$$x_o - The\ original\ value$$

$$n - Number\ of\ subjects$$

ii) Validity

Internal model validity was assessed by the ability to differentiate between pathology-free participants and those with more advanced pathology. The difference in disease progression scores, obtained from the testing folds, between the target and background groups was tested using independent-samples t-test. A *p*-value of ≤ 0.05 was used to indicate statistical significance and acceptable performance. The model should be valid when the background participants have lower disease progression scores compared with the target participants [235].

Failing to meet the above criteria would indicate that the model performance has low validity and stability [234-236].

6.3.3.4. Post-hoc statistical analysis

R 4.0.2 and R studio were used for post-hoc statistics and graphics. The log 10 method was applied to transform skewed data to approximately a normal distribution. To assess the pattern of changes through the disease progression for individual variables, the disease progression scores were divided into ten consecutive subgroups. Participants with score zero to 0.25 were in the first group, and then each group consisted of 20 consecutive participants. The first three groups were categorised as a low score (disease progression score from zero to < 0.3), medium score was for groups from four to seven (disease progression score from ≥ 0.3 to < 0.5), and high score represents groups from eight to ten (disease progression score ≥ 0.5). Variables were scaled between zero and one to allow relative comparison. Pearson correlation test was used to test the relationship

between the exercise outcomes and disease progression scores. A *p*-value of ≤ 0.05 was used to indicate statistical significance and a 95% confidence interval was used.

6.4. RESULTS

6.4.1. Baseline clinical characteristics

A total of 411 young adults (28.9 ± 5.7 years) with a range of blood pressure measures (94 mmHg, and 69 mmHg; the range for systolic and diastolic blood pressure measures, respectively) were involved to develop the disease progression model. About half of the cohort are males (51.6%) with an average BMI of 26.29 ± 5 kg/m^2. Table 6.1 illustrates the baseline clinical characteristics of the cohort participants.

Table 6.1. Baseline clinical characteristics

	Study cohort n=411
Age	28.93 ± 5.74 (22)
Male, n (%)	209 (51.6)
Height (cm)	173 ± 10.03 (57)
Weight (kg)	79.2 ± 18.5 (135.4)
Body mass index (kg/m^2)	26.2 ± 5.01 (32.2)
Body surface area (m^2)	1.9 ± 0.21 (1.1)
Systolic blood pressure (mmHg)	132.2 ± 16.6 (94)
Diastolic blood pressure (mmHg)	81.7 ± 12.8 (68.7)
Cholesterol level (mmol/L)	4.5 ± 1.1 (9.4)
HDL level (mmol/L)	1.3 ± 0.3 (2.6)
LDL level (mmol/L)	2.7 ± 0.8 (5)
Triglycerides level (mmol/L)	1.2 ± 0.9 (5.03)
Cholesterol to HDL ratio	3.5 ± 1.2 (10.7)
Smokers, n (%)	45 (11.6)
On antihypertension medication, n (%)	124 (31.5)

Data is presented as mean ± standard deviation (range) for continues variables, and frequency and percentage for categorical variables.

6.4.2. Disease progression model development

Following to the data processing step described in section 6.3.3.1., a total of 68 clinical and echocardiography variables (age, BMI, and 66 echocardiography variables) were included to develop the disease progression model (Table 6.2). After the contrastive dimensionality reduction of the data and assignment of weightings to the variables reflecting their contribution to the model development, the node-to-node distance was measured, and each participant was assigned to a location on the principal component space with a disease progression score according to the shortest path. The relationship between the disease progression scores with clinical systolic blood pressure for all participants is shown in Figure 6.2. The model development steps and outcomes are demonstrated in Appendix 6.1.

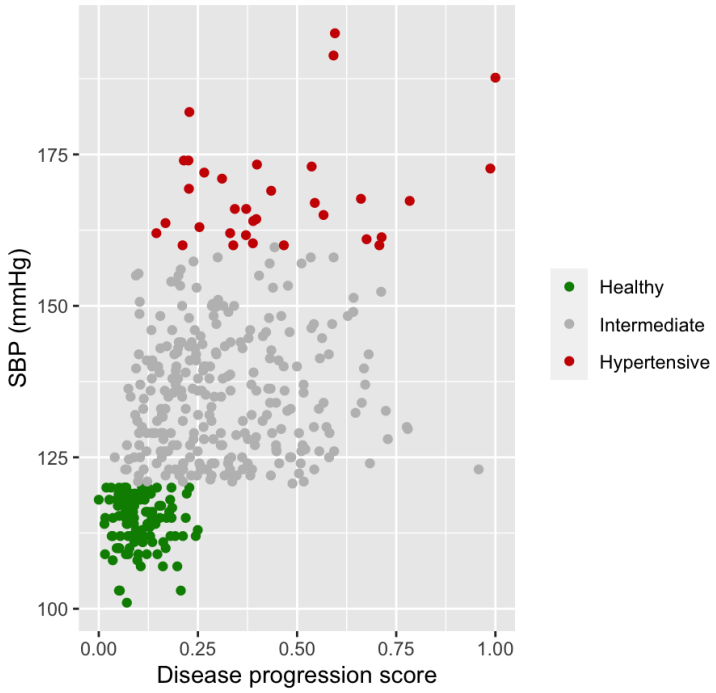


Figure 6.2. The disease progression score and systolic blood pressure.

A scatter plot to demonstrate the relationship between disease progression scores and clinical systolic blood pressure for all participants. The green dots represent participants in the background group (healthy), the red is for the target group (hypertensives), and the grey dots are for the intermediate group. The intermediate group was not involved in the model development.
SBP, systolic blood pressure

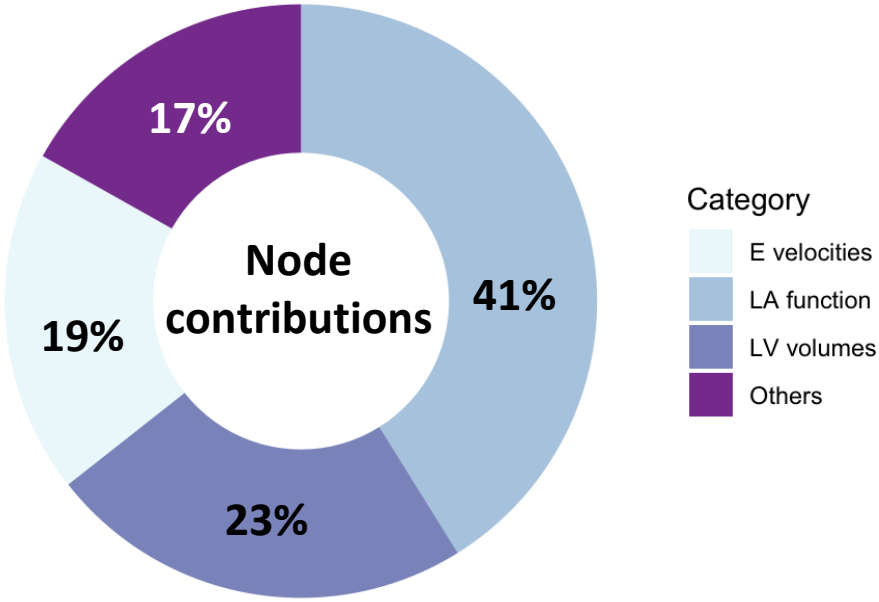
Table 6.2. Variables included for the disease progression model development

1. Age (years)	35. Lateral a' velocity (cm/s)
2. Body mass index	36. Septal s' velocity (cm/s)
3. Heart rate (bpm)	37. Septal e' velocity (cm/s)
4. Interventricular septum (cm)	38. Septal a' velocity (cm/s)
5. LV internal diastolic dimension (cm)	39. $e'_{average}$ (cm/s)
6. LV posterior wall thickness (cm)	40. $E/e'_{lateral}$
7. LV internal systolic dimension (cm)	41. E/e'_{septal}
8. LV ejection fraction, Teichholz (%)	42. $E/e'_{average}$
9. LV outflow tract (cm)	43. Aortic valve max velocity (cm/s)
10. LV relative wall thickness	44. LVOT velocity time integral (cm)
11. LV mass (g)	45. Pulmonary valve max velocity (cm/s)
12. LV mass index (g/m^2)	46. Pulmonary artery acceleration time (ms)
13. LV 4-ch end diastolic volume (ml)	47. RV basal dimension (cm)
14. LV 4-ch end systolic volume (ml)	48. RV mid dimension (cm)
15. LV 4-ch ejection fraction (%)	49. RV length (cm)
16. LV 4-ch stroke volume (ml)	50. RA volume (ml)
17. LV 2-ch end diastolic volume (ml)	51. Tricuspid regurgitation max velocity (cm/s)
18. LV 2-ch end systolic volume (ml)	52. TAPSE (cm)
19. LV 2-ch ejection fraction (%)	53. RV s' velocity (cm/s)
20. LV 2-ch stroke volume (ml)	54. RV e' velocity (cm/s)
21. LV biplane end diastolic volume (ml)	55. RV a' velocity (cm/s)
22. LV biplane end systolic volume (ml)	56. Isovolumetric contraction time (s)
23. LV biplane ejection fraction (%)	57. Isovolumetric relaxation time (s)
24. LV biplane stroke volume (ml)	58. Ejection time (s)
25. LV biplane cardiac output (ml/min)	59. LV Global longitudinal strain (%)
26. LA 4-ch volume (ml)	60. LA Peak longitudinal strain, 4-ch reservoir (%)
27. LA 2-ch volume (ml)	61. LA Peak contraction strain, 4-ch booster pump (%)
28. LA biplane volume (ml)	62. LA 4-ch conduit (%)
29. Mitral valve E velocity (cm/s)	63. LA Peak longitudinal strain, 2-ch reservoir (%)
30. Mitral valve A velocity (cm/s)	64. LA Peak contraction strain, 2-ch booster pump (%)
31. E/A	65. LA 2-ch conduit (%)
32. Deceleration time (ms)	66. LA Peak longitudinal strain – biplane reservoir (%)
33. Lateral s' velocity (cm/s)	67. LA Peak contraction strain – biplane booster pump (%)
34. Lateral e' velocity (cm/s)	68. LA biplane conduit (%)

LV, left ventricle; LA, left atrium; 4-ch, four-chamber; 2-ch, two-chamber; LVOT, left ventricular outflow tract; RV, right ventricle; RA, right atrium; TAPSE, tricuspid annular plane systolic excursion.

6.4.2.1. Variable contributions

A total of 21 variables were identified to contribute to the model development (more than 80%). Based on structural and functional cardiac assessment, these variables can be grouped in three categories: i) Left atrial structure and function; ii) Left ventricular volumes; and iii) E Doppler velocities. Figure 6.3 illustrates the contribution percentage of the three categories with the sum percentage of the remaining variables (47 variables).



LA 41%	LV 23%	E velocities 19%	Others 17%
Conduit bp – 6.6%	Systolic diameter – 9.2%	$E/e'_{Average}$ – 6.3%	The remaining 47 variables
Conduit 4ch – 6.03%	EDV 2ch – 3.5%	E/e'_{medial} – 4.5%	
Reservoir bp – 5.5%	EDV bp – 3.4%	$E/e'_{lateral}$ – 3.8%	
Conduit 2ch – 4.8%	SV 2ch – 2.9%	e'_{medial} – 2.5%	
Reservoir 2ch – 4.1%	ESV bp – 2.5%	$e'_{lateral}$ – 1.6%	
Pump bp – 4.04%	ESV 4ch – 1.7%		
Pump 2ch – 3.1%			
Reservoir 4ch – 3.1%			
Volume bp – 2.2%			
Pump 4ch – 1.6%			

Figure 6.3. Variable contributions to the disease progression model.

Categories of the highest contributed variables in the disease progression model development with the percentage of contribution. Half of the model development was from the left atrial function (41%), followed by left ventricular volumes (23%) and the E velocities (19%). The remaining variables contribution was calculated at 17% of the total model development.

LA, left atrium; LV, left ventricle; EDV, end diastolic volume; ESV, end systolic volume; SV, stroke volume; bp, biplane; 4ch, four-chamber view; 2ch, two-chamber view.

6.4.2.2. Changes of individual variables throughout the disease progression

The individual variable changes across the disease progression score (from zero to one) were studied for each contributing variable.

Figure 6.4 demonstrates the mean value for each of these variables throughout the disease progression in a heatmap. Left atrial reservoir and conduit function appear to have the same pattern as the E' medial and lateral velocities, in which they decrease as the disease progression score increases. In contrast, E/E' ratios and the left atrial pump function have similar patterns of remodelling.

