Improved Characterisation of Hypertension in Atrial Fibrillation: Role of Central Blood Pressure and Aortic Stiffness Assessment

Dr Kashif Bashir Khokhar

BSc. MBBS MRCP FRACP FCSANZ

Centre for Heart Rhythm Disorders

Royal Adelaide Hospital

School of Medicine

The University of Adelaide

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To my parents, and family

To my wife Fareeha and my daughter Arshiya

In loving memories of my twins Hadiya and Haniya

Table of Contents

Abstract

Atrial Fibrillation (AF) is the most common sustained arrhythmia; however its underlying mechanism is yet to be fully characterised. Emerging data have elucidated the strong correlation of the arrhythmia with uncontrolled cardiovascular (CV) risk factors. Amongst these, hypertension is the most common population attributable risk associated with AF. However, treatment goals for blood pressure in AF remains undefined. The brachial blood pressure is recognised as an important predictor of future cardiovascular events. However, as compared to brachial, central blood pressure is more strongly related to CV outcomes. Aortic stiffness as a surrogate for persistently high central blood pressure, is of independent value in predicting AF outcomes. Further, certain anti-hypertensives can have a differential impact on brachial and central blood pressure. This may have important clinical implications in ongoing management of hypertension. However, further studies are required to demonstrate independent value of targeting central blood pressure to improve CV endpoints.

This thesis evaluates the association of hypertension and aortic stiffness as a surrogate for central blood pressure with AF. Chapter 1 provides a comprehensive review of the literature linking hypertension (HTN) and AF. Additionally, a clinical assessment tool is proposed to better characterise atrial remodelling and end organ injury due to HTN. Pre-HTN is not benign and associated with increased risk of developing AF. Chapter-2 summarises the association of pre- HTN and new-onset AF by presenting the systematic review and meta-analysis of current published literature. Multiple studies have also

reported the independent value of aortic stiffness in predicting CV and mortality outcomes. However, its association with new-onset AF is evolving. In Chapter 3, we present the systematic review and meta-analysis of all the published prospective trials associating increased aortic stiffness with AF, CV and all-cause mortality. Despite its adjunctive value, aortic stiffness assessment is sparingly used in clinical CV risk profiling. Chapter 4 summarises and critically appraises the methodology adapted by commercially available devices to evaluate central blood pressure indices and aortic stiffness to improve clinical integration of these tools in ongoing CV risk factor management in AF. However, none of these devices has been validated to assess central BP and aortic stiffness during AF. In Chapter 5, we present our findings of IMPULSE AF validation study (Trial Id: ACTRN12616001225404). It is the first study to evaluate non-invasive central blood pressure and aortic stiffness assessment during AF. We validated non-invasive CBP indices assessment by SphygmoCor against invasive aortic root pressure and reported reliable assessment of CBP indices and aortic stiffness during rate-controlled AF. Exaggerated BP response to exercise can unmask pre- HTN and has been associated with adverse CV outcomes. Chapter 6 characterises the difference of central and peripheral blood pressure indices response to exercise in our AF cohort. As compared to controls, AF patients were reported to have normal resting central BP indices. However, during exercise impaired conduit arterial compliance was found in AF patients. This may reflect a residual aortic stiffness associating AF with persistently high central BP.

This thesis recognises the additional value of non-invasive central BP indices and aortic stiffness assessment to better characterise HTN and its associated end organ injury in AF. Our studies have expanded the scope of central pressure wave and velocity assessment in

AF and during exercise. However, further work is needed to establish central blood pressure and aortic stiffness as a treatment target to prevent HTN induced CV events.

Key words: Hypertension, Pre-Hypertension, Central Blood Pressure, Aortic Stiffness, Atrial Fibrillation

Declaration

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Chapter 3

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v. Finalist for the Nimmo Prize for Full-Time Research, Royal Adelaide Hospital, Adelaide, 2018

Abbreviations

AAD:	Ascending aorta distensibility
AF:	Atrial fibrillation
AS:	Aortic Stiffness
BP:	Blood Pressure
CBP:	Central Blood Pressure
CfPWV:	Carotid-femoral pulse wave velocity
CV:	Cardiovascular
HTN:	Hypertension
PP:	Pulse pressure
Pre-HTN:	Pre-hypertension
PWV:	Pulse wave velocity

Chapter 1

Hypertension and Atrial Fibrillation: Characterising Target Organ Injury

1.1 INTRODUCTION

Epidemiological studies have shown increasing incidence of atrial fibrillation (AF) with hypertension (HTN) (1). Despite its recognition as the most prevalent risk factor responsible for the development of AF in the population, the target blood pressure (BP) concerning primary and secondary prevention of AF is yet to be defined (1). Additionally, it is still unclear if the correlation of high BP with increased incidence of AF is linearly related or if there is a threshold when atrial remodelling would occur (2, 3). Further, the definition of HTN is evolving and optimal treatment goals are still indistinct. Pre- HTN defined as a BP range of 120-139/80mmHg is not benign. Studies have reported increased risk of cardiovascular (CV) morbidity and new-onset AF with pre-HTN (4, 5). The recent updated guidelines are advocating strict blood pressure (BP) control of 120/80mmHg (6). However, studies have not shown a consistent trend of better AF outcomes with aggressive BP control. (7-11).

Of note, individuals with HTN often have CV comorbidities and other CV risk factors (12, 13). Unattended CV risks accelerate the progression from pre-hypertension with asymptomatic CV adaptations to established HTN and end organ disease with AF. However, this typical pattern of progression is not always seen and individuals with HTN induced CV remodelling have reported variable symptomatic intensity. The conventional

CV risk models characterise elderly hypertensive as high risk of future CV events in next 5-10 years, as compared to vulnerable young with sub-clinical HTN despite their premature and predicted long exposure to high BP. Moreover, the significance of temporal variation in BP, its response to stress including exercise and the independent role of persistently high central high blood pressure leading to aortic stiffness is not very well defined in HTN treatment guidelines.