In

Figure 6.5, the biplane values of left atrial and ventricular variables and the average E/E' ratio were selected to be studied through the three categories: low, medium, and high score. The radar chart illustrates the pattern of remodelling for each group based on eight echocardiography variables. The low score participants (yellow chart) had the highest left ventricular systolic diameter and left atrial reservoir and conduit function. Also, they had the lowest left atrial pump function, left atrial volume, and E/E' ratio. In contrast, high score participants (blue chart) had the highest left atrial pump function, and E/E' ratio, but the lowest left atrial conduit, left ventricular diameter and volumes.

The continuous relationships between the disease progression score and left atrial structure and function, left ventricular measures, and E Doppler velocities are illustrated in Figure 6.6. Left atrial conduit and reservoir function appear to reduce as the disease progress, but with a steeper reduction in the conduit function (Figure 6.6 A). Left atrial volume appears to increase rapidly until the disease progression score is 0.4 and then it increases in a slower rate with a maximum increase at score

one. Figure 6.6 panel B demonstrates the changes in left ventricular systolic dimeter and left ventricular volumes. All measures have the same pattern of changes through the disease progression score with their peak is at 0.4 but the systolic diameter peaks earlier at 0.25. The change in E Doppler velocities is shown in Figure 6.6 panel C with a steep increase of E/E' ratio after 0.5 and the same pattern of reduction for lateral and medial E' velocities. In Figure 6.6 panel D I combined several variables to assess their pattern of remodelling relative to each other. Left atrial volume and left ventricular end diastolic volume appear to have the same pattern of increase, but at 0.4 left atrial volume continue to increase while the left ventricular end diastolic volume decreases. The left atrial conduit function and E/E' ratio appear to alter in an opposite direction through the course of the disease progression.

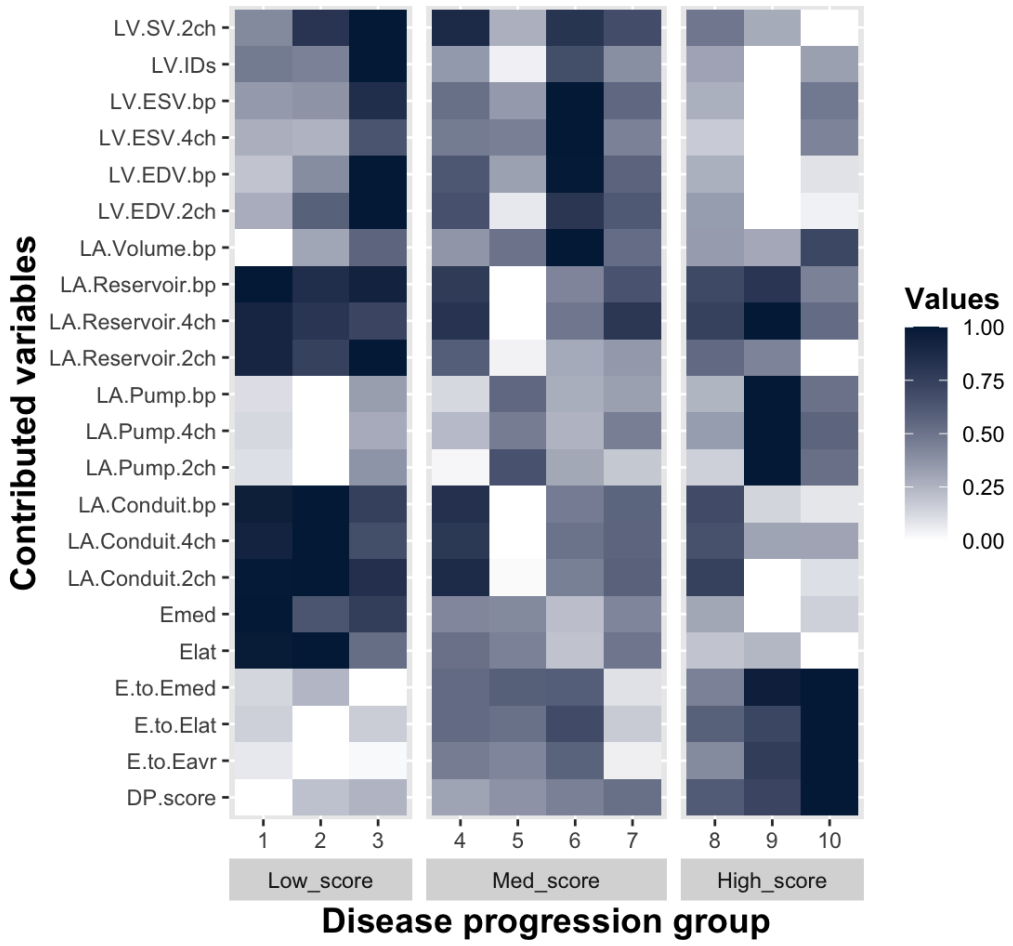


Figure 6.4. The change of each contributed variable throughout the disease progression model.

A heatmap demonstrating the mean value of each contributed variable throughout the disease progression. The disease progression score was divided into ten consecutive subgroups. The first three groups were categorised as a low score (disease progression score from zero to < 0.3), medium score was for groups from four to seven (disease progression score from ≥ 0.3 to <0.5), and high score represents groups from eight to ten (disease progression score ≥ 0.5). All values were rescaled from zero to one to allow comparison between variables. The highest value (one) is presented as the darkest in the scale and white reflects the lowest value (zero).

LV.SV.2ch, left ventricular stroke volume measure from the apical two-chamber view; LV.IDs, left ventricular internal diameter at end systole; LV.ESV.bp, biplane left ventricular end systolic volume; LV.ESV.4ch, left ventricular end systolic volume measured from the apical four-chamber view; LV.EDV.bp, biplane left ventricular end diastolic volume; LV.EDV.2ch, left ventricular end diastolic volume measured from the two-chamber view; LA.Volume.bp, biplane left atrial volume; LA.Reservoir.bp, biplane left atrial reservoir strain; LA.Reservoir.4ch, left atrial reservoir strain measured from the apical four-chamber view; LA.Reservoir.2ch, left atrial reservoir strain measured from the apical two-chamber view; LA.Pump.bp, biplane left atrial pump strain; LA.Pump.4ch, left atrial pump strain measured from the apical four-chamber view; LA.Pump.2ch, left atrial pump strain measured from the apical two-chamber view; LA.Conduit.bp, biplane left atrial conduit strain; LA.Conduit.4ch, left atrial conduit strain measured from the apical four-chamber view; LA.Conduit.2ch, left atrial conduit strain measured from the apical two-chamber view; Emed, e' velocity measured from the medial wall; Elat, e' velocity measured from the lateral wall; E.to.Emed, the ratio of mitral valve E velocity to medial e' velocity; E.to.Elat, the ratio of mitral valve E velocity to lateral e' velocity; E.to.Eavr, the ratio of mitral valve E velocity to average e' velocity; DP.score, disease progression score.

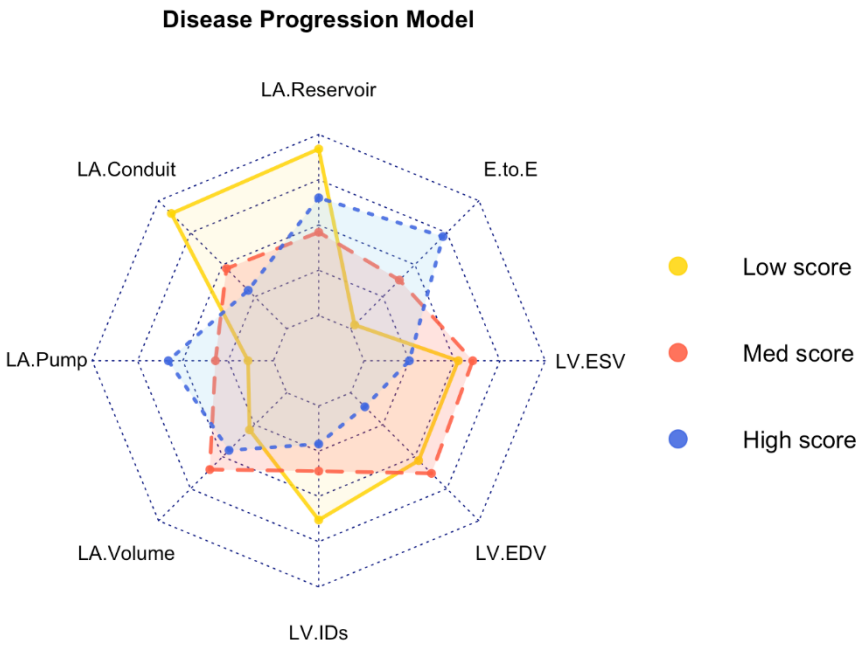


Figure 6.5. The pattern of cardiac remodelling in low. medium, and high score participants.

To evaluate the pattern of changes in echocardiography phenotypes for participants with low, medium, and high disease progression scores, echocardiography data were plotted in a radar chart. A group of the highest contributed variables was selected (biplane and average measures), and all values were rescaled from zero to one to allow comparison between variables. Low score participants had the highest mean of left atrial reservoir, left atrial conduit, and left ventricular systolic diameter (yellow chart), while the left atrial pump and E/e' ratio were the highest in the high score group (blue chart).

LA.Reservoir, biplane left atrial reservoir strain; LA.Conduit, biplane left atrial conduit strain; LA.Pump, biplane left atrial pump strain; LA.Volume, biplane left atrial volume; LV.IDs, left ventricular internal diameter at end systole; LV.EDV, biplane left ventricular end diastolic volume; LV.ESV, biplane left ventricular end systolic volume; E.to.E, the ratio of mitral valve E velocity to average e' velocity.

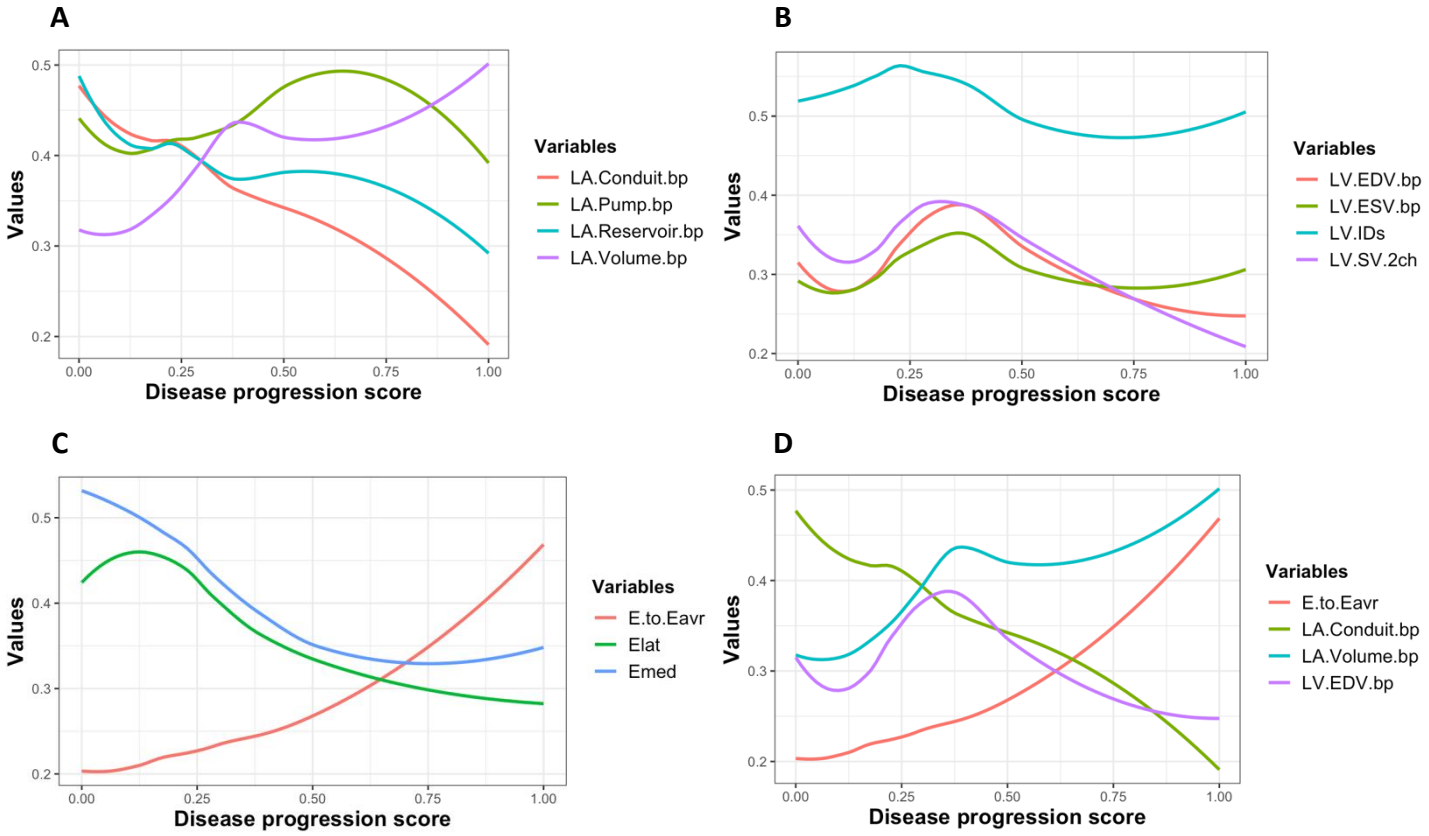


Figure 6.6. The continuous relationships between the disease progression score and echocardiography variables.