Given the expanding prevalence of HTN in the community (14), a detailed appraisal of pre-clinical manifestations of CV remodelling is warrantied to detect early and subtle deviations to better predict hypertension induced end-organ injury and its association with AF.

1.2 GLOBAL AF BURDEN

Epidemiological parallels are evident with the rising burden of AF and HTN (1, 15, 16). Despite reported racial and regional variabilities, the prevalence and incidence of AF are increasing with the addition of approximately 5 million new cases per year globally (17). The age-adjusted, worldwide prevalence of AF in 2010 was reported to be 0.5% and 33 million individuals were found to be affected by the condition (17, 18). As age is a major contributor to AF burden, an increased arrhythmia prevalence of 8-15% was reported in elderly population (19). In a recent review, Wong et al. projected a 12-fold increase in AF incidence in Australasia as compared to their American counterparts with an estimate of 49 million men and 23 million women affected by AF by the year 2050 (20). The tide of AF will continue to rise because of the ageing population, increasing prevalence of hypertension, better arrhythmia detection, the obesity epidemic and improved survival rate for patients with heart failure as well as coronary artery disease (CAD)(17, 21). AF

portends a 5-fold risk of disabling stroke (22). AF is associated with a 3-fold increased risk of heart failure (23) with doubling of dementia risk (24) and increased all-cause mortality (25). Although aggressive risk factor modification is recognised as an important pillar of AF treatment (26), the lack of established BP targets highlights gaps in the evidence. Hence, studies to define BP targets are urgently required to prevent HTN induced pre-mature end organ injury predisposing to AF.

1.3 ESCALATING BURDEN OF HTN- IMPACT OF REVISED AHA GUIDELINES

Recently updated American College of Cardiology (ACC)/American Heart Association (AHA) guidelines reduced the threshold to diagnose HTN in order to prevent, recognise and promptly manage the end-organ injury, incurred by BP levels previously classified as "pre-hypertension". These guidelines have categorised BP into normal (less than 120/80mmHg), and elevated (systolic 120-129 and diastolic < 80mmHg). HTN was further characterised as stage I (systolic 130-139 or diastolic 80-89mmHg) and stage II (≥ 140/90mmHg) (27). The re-classification of HTN by AHA exposes the magnitude of health burden posed by HTN. These guidelines strongly promote lifestyle modification with prompt introduction of pharmacotherapy in individuals not achieving treatment targets. With the introduction of these updated guidelines, nearly half of the US adult population (46%) is deemed to have HTN (27). The prevalence of HTN was found to be 26% in Australian Adult population. The HTN was defined as brachial BP of >140/90 mmHg or use of medications to lower the BP (28). However, by adapting ACC/AHA guidelines with a BP cut-off point of 130/80 to diagnose HTN, the prevalence of the condition in Australia is almost doubled to 51% (29). The impact of the increasing prevalence of HTN will be more profound in elderly and individuals with co-morbid conditions. Additionally, concerns are

raised about the cost-effectiveness and potential side effects of anti-hypertensive treatment offered to individuals labelled as hypertensive by adapting ACC/AHA 2017 guidelines.

Despite the proposed holistic approach with focus on management of co-morbidities and socioeconomic stressors, fundamental questions concerning target BP and its supporting evidence remain. The European Society of Cardiology (ESC)/European Society of Hypertension (ESH) suggested instigation of pharmacotherapy in individuals with an average resting day time BP of ≥140/90 as compared to more aggressive approach adapted by ACC/AHA (30). Interestingly, less than 20% of the recommendations by these guidelines are supported by strong evidence base (Class I, Level of Evidence). The strong advocacy for BP targets <130/80 for a general population with CVD risk of >1%/year is largely based on Systolic Blood Pressure Intervention Trial (SPRINT). However, SPRINT investigators excluded diabetics, previous strokes and majority of patients commenced on anti-hypertensive treatment. Concerning outcomes, a relative risk reduction of 16-18% by aggressive BP control (<130/80 mmHg) was only recorded for stroke and major adverse cardiovascular events (MACE).

From a clinical perspective, treatment of hypertension must be customised according to a cumulative hazard due to the presence of co-existing CV risks including diabetes, obstructive sleep apnoea, obesity and dyslipidaemia. The AHA guidelines recommended pharmacotherapy for patients with stage I HTN with an atherosclerotic cardiovascular disease (ASCVD) risk of >1%/year (27). In general, these risk assessment tools including the Framingham risk calculator are derived from epidemiological studies and tend to overestimate the risk (1, 21, 31). Moreover, they are not adequately tested in terms of CV

outcomes (8, 32). The beneficial impact of targeting BP 120/80 was mostly recorded for individuals with 18% risk of CVD over 10 years. Hence, this 1% /year CVD risk is arbitrary and has to be further supported by outcome studies. Additionally, the standardised methodology to estimate BP must be established across the clinical trials to minimise the inter and intra-observer variability. Notably, these guidelines did not consider AF as a potential marker of end-organ injury in HTN. Furthermore, the adjunctive but independent role of exaggerated BP response to exercise and conduit arterial stiffness as a surrogate of persistent central high BP, was not explored.

1.4 ASSOCIATION OF HYPERTENSION WITH AF

1.4.1 A Complex Pathophysiological Nexus

HTN has an independent, strong and graded association with AF (4, 33). The left ventricular hypertrophy, left atrial dilatation, central arterial stiffness and endothelial dysfunction are important mediators, associating HTN with AF (16, 34-37). Despite the observed strong correlation between AF and HTN, the underlying pathophysiology is still incompletely understood. Moreover, in hypertensive individuals, development of AF is not widely recognised as an end organ insult.

Several experimental HTN models have evaluated the connection between HTN and AF (Table -1.9.1) (38-40). HTN triggered structural and electrophysiological transformation of left atrium (LA) (39). Moreover, the extent of the LA remodelling was found to be dependent upon the duration of hypertension (41, 42).

Electrophysiologically, the remodelled LA due to HTN exhibited gap-junction transformation, altered calcium handling, anisotropy with reduced refractoriness and

slow conduction velocity that promote re-entry to sustain and perpetuate AF (43, 44). Hemodynamically and structurally, sustained high blood pressure reduces left ventricle (LV) compliance and increases the left atrial stretch resulting in dilatation of the atria (45). An impaired left ventricle (LV) diastole resulted in escalated pulsatile load and left atrial dilatation predisposing to AF (46, 47). In addition, increased ventricle stiffness led to activation of renin-angiotensin-aldosterone axis (RAA)and sympathetic system. HTN also promotes atrial remodelling through activation of composite signalling pathways involving angiotensin, growth factors, inflammatory cytokines, and endothelin resulting in atrial interstitial fibrosis, electro-anatomical heterogeneity and dysfunctional cellular calcium handling (43). Moreover, paroxysms of AF further impair LA function and facilitate AF through ongoing structural and electrical adaptations. The altered atrial substrate with the combination of electrical, anatomical and cellular transformation can potentially instigate and sustain AF in hypertensive animals (21, 43). These findings from the animal studies can help explain the increased risk of AF reported in hypertensive individuals with dilated LA and increased LV thickness.

A number of studies including Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) reported the association of HTN and electro-anatomical LA remodelling, manifested as LA dilatation, with increased AF, heart failure and mortality (45, 48, 49).

Interestingly, the co-existence of CV risks including obesity and OSA with HTN escalate the electro-anatomical transformation of LA with changes of the regulatory mechanisms resulting in left atrial dilatation and increased risk of new onset AF (15, 22). A graded

association is reported between LA adaption and intensity as well as chronicity of these risks driving the chamber transformation (50).

1.4.2 Hypertension and New-Onset AF

The majority of the AF cases are a consequence of electro-anatomical remodelling of the left atrium, precipitated by a multitude of cardiovascular risks (34). Epidemiological studies have established hypertension as a predominant yet modifiable factor in the development of atrial fibrillation (23, 51). However, it is not clear if the association of AF with HTN is linear or threshold dependant. In approximately 70% of patients, HTN was seen with other cardiovascular morbidities such as diabetes, chronic kidney disease and stroke (51).

Even a marginally increased BP of >130/80 mmHg was found to be associated with 40% escalated risk of adverse CV outcomes (11, 13). In otherwise healthy individuals, an independent association of pre-HTN (129-139/80 mmHg) with incidental AF has been reported by population studies (4, 10, 52). A 1.5-fold increase in incidental AF was noted in middle age Norwegian men with sustained BP of 129-139/80 mmHg (53). Similarly, a 28% increased risk of new-onset AF was described by investigators of Women's Health Initiative Study in patients with BP of >130/80mmHg (52). A recent epidemiological study has reported the evolution and impact of BP on risk of development of incidental AF over a period of 15years. As compared to their normotensive (BP 120/80mmHg) counterparts, individuals with persistent HTN (BP 140/90mmHg) or increased resting pulse pressure were shown to have two-fold increased risk of new-onset AF (54). The Atherosclerotic Risk in Communities (ARIC) study reported HTN as the most important contributor, accounting for 22% of new onset AF burden in their cohort (15). In addition, Multi-Ethnic

Study of Atherosclerosis (MESA) recorded a graded association between BP and AF. Over a 5-year follow up period, one-third of the MESA cohort developed HTN with a reported 4-fold increased risk of AF. As compared to normal BP, even pre- HTN was associated with 80% higher risk of AF (5).

Hypertension is also widely prevalent in AF patients. Recently reported trials involving Novel oral anti-coagulants have reported a very high (> 75%) incidence of HTN in their AF cohorts. The incidence may well be under reported by these studies, as HTN was defined as persistent BP of >140/90mmHg during screening in participants not on active anti-HTN treatment. (55-57).

1.4.3 BP Targets for Patients Undergoing AF Ablation

Current literature supports an aggressive approach to target BP in AF to improve the success of catheter ablation, reduce progression of the atrial remodelling and HTN related cardiovascular complications including escalated risk of stroke, bleeding, renal impairment and heart failure. (47, 58) However, optimal blood pressure treatment targets post AF ablation are yet to be defined. The SMAC-AF study did not reveal any significant advantage of achieving mean BP target close to 120/80mmHg as compared to 130/80mmHg with no differences in AF outcomes post ablation over 3-6 months follow up. (46) The same observation was reported by post-hoc analysis of AFFIRM during a mean 6 years follow up of rhythm control arm. (59)

As AF is a result of multiple modifiable risk factors, it is likely that studies examining a sole risk factor may be inadequate. The above-mentioned studies are likely to lack statistical power to detect any differences especially with the short follow-up duration in the SMAC-AF study. Nevertheless, these observations point to the importance of a holistic risk factor

management approach that addresses all the modifiable risk factors (e.g. sleep apnoea management, alcohol reduction, glycaemic control, weight management and exercise) to prevent AF in conjunction with high BP treatment (34). Second, brachial blood pressure is not a sensitive indicator of central pulsatile load an atrium is subjected to. Perhaps, assessment of central BP and aortic stiffness indices may provide a better therapeutic target. Third, better risk stratification tools may be required to expose sub-clinical hypertension induced end organ and CV remodelling.

In addition to conventional cardiovascular risks, discrete factors including obstructive sleep apnoea, high pulse pressure, aortic stiffness, obesity and genetic susceptibility are reported to accelerate atrial remodelling, development of AF and poor outcomes post ablation (Figure-1.8.1), (60-62). Therefore, patients with elevated BP require extensive risk profiling to expose and target relatively early signs of end-organ insult including impaired atrial, ventricular and vascular compliance to improve their clinical outcomes.

1.5 IMPORVED CHARACTERISATION OF HTN INDUCED END-ORGAN INJURY AND ITS ASSOCIATION WITH INCIDENTAL AF

A novel clinical approach in addition to the conventional CV risk stratification, is therefore needed to better characterise sub-clinical manifestation of end organ injury to improve predictability of new-onset AF in the hypertensive patients (Table 1.9.2).