Line charts to illustrate the continuous relationship between the disease progression score and left atrial structure and function (A), left ventricular measures (B), and E Doppler velocities (C). In panel D several variables were combined to assess their pattern of remodelling relative to each other.

LA.Conduit.bp, biplane left atrial conduit strain; LA.Pump.bp, biplane left atrial pump strain; LA.Reservoir.bp, biplane left atrial reservoir strain; LA.Volume.bp, biplane left atrial volume; LV.EDV.bp, biplane left ventricular end diastolic volume; LV.ESV.bp, biplane left ventricular end systolic volume; LV.IDs, left ventricular internal diameter at end systole; LV.SV.2ch, left ventricular stroke volume measure from the apical two-chamber view; E.to.Eavr, the ratio of mitral valve E velocity to average E' velocity; Elat, E' velocity measured from the lateral wall; Emed, E' velocity measured from the medial wall.

6.4.2.3. Left ventricular mass contribution

Although the model development was exclusive on echocardiography parameters, a total of 152 participants, who were included in the disease progression model, completed an additional cardiac magnetic resonance imaging with detailed assessment of left ventricular mass. The continuous relationship between the disease progression score and left ventricular mass and its indexed value by left ventricular volume obtained by cardiac magnetic resonance is presented in Figure 6.7. The line chart illustrates that left ventricular mass is high at score zero which is followed with a dip and increased again at score 0.25. In contrast, at score zero, indexed left ventricular mass was the lowest with a steady increase shown after 0.25.

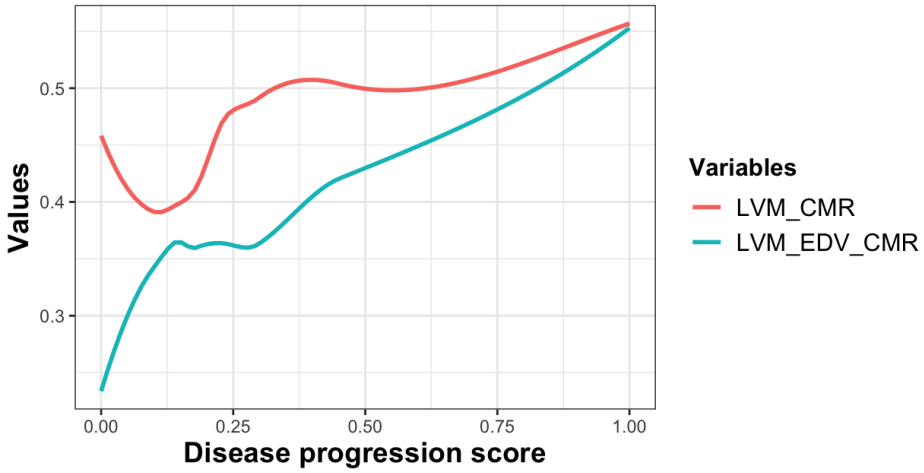


Figure 6.7. The relationship between the disease progression score and left ventricular mass measured using magnetic resonance imaging.

This line chart demonstrates the continuous relationship between the disease progression score and left ventricular mass (red line), and left ventricular mass indexed to left ventricular end diastolic volume (blue line) measured by cardiac magnetic resonance imaging.

LVM_CMR, left ventricular mass estimated using cardiac magnetic resonance imaging; LVM_EDV_CMR, left ventricular mass indexed to left ventricular end diastolic volume, estimated by cardiac magnetic resonance imaging.

6.4.2.4. Association with left ventricular response to exercise

Participants in the suboptimal blood pressure group (≥120/80 mmHg, studied in chapter 4 and 5), had higher disease progression scores compared to the optimal blood pressure group (p<0.0001), as demonstrated in Figure 6.8 panel A. Panel B illustrates the relationship between the disease progression score and left ventricular ejection fraction during exercise. Higher disease progression scores appear to be related to lower left ventricular response to moderate exercise, however, this relationship not statistically significant (p= 0.075).

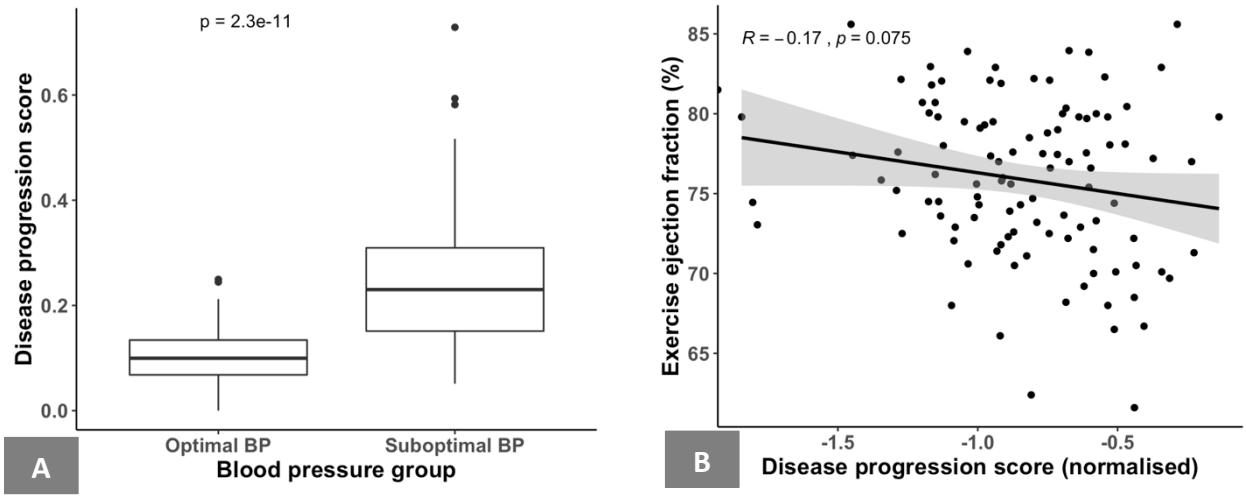


Figure 6.8. The relationship between the disease progression score and left ventricular ejection fraction during moderate exercise

Panel A demonstrates the differences in the disease progression score between suboptimal and optimal blood pressure groups. The relationship between the disease progression score and left ventricular ejection fraction measured during moderate exercise is shown as a scatter plot in panel B.

6.4.3. Model performance and validation

The results of the five K cross-validation for the model stability showed that when 20% of the dataset was taken off the model for testing, the new disease progression scores were correlated with the original score (r=0.71, p<0.0001). The RMSD was calculated for each fold and then averaged at 0.2. In addition, the mean disease progression score was different (p<0.0001) between the background and the target group (Table 6.3) when they were held out of the model. Thus, the validation criteria for the disease progression model performance were met.

Table 6.3. Disease progression scores difference between background and target groups

	Background n=111	**Target n=33**	***P* value**
Disease progression score, mean ± SD	0.2 ± 0.17	0.4 ± 0.21	<0.0001

6.5. DISCUSSION AND CONCLUSION

In this chapter, by applying the cTI algorithm on a cross-sectional rich dataset of clinical and echocardiography variables, I developed a disease progression model of hypertension in young adults. Participants were assigned with a disease progression score from zero to one based on the relative variances to the background group. Participants with a score close to zero are healthier compared to those with a score close to one. After developing the model, most important echocardiography parameters relevant to the disease progression of hypertension were identified and the pattern of changes of these parameters from health to disease was studied. This helped to study and compare the cardiac characteristics between participants with high and low disease progression score. In addition to this, the disease progression score was higher in participants with suboptimal blood pressure who had reduced left ventricular ejection fraction during exercise (Chapter 4, section 4.4).

In the previous chapters, I identified that the reduction in left ventricular ejection fraction during exercise can be predicted from changes in left atrial booster pump function at rest. Using single parameters in prediction models may not have given the full picture due to hidden interactions between parameters [224]. Therefore, in this chapter I aimed to develop a disease progression model that combines the effect of relevant clinical and echocardiography data on a relatively large cohort of young adults by using semi-supervised machine learning methods.

In this chapter, the novel cTI algorithm was applied to clinical cardiovascular echocardiography-based features for the first time. Recent studies have demonstrated that a combination of parameters can hold more value than single parameters [107, 108]. The combined effects of multiple echocardiography features, using machine learning tools, provides an additional prognostic value in patients with hypertension [185] and improve the

understanding of the disease in patients with heart failure [165, 171]. Therefore, the strength of this work also lies in the combination of echocardiography features, including 2D images, Doppler velocities, and speckle tracking features in this hypertension progression model. This could provide an insight of the subclinical cardiac remodelling secondary to blood pressure elevation in young adults.

Due to the non-linear nature of cardiac remodelling in hypertension, it has been challenging to study the disease progression without longitudinal follow-up data [18, 29]. The cPCA tool uses non-linear modelling to generate the disease progression scores and has achieved better performance compared to other dimensionality reduction approaches, such as traditional PCA and non-linear Uniform Manifold Approximation and Projection [228, 229].

As a secondary aim of the model development, I identified 21 echocardiography features that are mostly relevant to the hypertension progression in young adults. A higher disease progression score was associated with lower left atrial function and higher E/E' ratio. These findings are consistent with previous studies that reported the prognostic value of left atrial function in hypertension as individual parameters for the prediction of adverse cardiovascular events [237, 238]. Although signs of left ventricular hypertrophy secondary to hypertension have been widely linked with poor prognosis later in life [29, 101, 115], wall thickness parameters and left ventricular mass contributions were not as significant as left atrial and other diastolic parameters in this disease progression model. I was able to differentiate physiological increase in left ventricular mass from pathological hypertrophy when the left ventricular mass obtained from cardiac magnetic resonance was plotted against the disease progression score. Physiological hypertrophy can be developed in young athletes as a result of sustained vigorous physical activities [239]. Participants with physiological hypertrophy (increased mass but normalised when indexed to left ventricular volume) had lower disease progression scores compared to participants with pathological

hypertrophy as shown in Figure 6.7. A disease progression score based on echocardiography data may help to identify those with pathological hypertrophy without the need to perform magnetic resonance imaging and therefore may help clinicians to adjust and personalise the management plan.

For the final aim, I studied the relationship between the outcome of this model, the disease progression score, and the adverse cardiovascular response to physical exercise identified in Chapter 4. Even though the exercise outcome data were not included in the disease progression model development, participants in the suboptimal blood pressure group had higher disease progression scores compared to the optimal blood pressure group. The fact that the relationship between the disease progression score and left ventricular ejection fraction during exercise was not statistically significant may be explained by the difference in classification cut-off values of resting systolic blood pressure measures compared to the classification used in Chapter 4. In Chapter 4, participants were classified into two groups; suboptimal blood pressure ($\geq$ 120/80 mmHg), and optimal blood pressure (< 120/80 mmHg), while in the disease progression model participants with systolic blood pressure < 120 mmHg were in the background group, those with systolic blood pressure $\geq$ 160 mmHg were in the target group, and the intermediate group was for those with systolic blood pressure $\geq$ 120 mmHg and < 160 mmHg. A new model based on the cardiac response to exercise, or another cut-off classification of blood pressure could provide better results and would be a helpful tool to identify patients who may have less benefit from prescribed exercise interventions due to subclinical cardiac abnormalities.