1.5.1 Left Atrium Remodelling Assessment and its Association with AF

Left atrium (LA) is the most posteriorly located of the cardiac chambers. The pulmonary veins traverse the relatively fixed posterior wall of the LA with left veins positioned slightly higher than the right. Electro-anatomical characteristics of pulmonary veins (PVs) render them pro-arrhythmic due to the epi-endo gradient of refractoriness and patchy

muscular sleeve at the veno-antral junction (63). Despite the reported strong association of LA enlargement with AF, stroke and mortality (48, 50, 64), the most commonly used risk scores predicting thromboembolic complications in AF, including CHA_2DS_2-VASc, do not include LA dilatation in their stratification scheme (3).

In general, LA size is derived by anteroposterior diameter from a parasternal long-axis view with standard 2-dimensional echocardiography. But the volume assessment of LA is more useful, as LA dilatation can be asymmetrical due to the relatively fixed posterior wall (48). The normal reference range for LA volume indexed to body surface area (BSA) is 16-34ml/m^2 (65) . However, the electrophysiological transformation precedes atrial dilatation as one-fifth of the hypertensive patients with AF demonstrated preserved LA size (66). In AF patients with preserved LA volume, cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement can be useful to characterise LA and its scar burden to help predict arrhythmia recurrence. Based on LA late gadolinium enhancement, a grading system for LA fibrosis was proposed by DECAAF study investigators (67). Stage I has <10% fibrosis of LA wall as compared to stage IV with >30% fibrosis burden involving the LA wall. Each 1% increase in LA fibrosis was found to be independently associated with 6% increased risk of AF recurrence post ablation at 325 days follow-up (67).

Concerning AF outcomes, assessment of LA physiology can expose sub-clinical remodelling not obvious on anatomical description of the chamber (66, 68). LA is a dynamic structure, which expands to act as a reservoir during LV systole, and works as a passive as well as an active conduit during early and late LV diastole respectively. Doppler, 2-dimensional echocardiography and CMR can be used to estimate LA physiology

including LA appendage (LAA) ejection velocity, LA emptying fraction (LAEF), early to late mitral inflow velocities ratio and tissue Doppler to quantify LA strain. Although a standardised approach regarding LA physiology assessment is yet to be adopted, the normal reference value of LAEF and LAA ejection velocity is defined as 45% and 40cm/sec respectively (66). A detailed structural and functional evaluation of LA in patients with pre-hypertension, HTN and "lone" AF, can be valuable to illustrate pre-mature remodelling of LA in order to instigate aggressive risk factor modification to improve AF outcomes. A list of common clinical methods to characterise LA is detailed in Table-2.

1.5.2 Left Ventricle Hypertrophy Screening to Predict New-Onset AF

HTN induced left ventricle hypertrophy (LVH) is an increase in LV mass or thickness, due to sustained amplification of pulsatile load attributable to high blood pressure. In general, M-mode and 2-dimensional echocardiography is used to estimate LVH. In men, the LVH is defined as LV mass of >115g/m^2 indexed to the BSA by linear measurements and 102g/m^2 using 2-dimensional echocardiography. On the other hand, in women, the upper reference limit of normal LV mass is 95g/m^2 by linear measurements and 88g/m^2 by 2-dimensional echocardiography (65). As a modifiable factor, LVH is strongly associated with increased incidence of AF, independent of baseline BP. Unattended CV risks such as obesity and OSA, can also lead to early and progressive changes in LV mass resulting in LVH, in addition to HTN (69, 70). In general, LVH results in increased LA stretch subsequent to diastolic impairment and reduced LA emptying. The persistently increased LA stretch results in chamber dilatation, which is found to be independently associated with incidental AF (68). Moreover, persistent hemodynamic LV overload activates the neurohormonal, oxidative and inflammatory pathways which further remodel the cardiac chambers. Epidemiological studies have reported a variable range of incidental LVH,

wavering from 10-77%. Enrolment of a heterogeneous population with distinct CV risk profiles help explain the reported differences in the prevalence of LVH. A graded association was observed concerning the presence of LVH and CV risks, the lowest (9-17%) being reported for population-based studies and the highest (60-77%) for elderly hypertensive patients with multiple CV morbidities (71, 72). In general, echocardiography is used to confirm the presence and pattern of LVH. The pattern of LVH can be concentric or eccentric. The latter confers more restrictive diastolic filling and have stronger association with AF recurrence (73).

Importantly, sustained hypertension can cause sub-clinical LVH that is associated with increased incidence of new-onset AF as reported by MESA study (74). LVH is also correlated with poor outcomes in patients with known AF including post ablation (69). Off note, LVH is a modifiable factor and regression of LVH translated into improve AF and CV outcomes independent of blood pressure control (75). Therefore, LVH screening by echocardiography in patients with sub-clinical HTN is valuable to characterise blood pressure induced premature end-organ injury and possible prevention of AF by targeting BP aggressively and prompt attention to other risk factors.

1.5.3 Role of Exercise-Induced Arterial Hypertension (EIAH)

In general, baseline BP is recorded after 5-10 minutes rest to preclude amplified BP response to “stress”. The predictive relevance of exaggerated BP response to exercise in AF is still unclear. Moreover, hypertensive response to exercise is not very well defined. A meta-analysis of 12 longitudinal studies described exercise-induced arterial HTN (EIAH) as a systolic pressure recording of 230mmHg on moderate exertion (76). EIAH to moderate exertion imposed a 36% increase in CV events and mortality after adjusted for age, office

BP recording and conventional CV risk factors (76). EIAH is shown to be associated with LVH, which is a major driver of atrial remodelling and AF (77, 78). Exaggerated BP response to exercise can help identify patients at risk of developing HTN with premature CV remodelling including AF. Further, estimation of BP indices response to exercise including pulse pressure assessment can unmask residual central arterial stiffness that is associated with increased risk of new-onset AF and poor outcomes post AF ablation (35, 61).

1.5.4 The Central Blood Pressure and Conduit Arterial Compliance Assessment

As compared to brachial blood pressure, central blood pressure (CBP) and aortic stiffness assessment is more relevant to estimate central pulsatile load and demonstrated improve predictability of new-onset AF (79). Population studies revealed that up to 70% of the participants characterised as pre-hypertensive on brachial BP assessment, actually had central high BP (80). Despite good brachial BP control, patients with impaired central arterial compliance have poor AF outcomes and are at increased risk of adverse CV events (81). Historically, measurement of CBP required central arterial catheterisation for direct manometry. However, a variety of cuff based devices can be used to estimate CBP as well as aortic pulse wave velocity (aPWV) to calculate aortic stiffness, non-invasively (82).

In general, non-invasive aortic stiffness assessment is performed by aPWV appraisal, central pulsatile load and ascending aortic distensibility estimation. The aforementioned methods essentially estimate aortic response to pulsatile pressure and volume load during ventricular-arterial coupling. As the conduit artery remodels, the aPWV increases, the pulse pressure amplifies and proximal aorta distensibility diminishes (83). The aPWV is calculated from the distance travelled by the pulsatile wave between two vascular sites

and dividing it by transit time. The carotid and femoral arteries are the most common vascular points used to determine carotid-femoral PWV (cf-PWV) and is recognised as a "gold standard" to calculate the aortic stiffness (30). However, the independent association of increased cf-PWV and reduced aortic distensibility with poor AF outcomes is yet to be established. Notably, increased pulse pressure (>60mmHg) as a surrogate of aortic stiffness is found to be independently associated with increased incidence of AF and also linked to worse outcomes post AF ablation (61, 83). Pulse pressure (PP) estimation can be easily derived by subtracting systolic from diastolic BP and particularly useful in middle aged (40-60 years) individuals to expose vascular remodelling and increased risk of AF. As a modifiable factor, pre-mature central arterial stiffness estimation can offer improved risk factors modification in patients with AF(61). Nonetheless, further studies are required to illustrate better AF outcomes by targeting central blood pressure indices.

1.5.5 Appraisal of Endothelial Dysfunction in Elevated BP

Though the precise sequence of events leading to hypertension-induced end-organ injury is yet to be explicated, increased incidence of endothelial dysfunction is described in individuals with HTN (84, 85). Endothelial dysfunction is a structural or functional breach of the vascular inner lining with a predilection to inflammation and thrombosis. Though not performed routinely in clinical settings, endothelial dysfunction is a common finding in HTN induced micro and macro-vascular remodelling. It can be assessed non-invasively by flow-mediated vascular dilatation (FMD) (86) and is being increasingly described in AF patients with pre-hypertension and HTN (84, 85, 87). FMD is a direct marker of nitric oxide bioavailability and is predictive of future risk of development of hypertension. Each

one unit decrease in FMD is associated with 16% escalated risk of hypertension independent of age and baseline BP (88).

Systemic endothelial dysfunction is also well recognized in patients with persistent atrial fibrillation and left atrial remodelling (86). The exact mechanism associating left atrial remodelling with endothelial dysfunction is under considerable debate. It is postulated that irregular heart rate and turbulent flow with abruptly changing vascular wall stress along with systemic inflammation due to uncontrolled CV risks in AF, resulted in reduced nitric oxide assembly and decrease endothelial nitric oxide expression. The nitric oxide activity can be gauged by decline in plasma nitrite/nitrate levels in AF (85, 89). The systemic inflammation, neurohormonal activation through renin aldosterone and angiotensin pathway with ongoing oxidative stress are other possible mechanisms linking endothelial dysfunction to vascular and atrial remodelling (43). The angiotensin convertase enzyme inhibitors have shown a modest decelerating effect on vascular remodelling, independent of CV risk factors by inhibiting renin-angiotensin and aldosterone system activation and reducing systemic inflammation promoting atrial fibrosis (90). As a reversible factor, endothelial dysfunction can be linked to the pathogenesis of HTN induced AF. Therefore, the functional endothelial assessment can improve characterisation of sub-clinical HTN and in “lone” AF patients.

1.5.6 High Urinary ACR and AF Incidence

The high urine albumin: creatinine ratio (ACR) is defined as >2.5mg/mmol and >3.5mg/mmol in men and women respectively. Increased urinary ACR is a marker of renal micro-vascular injury and endothelial dysfunction that can be detected in elevated BP patients with preserved estimated glomerular filtration rate (eGFR). ACR is further

graded as per quantitative urinary protein leak per mg of creatinine, categorised as mild (ACR<3mg/mmol), intermediary (ACR 3-30mg/mmol) and severe (>30mg/mmol) (91). Pre-HTN range of BP (≥ 130/80mmHg) is independently associated with a twofold increased risk of albuminuria (92). Furthermore, a graded association between urinary ACR and new onset of AF independent of baseline eGFR was reported by epidemiological studies (93, 94). The urinary ACR estimate is universally available and can be easily incorporated in risk profiling tools to predict AF particularly in patients with moderate to high burden of CV risk. However, further prospective studies are required to explore the independent association of increased urinary ACR with escalated risk of AF.

1.5.7 Screening for Hypertensive Retinopathy

A graded association is noted between hypertensive retinopathy and incidental AF (95). Retinopathy is also correlated with proteinuria, LV diastolic dysfunction and enlarged LA in HTN (95). Retinopathy represents microvascular remodelling due to endothelial dysfunction, and hypoxic vascular injury consequential to persistent high blood pressure. Early HTN induced retinopathy presents as segmental or generalised arterial sclerosis characterised as arterio-venous (AV) nipping or "silver wire arterioles" respectively. A further breach of retinal vascular integrity leads to oedema and retinal haemorrhages. In patients with sub-clinical HTN, retinal screening can be a helpful tool to improve risk profiling and prevention of premature organ insult by targeting BP and its associated CV risks aggressively.