6.5.1. Study limitation

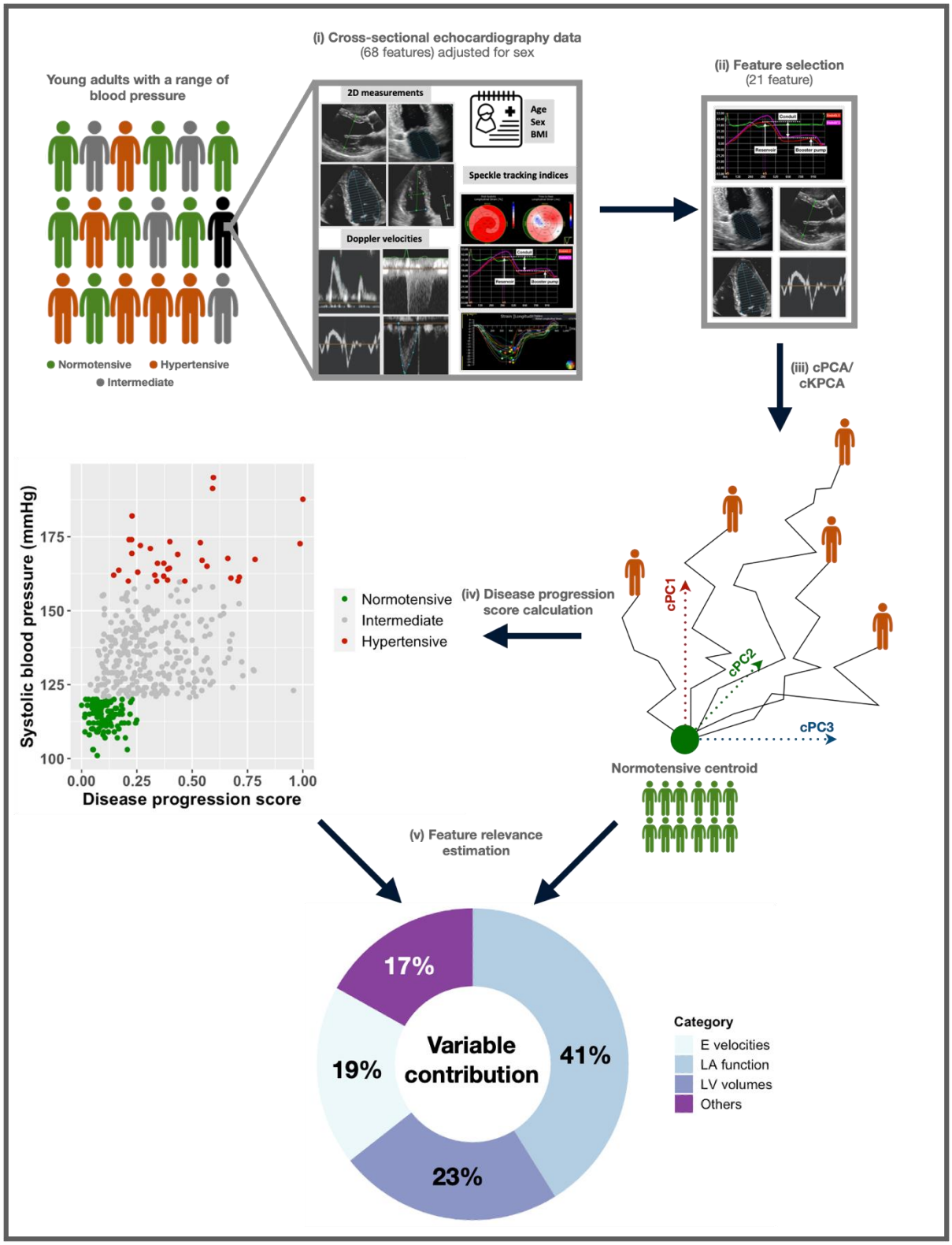
The work in this chapter has some limitations. First, as this is the first application of the cTI algorithm on clinical cardiovascular imaging data, the study sample is relatively small compared to previous applications on genetic data. The model performance could be improved with a larger cohort of young adults. Second, the majority of participants (> 90%) included to develop the model were recruited at a single centre, which might introduce sources of bias in the findings. Third, having identified the important echocardiography variables relevant to hypertension progression in young adults, some of the variables are not often obtained in clinical practice, such as left atrial strain parameters. This, therefore, could limit the generalisability of the results to real world practice. Fourth, a high cut-off value of systolic blood pressure (≥ 160 mmHg) was selected to clearly differentiate the target participants from the background. However, some participants in the intermediate group were diagnosed with hypertension and on anti-hypertension treatment. A lower cut-off value could be valid but requires future research. Fifth, although the pattern of remodelling of the contributed variables across the disease progression score (from zero to one) was consistent with the current literature of older hypertensives, the clinical meaning of the disease progression score requires further studies. Finally, due to the limited timeframe of my DPhil, the model performance was not tested on an independent dataset. To ensure the validity of the disease progression model for clinical use, further validation is required on an additional dataset with the clinically recommended set of echocardiography variables.

6.5.2. Conclusion

Using baseline clinical and echocardiography data from a cross-sectional dataset, I was able to study the disease progression of hypertension in young adults. I also identified the important echocardiography features relevant to hypertension in this cohort. To understand the clinical value of the disease progression score, more research is needed. Further validation for the disease progression model on new datasets is also required.

6.6 Appendices

Appendix 6.1. The steps and outcomes of the disease progression model



7. DISEASE PROGRESSION MODEL APPLICATIONS

7.1. ABSTRACT

Aims: In this chapter, I aimed to investigate the value of the disease progression model I developed in the previous chapter for potential clinical applications. I investigated whether people with different clinical stages of hypertension had different disease progression scores, whether the score was associated with an established modifiable cardiovascular risk score, and whether an exercise intervention could change the disease progression score.

Methods: Participants who have a disease progression score generated in the previous chapter (n=411) were included. Each participant was classified to a clinical stage of hypertension based on the referral and anti-hypertension treatment status. For a subgroup of participants (n=179), a cardiovascular risk score was calculated using eight modifiable risk factors for whom this data was available. In addition, a new disease progression score was generated from the 16-week follow-up data of participants who participated in the exercise intervention trial (n=126).

Results: Participants who had been on a longer duration of treatment had higher disease progression scores compared with those with no treatment (p<0.001). The disease progression score was the lowest in participants who were not referred to a hypertension clinic and were not on treatment (p<0.001). Participants with the most adverse risk factors had the highest disease progression scores and vice versa (p<0.0001). Participants with improved disease progression score post-exercise intervention had higher ventilatory threshold levels (p=0.01) and spent more active days at the gym (p=0.015). In addition, participants who met the compliance criteria for the exercise sessions had a smaller change in the disease progression score from baseline compared to non-compliant participants (p=0.043).

Conclusion: Although the disease progression score was generated from baseline echocardiography data, it was associated with different clinical stages of hypertension, consistent with an established modifiable cardiovascular risk score, and its improvement post 16-week exercise intervention was associated with higher fitness levels. These findings provide preliminary evidence of the clinical value of this score. Further work is needed to determine whether the disease progression score could be clinically applied to better improve hypertension management in younger patients.

Publication Status: The methods and results presented in this chapter have been filed for a patent application (No. 2113322.8) on 17th September 2021. A manuscript is being prepared to be submitted to The Lancet.

7.2. INTRODUCTION

Multiple risk score models have been recommended to estimate the cardiovascular and cerebrovascular risk as per the hypertension management guidelines in clinical practice [195, 240, 241]. However, these models have limitations, particularly in the risk assessment for younger patients due to insufficient longitudinal data [18]. Despite this, observational studies showed that uncontrolled hypertension during adulthood is associated with an increased risk of adverse outcomes in later life [7, 8, 242, 243].

Blood pressure control can be achieved by pharmacological and/or non-pharmacological interventions. Both approaches have shown a beneficial effect in lowering blood pressure measures and reducing the risk of cardiovascular, cerebrovascular, and renal adverse events [11]. Non-pharmacological interventions, such as adhering to regular physical activity, weight reduction, and diet modifications, are usually prescribed for patients with mild hypertension to prevent or delay the need for pharmacological intervention [10]. In patients with more severe hypertension, especially those with high risk of cardiovascular disease, pharmacological treatment is recommended [10, 11]. Randomised clinical trials have demonstrated that a reduction of ten mmHg in systolic blood pressure or five mmHg in diastolic blood pressure is associated with a 20% reduction of adverse cardiovascular events [10]. However, these studies were carried out on older, high-risk patients [10]. For younger patients, there is a lack of randomised clinical trials to assess the benefit of pharmacological or exercise interventions in lowering blood pressure levels.

Although studies have shown that uncontrolled blood pressure early in life is associated with a substantial increase in lifetime cardiovascular risk [4, 242], the

absolute 10-year risk remains relatively low in younger patients [8]. Therefore, a longer follow-up duration is needed to detect adverse events. A modifiable cardiovascular risk score using multiple risk factors has shown to be associated with early changes in cerebrovascular density and flow in young adults [195]. This score was adapted from established cardiovascular risk scores to include independent risk factors such as alcohol consumption and blood pressure measures during exercise [241, 244, 245].

Regular exercise activities can help to improve cardiovascular health and prevent adverse events later in life [246]. However, in terms of lowering blood pressure, the long-term effect of exercise remains understudied [46]. Previous studies are inconsistent in terms of exercise intensity, duration, and compliance, which may limit the generalisability of the results [46]. A recent meta-analysis of 14 studies in the effect of exercise in lowering blood pressure in young adults reported that supervised interventions with higher exercise intensities and longer session duration are associated with lowering blood pressure [46].

In the previous chapter, I developed a disease progression model of hypertension in young adults. The severity of progressive changes in cardiac structure and function secondary to hypertension was summarised in a single score from zero to one using echocardiography data from a cohort of young adults. Higher scores (closer to one) reflect worse disease progression. Participants included in the model came from different clinical stages of hypertension (i.e., referred to a hypertension clinic and/or received pharmacological therapy), and were exposed to different management plans (i.e., exercise interventions, and pharmacological treatment). Therefore, I aimed to investigate the clinical value of the disease progression score by testing the following three questions:

i. Does the score differ between individuals in different clinical stages of hypertension?

ii. Is the disease progression score consistent with an established modifiable cardiovascular risk score?

iii. Could a 16-week exercise intervention improve the score?

In addition, I aimed to study the clinical and echocardiographic characteristics of selected participants with different disease progression scores.

7.3. METHODS

7.3.1. Study population

The study cohort selected for this chapter is the same cohort studied in Chapter 6, described in the Methods, section 6.3.1. Study population. A detailed description of the participant recruitment process and selection criteria are provided in Chapter 2 (section 2.6.3).

7.3.2. Study measures

In addition to the study measures described in Chapter 6 (section 6.3.2. Clinical investigations and variables), I added the following measures to achieve the aims of this chapter:

- **Anti-hypertension treatment data**

  The status of whether participants were on anti-hypertension treatment or not was collected for all participants. Participants who were included in the disease progression and had no treatment information were excluded. For participants referred to the hypertension clinic, data were collected from their medical notes and the NHS Electronic Patient Record. Those who were not referred to a clinic completed a questionnaire at the end of their baseline study visit about their medical history and anti-hypertension medication intake. The duration of treatment, the number of medications, the doses and the type of medications were also collected. Based on these data, participants were classified into four stages of clinical hypertension as follows:

A. No referral to a hypertension clinic with no pharmacological treatment
B. Referred to a clinic but with no pharmacological treatment
C. Referred with less than two years of pharmacological treatment
D. Referred with more than two years of pharmacological treatment

- **Cardiopulmonary exercise testing (CPET)**

  The CPET was performed for a subgroup of participants from the cohort utilised in the disease progression model. The CPET procedure and protocol are described in detail in Chapter 3 (section 3.7).

- **Calculation of lifetime risk score of cardiovascular disease**

  The cardiovascular risk score was calculated for a subgroup of the participants included in the disease progression model, based on the following eight modifiable risk factors:

  1. Body mass index less than 25 kg/m^2.
  2. Highest tertile of cardiovascular fitness and/or physical activity.
  3. Alcohol consumption of less than eight drinks per week.
  4. Non-smoker for more than six months.
  5. Blood pressure on awake ambulatory monitoring lower than 130/80 mmHg.
  6. A non-hypertensive diastolic response to exercise (peak diastolic blood pressure less than 90 mmHg).
  7. Total cholesterol level lower than 200 mmol/L.
  8. Fasting glucose level lower than 100 mmol/L.

The score was calculated by awarding one point to the healthier category for each factor. These score criteria were adapted from established cardiovascular risk scores to include dynamic exercise blood pressure response [195]. Higher scores represent better cardiovascular health. The data collection process for each factor is described in detail in Chapter 3 (section 3.10).

- **Echocardiography imaging (obtained during visit 2)**

  Echocardiography data obtained at the 16-week follow-up visit after randomisation to either exercise intervention or control arms for a subgroup of participants were used in this chapter. Data collection and analysis were performed as described in Chapter 3 (section 3.5. Echocardiography imaging). In this chapter, the data were utilised to generate a new disease progression score for this group of participants.

- **Exercise intervention compliance data**

  A subgroup of the participants involved in the disease progression model were randomised to a 16-week exercise intervention as part of their participation in TEPHRA. The number of supervised sessions (active days in the gym) and daily physical activity (average daily steps) were recorded. The intervention compliance and adherence data were assessed following the below protocols:

  A. **Compliance per Protocol 1:** 80% attendance at supervised sessions.

B. **Compliance per Protocol 2:** 80% attendance at supervised sessions merged with the number of active days.

C. **High Dose Exposure in 16 weeks:** 80% attendance at supervised sessions, or MVPA-VPA greater than three hours per week (if evidence of wear time five times per week), or 10,000 steps per day every day averaged over wear time (if evidence of wear time five times per week).

D. **Maintained Dose Exposure up to 52 weeks:** Evidence that maintained activity between 16 and 52 weeks, wear time greater than three hours per week, and steps average 8000 or greater than 150 minutes MVPA per day.

A detailed description of the data collection is available in Chapter 3 (section 3.9).

7.3.3. Statistical analysis

R 4.0.2 was used for statistics and data visualisation in this chapter. Shapiro-Wilk test and visual assessment were used for normality. Participants were classified based on their clinical stage of hypertension in four categories: no referral or treatment, referred with no treatment, referred with less than two years of treatment, and referred with more than two years of treatment. One-way ANOVA test was applied to determine the disease progression score difference between the four categories, and the cardiovascular risk score groups. Comparisons between two groups for baseline continuous variables were performed using two-sided, independent samples Student t-tests for normally distributed data and Mann-Whitney for non-normally distributed data.

Participants who were randomised to the exercise intervention arm or control arm had another disease progression score generated from data collected during their 16-week follow-up visit. This new score was generated using MATLAB R2019b programming environment (Mathworks Inc., Natick, MA, USA). The follow-up data were imputed, adjusted, and standardised following the same methods used to generate the disease progression score in Chapter 6 (section 6.3.3. Statistical analysis). Pearson correlation tests were used to test the relationship between the change in disease progression score from baseline to 16-week follow-up and fitness variables including ventilatory aerobic threshold, peak exercise VO2, predicted peak VO2 percentage, the exercise intervention compliance protocols, and the number of active days. Independent samples Student's t-tests were also used to compare the differences in the score between compliant and non-compliant participants.

A p-value of ≤ 0.05 was used to indicate the statistical significance, and a 95% confidence interval was used.

7.4. RESULTS

7.4.1. Clinical stages of hypertension

A total of 396 participants were classified based on their clinical stages of hypertension into four groups. A group of 15 participants, who were referred to the hypertension clinic and had no treatment information, were excluded from this analysis. Participants with no referral or anti-hypertension treatment had the lowest disease progression score compared with those referred to the clinic (p<0.0001). In addition, participants who had been on pharmacological treatment for more than two years had higher disease progression score compared to participants with less than two years of pharmacological treatment (p=0.037). Figure 7.1 demonstrates the difference in the disease progression score among the four stages of clinical hypertension. The baseline clinical characteristics for each group are presented in Table 7.1. Linear regression analysis showed that the disease progression score is associated with the clinical stages of hypertension (β= 2.6, p<0.0001).

Table 7.1. Baseline characteristics of participants at four clinical stages of hypertension

	Group A n=246	**Group B n=24**	**Group C n=70**	**Group D n=56**	***P* value**
Age	26.5 ± 4.3	31.7 ± 5.1	31.9 ± 6.3	34.5 ± 4.9	**<0.001**
Male % (n)	50.8 (125)	37.5 (9)	45.7 (32)	42.9 (24)	0.49
SBP	124.4 ± 11.4	143.1 ± 17.7	142.6 ± 16.7	145.5 ± 16.2	**<0.001**
DBP	75.8 ± 9.6	91.9 ± 11.7	90 ± 13.4	90 ± 10.9	**<0.001**
Height	173.1 ± 9.2	175 ± 8.4	172.3 ± 11.4	173.5 ± 12.3	0.74
Weight	74.04 ± 13.8	82.3 ± 14.4	86.7 ± 19.8	93 ± 24.9	**<0.001**
BSA	1.9 ± 0.2	2.1 ± 0.1	2.05 ± 0.2	2.1 ± 0.2	**<0.001**
BMI	24.7 ± 3.8	27.1 ± 3.8	28.6 ± 5.1	30.8 ± 6.1	**<0.001**

Group A, No referral or treatment; Group B, Referred with no treatment; Group C, Referred with treatment < two years; Group D, Referred with treatment > two years; SBP, systolic blood pressure; DPB, diastolic blood pressure; BSA, body surface area; BMI, body mass index.

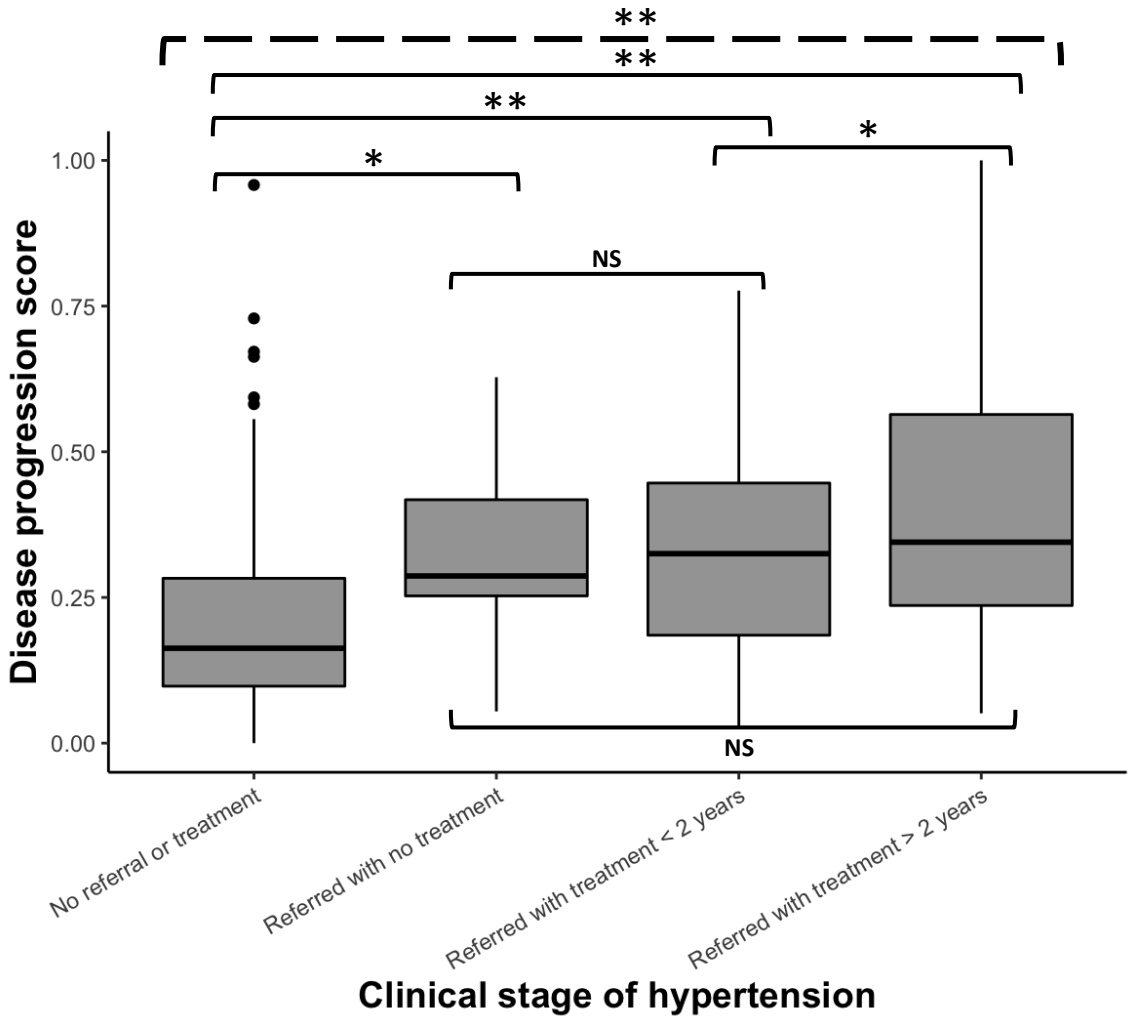


Figure 7.1. The disease progression score and clinical stages of hypertension.

This figure illustrates the differences in the disease progression scores based on the clinical stage of hypertension. Participants with more than two years of anti-hypertension treatment had a higher score (p=0.037) than those with shorter treatment duration. Participants with no referral or treatment had the lowest score (p<0.0001). The dashed line represents the difference between the groups and the solid lines for the two groups comparison.

** *P* value <0.001
* *P* value <0.05
NS *P* value >0.05

7.4.2. Association between the disease progression score and a cardiovascular risk score

To further understand the value of the disease progression score, for a subgroup of the participants (n= 179), the score was compared with an established cardiovascular risk score calculated from eight modifiable risk factors [195]. Participants in group 1 in the cardiovascular risk score had the most adverse risk factors, while those in group 4 had the lowest risk of cardiovascular disease. Baseline characteristics of this cohort of participants are presented in Table 7.2. Group 1 participants were the oldest (p=0.041) with the highest systolic (p<0.001) and diastolic (p<0.001) blood pressure and had the highest body mass index (p<0.001) compared to the other groups. Participants with the worst risk factors (group 1) had the highest disease progression scores (p<0.0001), as illustrated in Figure 7.2. Linear regression analysis showed that the disease progression score is associated with the modifiable cardiovascular risk score (β= -2.8, p<0.0001).

Table 7.2. Baseline characteristics of participants at four groups of cardiovascular risk score

	Group 1 n=29	**Group 2 n=49**	**Group 3 n=52**	**Group 4 n=49**	***P* value**
Age	28.48 ± 3.99	26.34 ± 4.76	25.96 ± 4.3	25.59 ± 4.62	**0.041**
Male %(n)	58.6 (17)	46.9 (23)	44.2 (23)	57.1 (28)	0.442
SBP	133.59 ± 13.02	127.1 ± 10.03	125.31 ± 9.45	117.55 ± 9.16	**<0.0001**
DBP	82.55 ± 8.17	78.22 ± 8.4	75.27 ± 9.82	69.27 ± 7.49	**<0.0001**
Height	171.62 ± 8.78	173.17 ± 9.81	173.28 ± 9.52	175.03 ± 9.86	0.486
Weight	83.42 ± 14.17	78.49 ± 15.68	74.16 ± 12.96	68.17 ± 10.48	**<0.0001**
BSA	1.99 ± 0.20	1.94 ± 0.23	1.88 ± 0.2	1.82 ± 0.19	**0.002**
BMI	28.47 ± 4.04	26.1 ± 4.14	24.62 ± 2.95	22.2 ± 1.87	**<0.0001**

Data are presented as mean ± standard deviation for continuous variables, and frequency and percentage for categorical variables.
SBP, systolic blood pressure; DPB, diastolic blood pressure; BSA, body surface area; BMI, body mass index.
Based on the estimated cardiovascular risk score, participants were allocated into four groups. Group 1 is for those with the most adverse risk factors, while group 4 is for participants with the lowest risk of cardiovascular disease.