1.6 PREVENTION OF AF- ROLE OF HTN and CV RISKS MANAGEMENT

1.6.1 HTN and CV Risk Stratification in AF

Epidemiological studies have established the role of multivariate risk prediction models to estimate overall CVD and AF risk in order to guide therapy (96). Factors including HTN, diabetes, and smoking are direct causes of CVD. Hence, they are defined as “major” risks (3). In general, individuals are graded into low, intermediate or high risk for future CVD events by employing a multivariable risk stratification tool (3). In addition to the patients requiring ongoing secondary prevention for CVD, individuals with more than one established major CV risk, are also categorised as “high” concerning future CV events. However, BP poses a dynamic risk and this continuum was neatly illustrated by Prospective Studies Collaboration, reporting doubling of cardiovascular and all-cause mortality risk for every increase by 20/10mmHg in BP, above a baseline of 115/75mmHg (7). The aforementioned observation was validated by a number of studies, reporting the association of elevated BP with incidental AF (4, 10, 52, 53). In addition to conventional cardiovascular risks, discrete factors including obstructive sleep apnoea, high pulse pressure, aortic stiffness, obesity and genetic susceptibility are reported to accelerate atrial remodelling and development of AF (Figure-1.8.1), (60-62). Nearly half of the stroke and ischemic heart disease (IHD), incidence can be attributable to systolic BP >130mmHg. However, only 50% of these individuals met the criteria for high blood pressure intervention as per current guidelines (97, 98). Importantly the SPRINT study recorded a 25% reduction in CVE and mortality in non-diabetic individuals with estimated CVD of 1.8%/year (9). However, the HOPE III study could not confirm SPRINT observations in participants with low (<10%) 10-year CVD risk (99). Therefore, BP treatment requires a customised approach according to the CV profile of an individual rather an arbitrary

target. Furthermore, our current practice of CV profiling is based on the algorithms, stating 5-10 years risk scores that shifts the focus towards elderly with increased burden of CV risks.

Despite their stratification as “low risk”, elevated BP in relatively younger subjects requires further attention to tease out premature CV remodelling by using novel strategies including aortic stiffness assessment to better predict morbidity and mortality outcomes. The younger patients with sustained pre-HTN are more prone to develop end-organ injury including AF because of their relatively prolonged exposure to chronically elevated pulsatile load (12). The treatment regime must account for multiple CV risks, present in the individuals with pre-HTN and established HTN. This customised strategy is cost effective and will help evolve BP management, guided by individual risks rather than arbitrary cut-points. This approach my help delivers potential benefits to each patient with the reduction in undesirable effects of interventions.

1.6.2 Risk Factor Management (RFM) to Prevent AF

Many studies focusing on underlying AF mechanisms have improved our understanding on the factors contributing to adverse electro-anatomical LA remodelling and AF development or sustenance (37, 38, 41, 43, 44). This approach helped identify the gaps in our knowledge and established the need of ongoing risk factor modification in AF management to improve outcomes. Investigators have recognised congestive heart failure (CHF), diabetes, HTN, LVH, coronary artery disease (CAD), obesity, smoking and valvular heart disease (VHD) as predominant modifiable risks ensuing accelerated electro-anatomical atrial remodelling followed by poor outcomes in AF (3, 100). As compared to HTN, factors like CHF and CAD are found to have a stronger association with AF (21).

However, due to its prevalence, HTN remains the predominant population-attributable risk driving the incidence of AF (21, 34, 45). In recent years, obesity, as a modifiable factor, is also recognised as a major driver of atrial remodelling (26, 101). Notably, published evidence demonstrated weight loss and aggressive risk factor management with target BP of <130/80 at rest and 200/100mmHg during exercise, as a key to improve AF outcomes in patients with BMI ≥27 Kg/m^2. A sustained weight loss of ≥ 10% with ongoing aggressive risk factor management in AF patients with a baseline BMI of ≥27 Kg/m^2 has a six-fold increased probability of arrhythmia-free survival over long-term follow-up of 5 years than those who gained weight or lost <3% of weight (101). The aforementioned observations led to the development of a customised and goal-directed team approach in AF management by keeping a primary focus on patient education, weight loss and aggressive risk factor modification (101, 102). The structured risk factor management programme was clinically and cost effective (103). The beneficial effects of weight loss were extended to the metabolic profile of the indexed patients with reported improvement in lipids, HbA1c, OSA and blood pressure control (104).

Nonetheless, it is not known that aggressive risk factor management carries additional hard endpoints benefits beyond AF outcomes including mortality, stroke, myocardial infarction and heart failure.

1.6.3 Pharmacotherapy in HTN Patients to Prevent AF

The close association of HTN with AF pose the opportunity to focus on HTN, as one of the major risk factors to prevent new onset and recurrence of AF. Defining HTN treatment goals to prevent AF is still a challenge as trial participants display significant heterogeneity regarding HTN induced target organ injury including LVH and baseline CV risk factors (90).

In younger patients with increased risk of CVD and premature cardiovascular remodelling, a more meticulous lifestyle change to address CV risk factor management and aggressive blood pressure control can potentially improve outcomes (9). Patients with left ventricle hypertrophy (LVH) with LA remodelling and/or left ventricle systolic dysfunction should be preferentially considered for angiotensin enzyme inhibitors or angiotensin receptor blockers (ARBs), as they are reported to be more effective (relative risk reduction of 25-35%) in primary prevention of AF (105, 106). Likewise, the use of beta-blockers can help maintain sinus rhythm in high risk population with history of myocardial infarction, left ventricle hypertrophy and systolic dysfunction (107). As compared to angiotensin receptor blockers, amlodipine was reported to be less effective in preventing AF (108). However, verapamil was found to be more effective in secondary prevention of AF (109). Notably, there is limited data to support the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers for secondary prevention of AF in hypertensive patients (110). The GISSI-AF trial showed no additional benefit of adding Valsartan to prevent recurrent AF post cardioversion (111). This highlights the importance of more extensive profiling of at-risk individuals to explore subclinical insignias of cardiovascular injury with the prompt introduction of aggressive risk factor modification and appropriate pharmacotherapy.