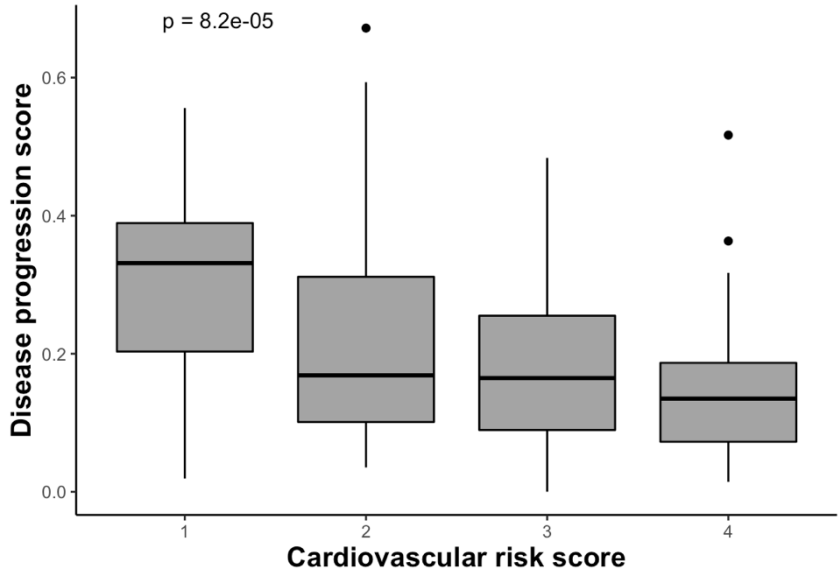


Figure 7.2. The relationship between the disease progression score and the modifiable cardiovascular risk score.

This figure illustrates the relationship between the disease progression score and the modifiable cardiovascular risk score. Participants with the most adverse risk factors (group 1) had the highest disease progression scores (p<0.0001).

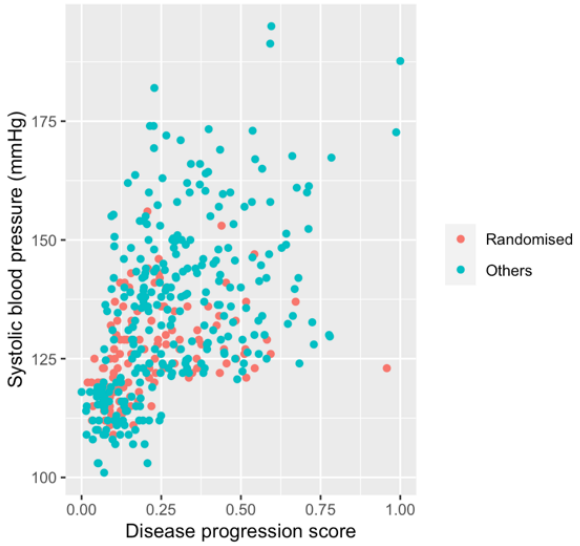
Based on the estimated cardiovascular risk score, participants were allocated into four groups. Group 1 is for those with the most adverse risk factors, while group 4 is for participants with the lowest risk of cardiovascular disease.

7.4.3. The effect of 16-week exercise intervention

In the subgroup of participants (n=126) included in the disease progression model development in Chapter 6 (Figure 7.3) who had participated in the exercise intervention trial, a second disease progression score was generated from their 16-week post-randomisation follow-up data. Participants' characteristics at baseline and 16-week post-randomisation are presented in Table 7.3. There was no difference between the exercise group and controls in the baseline clinical characteristics. Figure 7.4 illustrates the disease progression scores for this cohort at the baseline and 16-week follow-up visits (panel A). Panel B in Figure 7.4 shows the change in the score from baseline to after the intervention for the exercise group,

and panel C for the control group. Both panels demonstrate a heterogeneous response of reduction and increase in the disease progression score post-intervention. There was no difference in the disease progression score from baseline to post-randomisation between control and exercise arms, as shown in panel D.

In participants who had a lower disease progression after the exercise intervention relative to their baseline score, the reduction in score was associated with an increase in the ventilatory threshold levels (p=0.01), as demonstrated in Figure 7.5 A. However, it was not associated with the change in peak VO2 (p=0.31) or the predicted peak VO2 percentage (p=0.33). The change in the disease progression score was also correlated with the number of active days spent at the gym (r=-0.32, p=0.015) (Figure 7.5 B). There was no correlation between the change in the disease progression score and the average daily steps (r=0.1, p=0.423). Panel C in Figure 7.5 shows that participants who were compliant with the exercise intervention had improved their disease progression score compared to non-compliant participants (p=0.043) as per protocol 1. Compliance level per protocol 2 (p=0.22) and high dose exposure in 16 weeks (p=0.065) were not related to changes in the score. In addition, participants who did not maintain physical exercise up to 52 weeks had a lower disease progression score at baseline (p=0.015) than compliant participants (Figure 7.5 D).



This scatter plot shows the disease progression score for all participants included in the disease progression model. The red dots represent the disease progression score for the randomised group in TEPHRA. Others (blue dots) are participants from YACHT and HyperEcho studies.

Figure 7.3. The randomised participants in the disease progression score.

Table 7.3. Clinical characteristics of randomised participants at baseline and 16-week after randomisation

	Control n=66	Exercise intervention n=60	*p* value
Age (years)			
Baseline	27.2 ± 3.9	28.03 ± 3.5	0.211
16-week	27.7 ± 3.9	28.6 ± 3.5	0.183
Male % (n)	48.5 (32)	50 (30)	0.503
Systolic blood pressure (mmHg)			
Baseline	124.3 ± 8.8	127.5 ± 10	0.06
16-week	120.1 ± 9.8	121.9 ± 9.3	0.295
Diastolic blood pressure (mmHg)			
Baseline	77.3 ± 9.1	79.5 ± 8.1	0.161
16-week	74.3 ± 8.9	77.3 ± 8.8	0.061
Height (cm)			
Baseline	172.7 ± 8.6	172.7 ± 8.8	0.977
16-week	172.6 ± 8.5	172.6 ± 8.6	0.968
Weight (kg)			
Baseline	73.6 ± 11.1	74.4 ± 12.6	0.734
16-week	73.9 ± 10.6	73.6 ± 13.1	0.905
Body surface area			
Baseline	1.88 ± 0.17	1.88 ± 0.19	0.809
16-week	1.88 ± 0.17	1.87 ± 0.19	0.882
Body mass index			
Baseline	24.7 ± 3.1	24.9 ± 3.6	0.746
16-week	24.8 ± 3	24.7 ± 3.7	0.818

Data are presented as mean ± standard deviation for continuous variables, and frequency and percentage for categorical variables

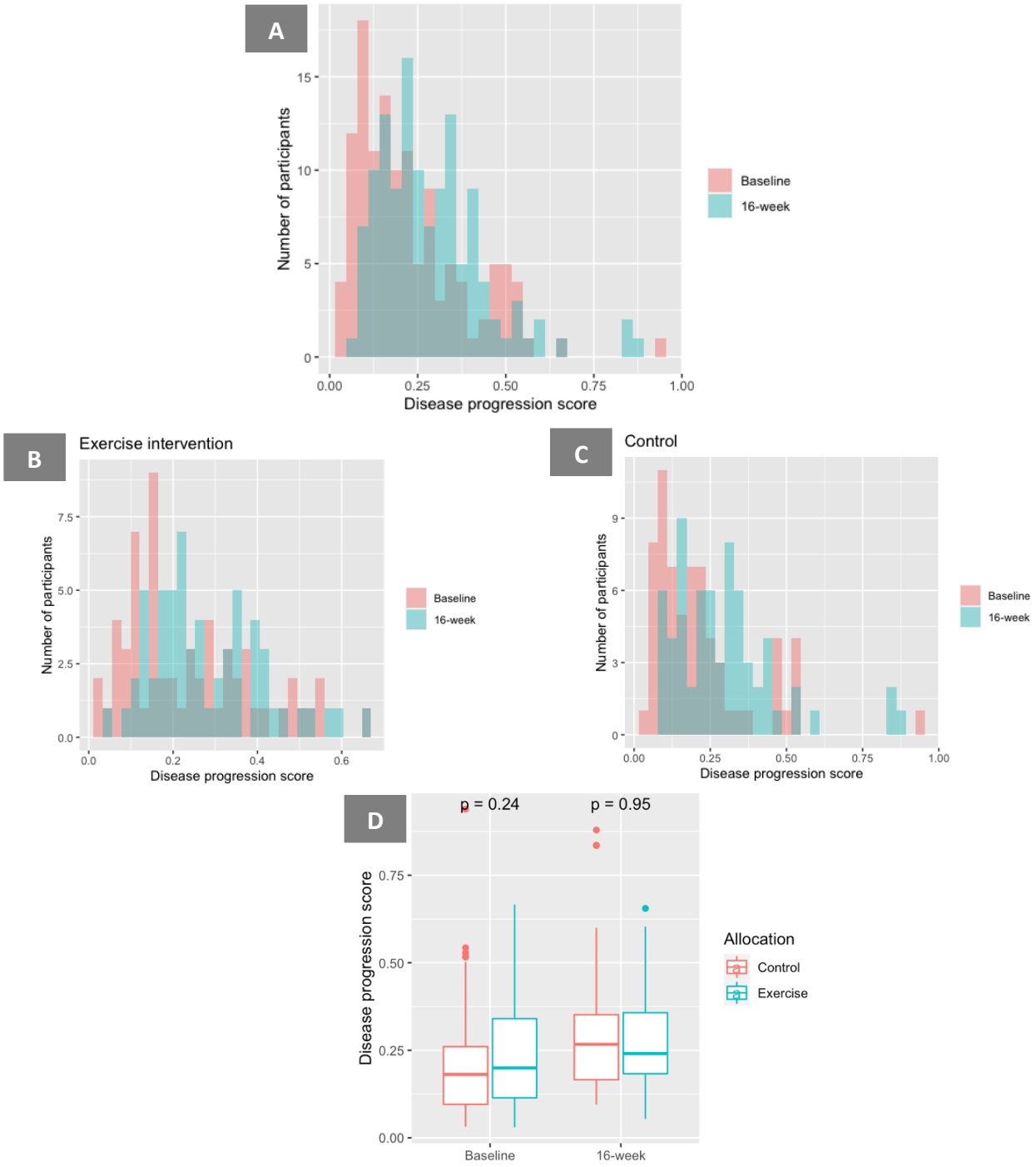


Figure 7.4. The difference between the disease progression score at baseline and at 16-week follow-up.

Histograms demonstrate the disease progression score for randomised participants at baseline and 16-week follow-up (A). Baseline and 16-week disease progression scores for the exercise and control groups are illustrated in panel (B) and (C), respectively. The box plots in panel (D) represents the mean differences in the disease progression score between the groups before (mean difference = 0.023) and after randomisation (mean difference = 0.014).

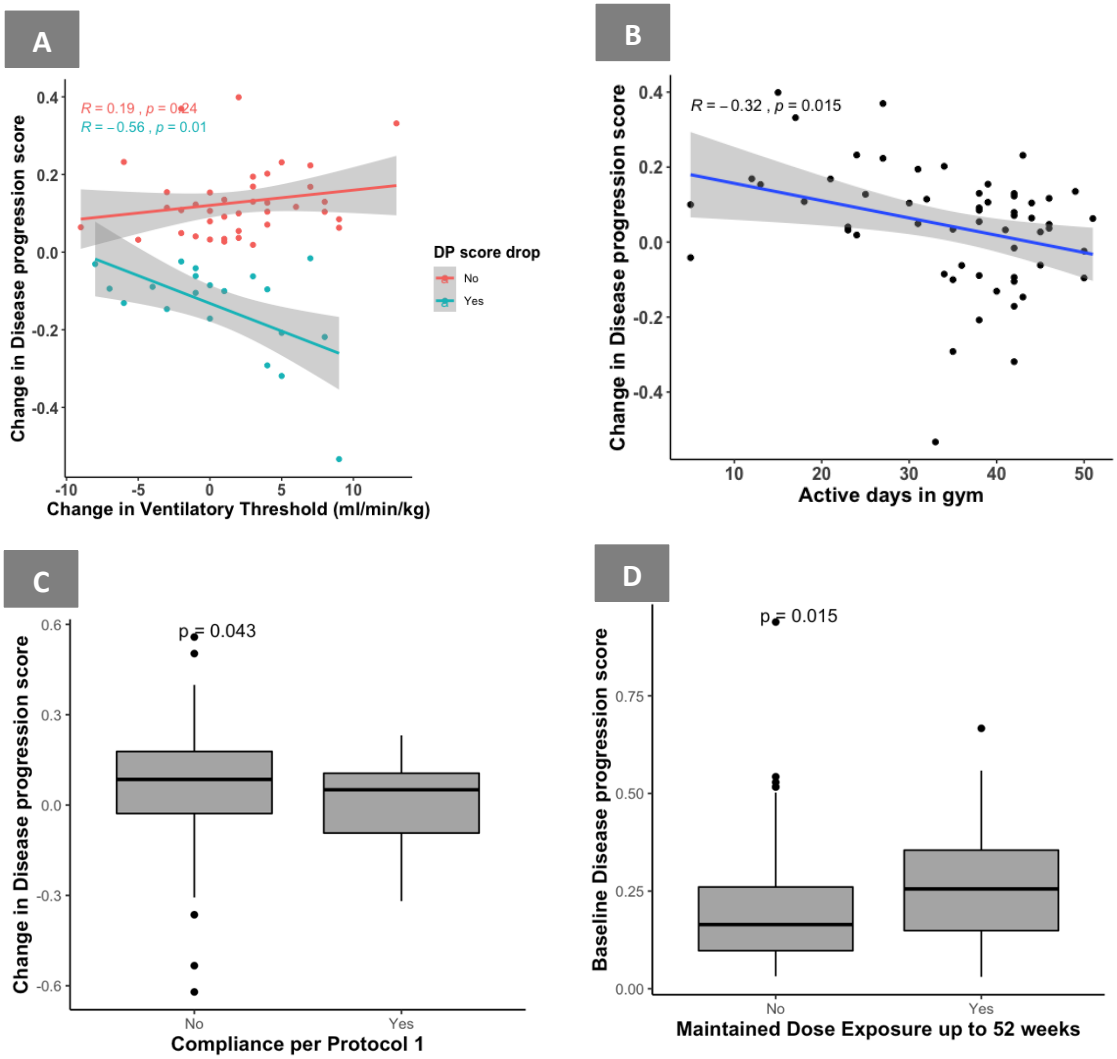


Figure 7.5. Relationships between the change in the disease progression score and physical activity measures.

The reduction in the disease progression score after a 16-week exercise intervention was associated with improved ventilatory threshold from baseline (p=0.01) (A). The reduction in the score was also associated with a higher number of active days at the gym (p=0.015) (B). Panel C illustrates that participants who complied to the exercise intervention had improved their score compared with non-compliant participants (p=0.043). The baseline disease progression score was lower in those who did not maintain physical exercise (p=0.015) for up to 52 weeks as shown in panel D.

DP, Disease progression

7.4.4. Individual clinical and echocardiographic characteristics (Case Study)

To study the clinical and echocardiographic characteristics, three participants with different disease progression scores were selected, as illustrated in Figure 7.6. One was a randomised participant allocated into the exercise intervention arm (case A), and another randomised participant from the control arm was selected (case B). The participant with the highest disease progression score was also selected (case C). Case A shows that the disease progression score reduced from 0.67 to 0.13 after the 16-week exercise intervention, but blood pressure measures remained similar. The participant had an improvement in fitness levels, left ventricular mass, and left atrial volume. While the participant from the control group (case B) also had similar blood pressure measures after a 16-week follow-up, the disease progression score did not change dramatically. In case C, in which the highest disease progression score was assigned, the participant had elevated blood pressure measures, was a smoker and on multiple medications with increased left ventricular mass index, left atrial volume index, and E/E' ratio.

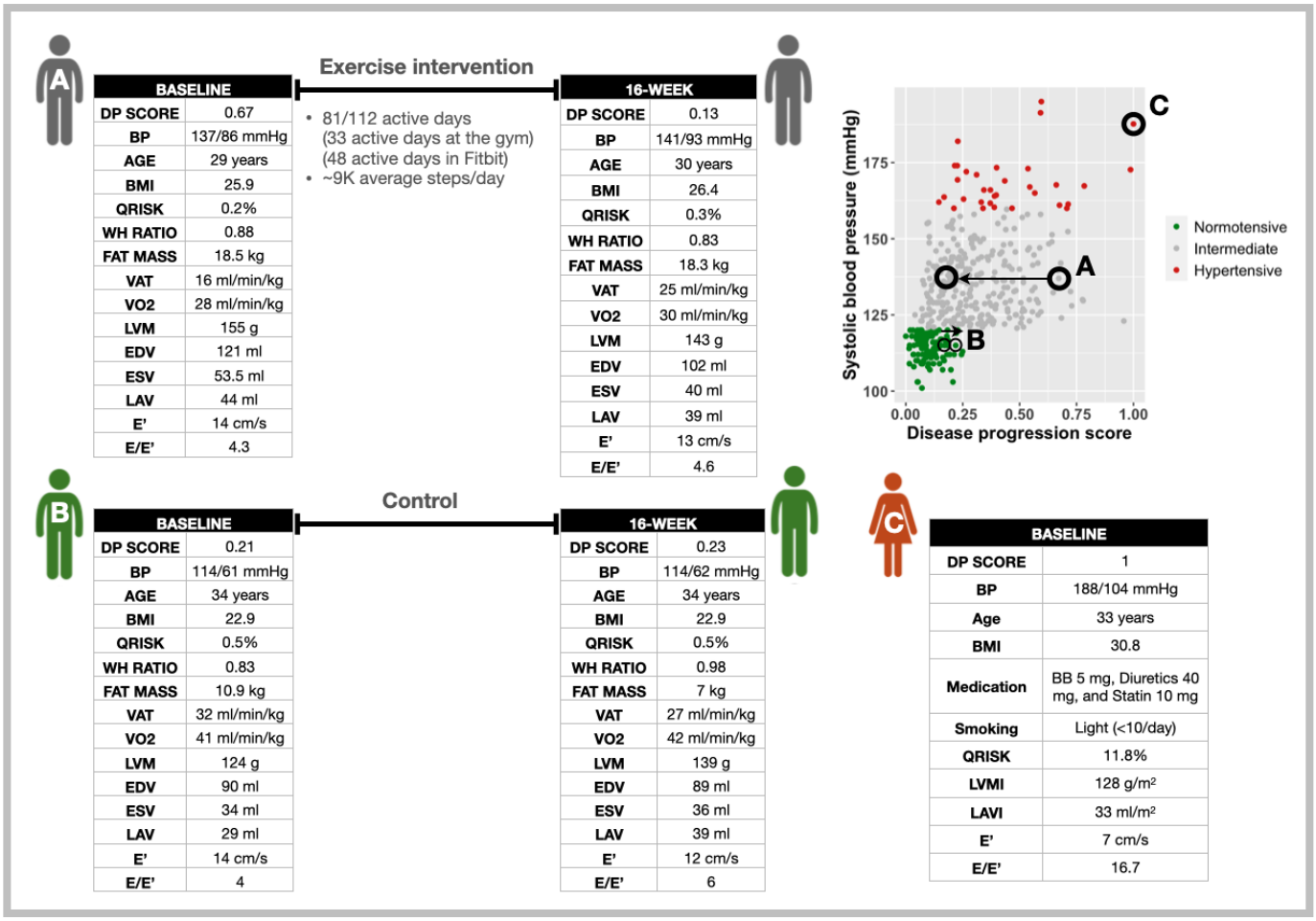


Figure 7.6. Individual clinical and echocardiography characteristics.

This figure presents three cases with their individual clinical and echocardiographic characteristics. Case A illustrates the clinical and echocardiographic characteristics for a participant who was randomised into the exercise intervention arm (at baseline and after the 16-week follow-up), while case B shows the characteristics for a participant from the control group (at baseline and after the 16-week follow-up). The characteristics of the participant with the highest disease progression score are presented in case C.

DP, disease progression; BP, blood pressure; BMI, body mass index; QRISK, QRISK3 score; WH, waste-hip; VAT, ventilatory aerobic threshold; LVM, left ventricular mass; EDV, end diastolic volume; ESV, end systolic volume; LAV, left atrial volume; BB, beta blocker; LVMI, left ventricular mass index to body surface area; LAVI, biplane left atrial volume index to body surface area.

7.5. DISCUSSION AND CONCLUSION

After developing a disease progression score for hypertension in young adults from a cross-sectional dataset of baseline clinical and echocardiography features in the previous chapter, I aimed to study its clinical value. I tested the following questions:

i. Does the score differ between individuals in different clinical stages of hypertension?
ii. Is the disease progression score consistent with an established modifiable cardiovascular risk score?
iii. Could a 16-week exercise intervention improve the score?

In addition, three cases were selected to study their individual clinical and echocardiography characteristics. The main findings of this chapter are: (i) longer duration of anti-hypertension treatment was associated with higher disease progression scores; (ii) participants who were not referred to a hypertension clinic had a lower score compared to those who attended the clinic; (iii) participants with high disease progression score had worse cardiovascular risk factors estimated by the modifiable cardiovascular risk score; (iv) there was no significant difference in disease progression scores between the exercise intervention and control groups, but disease progression score improvement after a 16-week supervised exercise intervention was associated with higher ventilatory threshold levels; and (v) the change in the score from baseline to after 16-week was independent of blood pressure measures, and the higher score reflected a more progressive stage of hypertension in the selected cases. Although there is a link between these results, each question will be discussed separately in the following sections.

7.5.1. Clinical stages of hypertension

I aimed to study whether the disease progression score, which was primarily generated from baseline echocardiography features and did not include information on treatment duration or severity of illness, varies depending on the stage of hypertension. Participants who were on a longer duration of anti-hypertension treatment had higher disease progression scores compared with those who were not on treatment. Participants who were not referred to a hypertension clinic had lower scores compared with referred participants regardless of whether they started treatment or not.

Previous randomised clinical trials have examined the effectiveness of pharmacological treatment in lowering blood pressure and reducing the risk of future cardiovascular events in patients with mild hypertension [247-249]. However, the trials that have reported a benefit of pharmacological therapy have focused on relatively higher-risk and older individuals [249]. Studies that have included low-risk hypertensive patients have shown no association between the blood pressure lowering treatment and cardiovascular events later in life [250-252]. Recent observational studies have also reported the lack of association between early pharmacological intervention and reduced mortality or cardiovascular events in low-risk patients with mild hypertension [156, 158]. This could be explained by the poor adherence level to anti-hypertension treatment in younger populations. The non-adherence level was the highest in patients aged between 18 and 34 years [157], which might be due to the lack of clinical symptoms and low level of interaction with health services [18]. In young patients with mild hypertension, poor adherence to

anti-hypertension treatment was associated with increased risk of adverse cardiovascular events later in life [158].

Because of the low prevalence of adverse events in younger populations and the unfeasible sufficient follow-up duration required to detect a treatment effect, the effect of anti-hypertension treatment in younger patients with hypertension remains understudied [11, 253]. The findings of this chapter demonstrate that it might not be possible to assess the effect of treatment using the disease progression score estimated from echocardiography features, but it could reflect the clinical stage of hypertension. The disease progression score could help differentiate patients with chronic stages of hypertension and advanced cardiac remodelling from those newly diagnosed, which may allow clinicians to identify those who may benefit from pharmacological therapy at an earlier stage.

7.5.2. Comparison with a modifiable cardiovascular risk score

I aimed in this section to compare the disease progression score with an established cardiovascular risk score. The clinically available and validated risk score models are based on an overall assessment of a combination of risk factors, such as blood results, resting and exercise blood pressure measures, and family history. In contrast, the disease progression model was mainly developed from a set of echocardiography features (the list of features is available in Chapter 6, Table 6.2). When the disease progression score was plotted with an established modifiable cardiovascular risk score based on eight risk factors, participants with greater risk factors had higher disease progression scores. Even though the disease progression

model did not include information about the alcohol consumption or lipid profiles, it was consistent with the modifiable cardiovascular risk score outcomes.

The use of ten-year risk prediction models is recommended in the hypertension management guidelines to support the decision of anti-hypertension treatment initiation [10-12]. For younger patients, particularly, there has been a certain level of limitation using these models [68, 69]. Researchers found that using 10-year risk prediction models in patients below the age of 40 leads to an overestimation of the risk and lack of validity [70, 71]. This is because the absolute ten-year risk in young patients is often low [26], and the risk prediction models were validated on data derived from older populations, which may be less applicable to younger patients [10, 11]. Further, due to the lack of longitudinal clinical studies with a sufficient follow-up duration in younger patients with hypertension [10, 11], risk prediction in this population remains limited. To overcome this limitation, the disease progression model was developed by extracting pseudo-temporal information from echocardiography cross-sectional data derived from young adults to assign each participant with a score. The disease progression score reflects the level of cardiac structural and functional alterations throughout the disease progression of hypertension as described in the previous chapter. In this chapter, I demonstrated that the disease progression score is consistent with the findings of an established modifiable cardiovascular risk score. Whether the disease progression score can be used as an alternative risk assessment score for younger patients with hypertension requires further research and validation.