The CV risks including BP is a continuum and patients with sustained pre-HTN are more likely to develop HTN. Therefore, screening for sub-clinical CV disease in addition to the conventional risk stratification as illustrated (Figure-1.8.2), can provide us with a window of opportunity to act promptly in order to prevent established clinical and more advanced form of HTN induced end organ disease. Once the HTN induced organ injury is clinically

established, its response to aggressively targeting BP varies according to the intensity of underlying CV remodelling. For example, a “J” curve association between BP and coronary perfusion is reported by targeting BP close to 120/80 in patients with advanced HTN and coronary artery disease (112). Therefore, individuals with pre-HTN with increased CVD risk should be offered an aggressive risk factor management and early intervention to achieve BP targets to help alleviate the burden of AF and CVD.

1.7 CONCLUSION

The rising tide of HTN and AF goes hand in hand with the increasing obesity and ageing population. Sustained HTN leads to electro-anatomical transformation of atria due to elevated central pulsatile load resulting in chronic atrial stretch and its neurohormonal sequelae. The close pathophysiological link between HTN and AF highlights the importance of recognising AF as a marker of an end organ insult in hypertensive individuals requiring tighter BP control. A sustained adherence to CV risk factor modification with prompt introduction of pharmacotherapy can potentially transform the natural history of pre-HTN/elevated BP and its attributed CV risks. However, further prospective studies are required to define blood pressure targets in AF and establish the role of detailed CV risk profiling to unmask sub-clinical disease in order to translate it into better outcomes.