7.5.3. Effect of a 16-week exercise intervention

I aimed to study the adaptation effect of a 16-week exercise intervention on the disease progression score for a subgroup of the participants. Performing regular aerobic exercise has shown a beneficial impact on lowering blood pressure levels [46] and is frequently prescribed to young, low-risk hypertensives to avoid or delay the initiation of pharmacological intervention [10, 11]. However, a heterogeneous blood pressure response to exercise has been observed in younger patients with hypertension [46]. This response could be related to a variety of factors, including the intensity of exercise, the level of adherence and compliance to exercise sessions, or subclinical cardiac abnormalities [46, 154]. In Chapter 4, I identified that participants with suboptimal blood pressure (≥ 120/80 mmHg) had lower left ventricular ejection fraction response during moderate physical exercise. The suboptimal blood pressure group also had a higher disease progression score, as shown in the previous chapter. In this chapter, a new score was generated using echocardiography data obtained after a 16-week exercise intervention.

The degree of reduction or increase in the disease progression score post the exercise intervention varies among participants. Participants who had an improved disease progression score (reduced) post-exercise intervention compared to the baseline score had better ventilatory threshold levels and spent more days at the gym. Previous studies demonstrated that the level of adherence and compliance to exercise sessions are associated with more sustained long-term benefits in controlling blood pressure [46, 254, 255]. This could explain the reduction in the disease progression score after the 16-week follow-up for the compliant participants, as shown in Figure 7.4 panel C. Interestingly, participants who did not maintain physical exercise activities for up to 52 weeks had a lower disease progression score

at baseline (Figure 7.4 D). Individuals with healthier cardiovascular structure and function may be less motivated to maintain regular physical activities. The disease progression scoring could assess the efficacy of exercise interventions on cardiac structure and function, which could help clinicians adjust the exercise prescription for younger patients.

7.5.4. Individual clinical and echocardiographic characteristics (Case Study)

To further understand the clinical meaning of the disease progression score, I selected three cases and studied their individual clinical and echocardiography characteristics. In case A, the change in the disease progression score from baseline to after 16 weeks of exercise was independent of the change in blood pressure measures. Although blood pressure measures and QRISK score did not reduce after the exercise intervention, the disease progression score was reduced. The reduction in the disease progression score was in line with the improvement in fitness levels and cardiac structure and function. Prior studies reported that better fitness levels are associated with a reduction in all-cause mortality and cardiovascular mortality secondary to high body mass index [256, 257].

In contrast, the disease progression score has increased slightly from 0.21 to 0.23 in the participant from the control group (case B), who had low levels of physical exercise during the 16 weeks. A sedentary lifestyle is highlighted as one of the major risk factors for cardiovascular disease in the hypertension management guidelines [10, 11]. The third case was the participant with the highest disease progression score, in which the participant had uncontrolled high blood pressure measures causing cardiac remodelling in the form of left ventricular hypertrophy

and increased left atrial volume. The participant was obese, a smoker, and on multiple medications. All these factors are associated with increased cardiovascular risk and adverse events [10, 11]. This participant was assigned with the highest score, even though the disease progression model was only developed from resting echocardiography data.

These cases emphasise that the disease progression score could reflect the severity of hypertension considering multiple factors, including blood pressure measures, fitness levels, and changes in cardiovascular structure and function.

7.5.5. Study limitation

The work in this chapter has some limitations. First, due to the relatively small sample size used to develop the disease progression model in the previous chapter, and even smaller samples were used in the applications in this chapter, the generalisability of the results to all young adult populations may be limited. Second, most of the randomised participants were relatively healthy with low disease progression scores at baseline compared to other participants in the model, as shown in Figure 7.2. Also, the 16-week exercise intervention may not be sufficient in duration to cause structural and functional changes in the heart. Therefore, further research on longer exercise duration may be needed to assess how exercise interventions may adapt disease progression scores.

7.5.6. Conclusion

In this chapter, I investigated the clinical value of the disease progression score through several applications. Although the disease progression score was mainly generated from echocardiography features, a longer duration of treatment

was associated with a higher score. The disease progression score was consistent with an established modifiable cardiovascular risk score. Furthermore, participants with 80% compliance (per protocol 1) to exercise sessions improved their baseline disease progression score compared to non-compliant participants. Improvement in the score after a 16-week exercise intervention was also associated with higher fitness levels. Further work is needed to determine whether the disease progression score could be clinically applied to improve hypertension management in younger patients.

8. CONCLUSIONS

In conclusion, this thesis has provided a comprehensive understanding and novel insights into cardiovascular phenotypic remodelling related to hypertension in a population of young adults. The identification of pre-clinical phenotypic biomarkers was achieved by conducting two approaches: (i) stressing the cardiovascular system by performing physical exercise testing, and (ii) applying machine learning tools to define cardiovascular phenotypes.

These approaches were tested on data from a relatively large cohort of young adults with a range of blood pressure levels, which included detailed assessment of cardiac structure and function using echocardiography imaging. For the first approach, cardiopulmonary exercise testing with stress echocardiography was performed in a subgroup of the cohort, allowing for investigation of the cardiac response to physical exercise and identification of pre-clinical cardiac remodelling. For the second approach, a novel semi-supervised machine learning algorithm was applied to develop a disease progression model, from which I identified the important echocardiography phenotypes related to elevated blood pressure measures.

The first thesis objective (Chapter 4) was to determine whether young adults with suboptimal blood pressure (≥ 120/80 mmHg) have different cardiac response to physical exercise compared to an age, sex, and frequency-matched optimal blood pressure (< 120/80 mmHg) group. Cardiopulmonary exercise testing with stress echocardiography imaging allowed detailed assessment of cardiac response to physical exercise. I found that young adults with suboptimal blood pressure levels had reduced left ventricular ejection fraction in response to moderate physical exercise compared with the optimal blood pressure group.

The second thesis objective (Chapter 5) was to predict the reduced left ventricular response to exercise from resting echocardiography features. Obtaining a comprehensive transthoracic echocardiography scan at rest allowed for performing detailed assessment of

ventricular and atrial function, including 2D measurements, Doppler velocities, and speckle tracking analysis. As a result, I demonstrated that left atrial pump function, estimated by the left atrial contraction strain, was associated with left ventricular ejection fraction during moderate exercise. This association remained significant when adjusting for potential confounders (age, sex, BMI, and mean arterial blood pressure).

The third thesis objective (Chapter 6) was to develop a disease progression model of hypertension in young adults using machine learning tools. Applying a contrastive trajectory inference algorithm on baseline cross-sectional echocardiography data of a relatively large cohort of young adults, I developed, for the first time, a disease progression model of hypertension in young adults. This model allowed: (i) combining the effect of several echocardiography variables; (ii) identifying the important variables relevant to hypertension; (iii) assigning participants with a unique disease progression score; and (iv) studying the changes of individual variables throughout the disease progression.

In the final results chapter (Chapter 7), I aimed to understand the clinical value of the disease progression score by testing three clinical applications. First, the differences in the disease progression score based on different clinical stages of hypertension. Second, a comparison of the disease progression score with a modifiable cardiovascular risk score. Third, the effect of 16-week exercise intervention on the disease progression score. Although the disease progression score was generated from baseline echocardiography data and did not include information on treatment duration, participants with longer duration of treatment had higher disease progression scores compared with those who were not on treatment. The disease progression score was also in line with the modifiable cardiovascular risk score. Further, when the exercise intervention was considered, the reduction in the score post exercise intervention was associated with improved fitness levels.

These results provide an overall picture of the spectrum of cardiac pathophysiological remodelling in young adults from early to more advanced stages of hypertension. The approaches I applied allowed to identify important echocardiography features relevant to blood pressure elevation in young adults and distinguish specific clinical implications.

First, the findings of using cardiopulmonary exercise testing with stress echocardiography imaging to assess the cardiac response to physical exercise allowed identification of participants who may require more personalised or aggressive blood pressure management. The use of exercise testing to identify those patients could be complicated in clinical practice due to the requirement of stress echocardiography during the exercise test. However, my findings revealed that left atrial contraction strain at rest is an independent predictor to left ventricular ejection fraction during moderate exercise intensity.

Second, the disease progression model development using machine learning tools on baseline echocardiography data has provided an extensive novel insight into cardiac changes throughout the disease progression of hypertension in young adults. The model outcomes helped to fill the gap in the literature about the long-term impact of blood pressure elevation on cardiac structure and function in a population of young adults. I have also shown the clinical implications of the disease progression score in differentiating participants with chronic hypertension compared to newly diagnosed participants. It is currently not yet possible to determine the effect of treatment using the disease progression score, the results of the clinical applications on the disease progression score demonstrate that the score could be improved after sufficient supervised aerobic exercise intervention sessions. Thus, using the score may help to provide more personalised management for

younger hypertensives. Further, it could be used as a non-invasive alternative risk assessment tool using echocardiography data only.

8.1. Future questions

My thesis work has helped in identifying key pathophysiological patterns of cardiac remodelling in young adults with elevated blood pressure for early prevention of cardiovascular disease in later life. However, the following three research questions are important and remain to be investigated:

1. **Is a reduced left ventricular response to exercise or left atrial remodelling in participants with suboptimal blood pressure reversible with pharmacological therapy?**

   In this thesis, participants with reduced left ventricular ejection fraction during exercise and impaired left atrial contraction function at rest were not prescribed with an exercise intervention or anti-hypertensive treatment. Recent studies in older hypertensives have demonstrated that, during early stages of hypertension, left atrial remodelling can be reversed with optimal blood pressure control [258, 259]. The reduction of left atrial reservoir, conduit, and pump function was improved following a successful treatment of beta-blockers and renin-angiotensin receptor blockers in patients with mild to moderate hypertension [258]. Whether this reverse effect of left atrial remodelling with pharmacological therapy can be achieved in younger hypertensives is unknown.

   A randomised clinical trial of pharmacological and exercise interventions in young adults with suboptimal blood pressure measures is needed to answer this question.

A sufficient follow-up duration is also required to assess the differences in the long-term effect on cardiac remodelling between these interventions.

2. **Which echocardiography features are most strongly associated with adverse cardiovascular events in later life?**

Although I have identified that left atrial contraction is an independent predictor of reduced left ventricular performance during physical exercise and the disease progression score is consistent with an established cardiovascular risk score, there was no longitudinal data of adverse cardiovascular events in the population involved in this thesis. Young adults with hypertension have a relatively short exposure of the disease and detection of adverse cardiovascular events may require follow-up of at least ten years. Due to the limited timeframe of my DPhil, my thesis analyses and results are mainly based on cross-sectional datasets. Therefore, associations between the identified echocardiography features and adverse events could not be inferred.

During my DPhil I have started a multi-central longitudinal study with 10-year follow-up data collection of young adults with hypertension. I am particularly interested in further exploring baseline clinical and echocardiography characteristics and their associations with adverse events.

3. **What are the key characteristics to assess the effectiveness of exercise and/or pharmacological interventions in lowering blood pressure in young adults?**

In the disease progression model based on cross-sectional echocardiography data, I found that participants with longer duration of pharmacological treatment had higher disease progression score, and those who spent more days at the gym

improved their score. These findings may help to adjust and personalise the intervention plan, but it is still not possible to determine the effect of treatment without follow-up data. Similar to the previous questions, randomised clinical trial with long-term sufficient follow-up duration is required to assess the effect of hypertension interventions in young adults.

8.2. Future work

I was fortunate to be able to initiate and conduct the HyperEcho study during my DPhil with the CCRF team. The HyperEcho study represents the real-world clinical management of young adults with hypertension and adds the long-term follow-up element. Data collected from the HyperEcho study will form the initial basis of my future work. In this thesis, the initial 190 participants recruited to the study were involved in the disease progression model development. Upon the completion of recruitment and data collection, I will be able to identify distinct clusters of young hypertensives, to assess the effect of hypertension management interventions in young patients, and to further study the association between baseline cardiovascular remodelling and adverse events within a 10-year follow-up period.

In addition, as a faculty member in the Cardiac Technology Department, College of Applied Medical Science at Imam Abdulrahman Bin Faisal University in Saudi Arabia, I aim to continue conducting clinical research on cardiovascular remodelling in young adults. According to the General Authority for Statistics 2020 report, two-third of Saudi Arabia's population is under the age of 35 years [260]. My goals would be to further study the prevention tools of hypertension in young adults as well as to increase the awareness of early-onset hypertension complications.

Further, to validate the novel methods used in my thesis, I am planning to establish a large multi-national cohort of young adults in collaboration with my team in Oxford.

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