Figure 1.8.1: Cardiovascular Risk Profiling in Pre-HTN and HTN

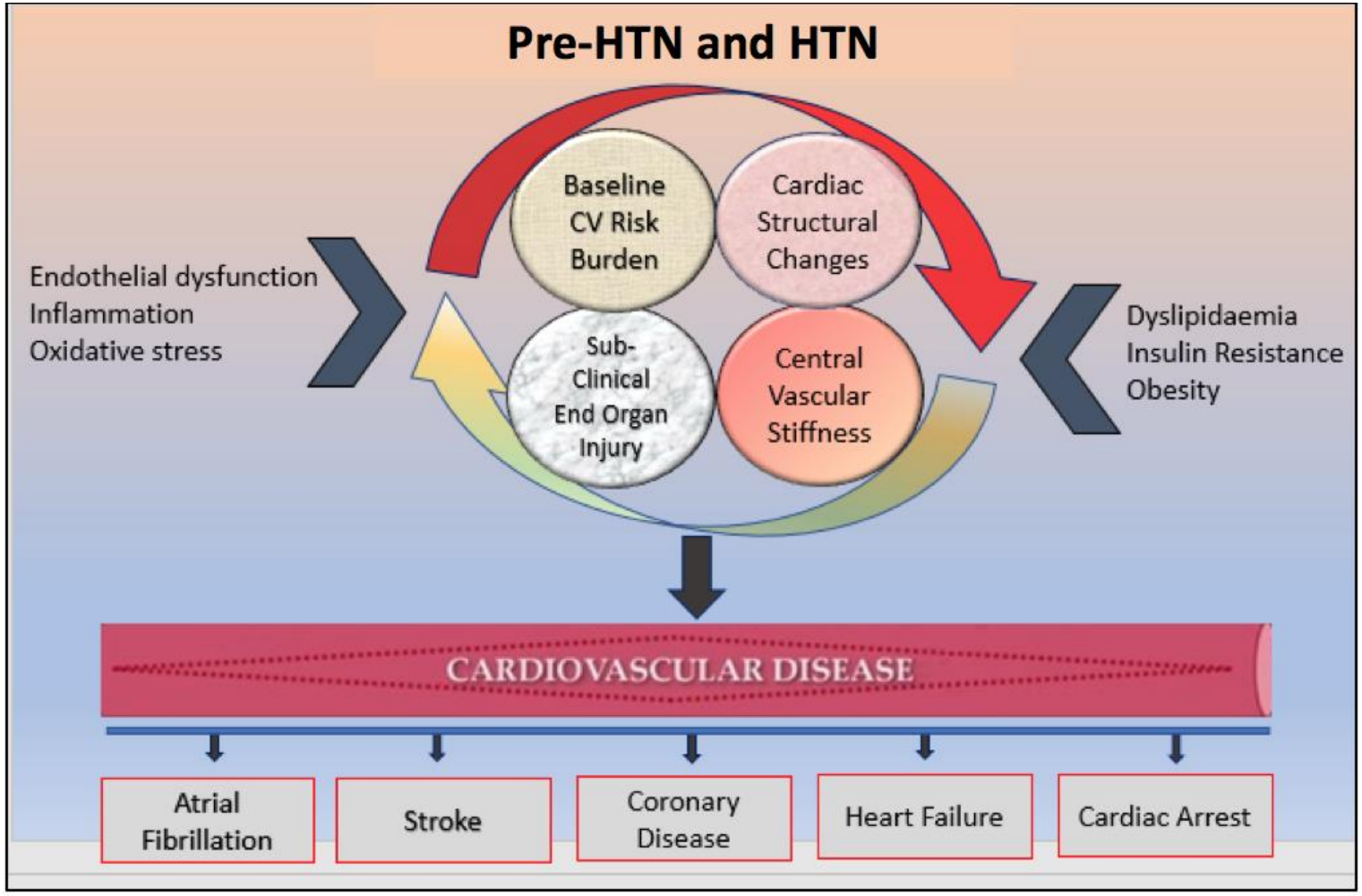


Figure 1.8.2: Characterising Sub-Clinical End-Organ Injury in HTN

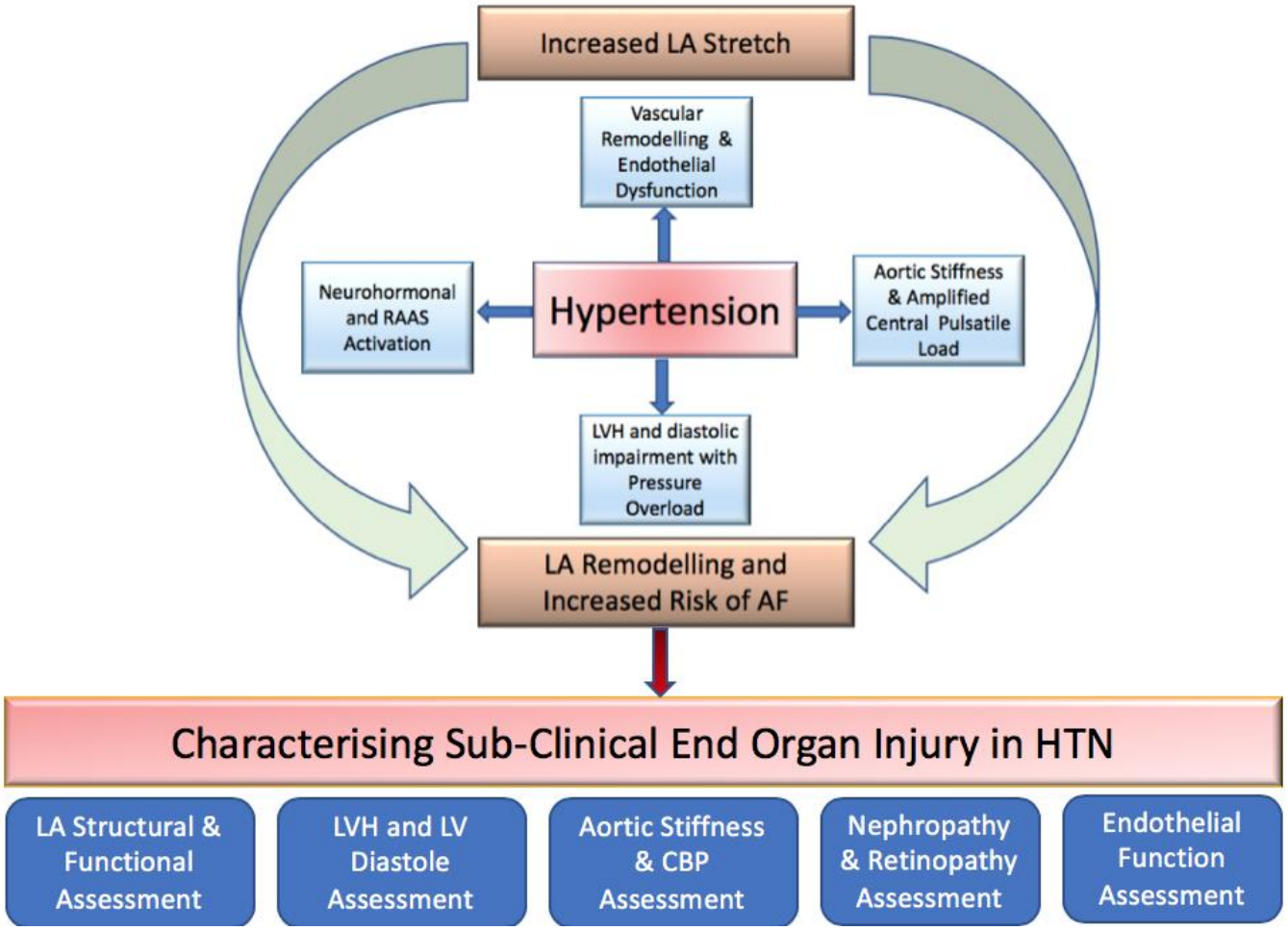


Table 1.9.1: Details of Animal Studies Illustrating Propensity of Hypertensive Hearts to Develop AF

Publishing Authors	Species Studied	Model	Parameters Studied	End Points in HTN Model
Kim et al (38)	Rats (Male Wistar)	Control vs Hypertensive (induced by partial constricting of ascending aorta)	LA fibrosis and dilatation. Pacing induced AF	Increased fibrosis and conduction heterogeneity, Dilated LA, Increased duration and incidence of AF
Lau et al (42)	Spontaneously HTN rats VS Controls (Age matched Wistar- Kyoto)	Electrophysiological characteristics of LA in 15-month old spontaneously HTN rat	Electro-anatomical properties of LA. AF inducibility	Progressive increased LA fibrosis and higher AF inducibility with macrophages infiltration in 15-month old HTN rats
Kistler et al (41)	Sheep	Control vs Hypertensive (Induced by prenatal corticosteroids exposure)	Hypertrophy and fibrosis of atrial myocyte. Pacing induced AF, LA conduction velocity	Conduction heterogeneity with increased AF inducibility
Lau et al (39)	Sheep	Control vs Hypertensive (1-Kidney, 1-Clip Model)	LA dilatation, dysfunction & fibrosis. AF inducibility & LA conduction velocity at 5,10 and 15 weeks of HTN	Sustained HTN (>10wks.) was associated with increased LA conduction heterogeneity and fibrosis resulting in increased duration of induced AF
Choisy et al (40)	Spontaneously HTN rats VS Controls (Age matched Wistar- Kyoto)	Electro-anatomical characteristics of LA	Induction of tachyarrhythmia and LA fibrosis at 3 and 11months	As compared to controls and 3 months old HTN rats, Increased LA fibrosis and tachyarrhythmia induction were seen in 11months old HTN rats

(HTN= hypertension, LA= left atrium)

Table 1.9.2: CV Risk Profiling of Patients with Elevated BP in Addition to Conventional Stratification

End-organ	Parameter	Assessment	Method	Normal value
Left Atrium (LA)	LA size	LA diameter /BSA (cm/m^2)	2DE and CMR	1.5-2.3cm/m^2 [65]
		LA volume indexed to BSA (ml/m^2)	2DE and CMR	34ml/m^2 [65]
		LA scar burden	CMR	< 5% of LA size [113]
Left Atrium	LA functional assessment	LA emptying fraction (LAEF)	2DE, CMR	LAEF >45%[66]
		LA appendage velocity	2DE	LAA velocity 40cm/s
		LA strain Presence of spontaneous contrast sign	2DE 2DE, CMR	Reservoir Strain 39% [114] Conduit Strain 23% [114] Contractile Strain 17% [114]
Left Ventricle Hypertrophy (LVH)	LV mass (LVM)/BSA (g/m^2)	LVM linear method	2DE	F (43-95)[65] M(49-115)[65]
		LVM 2DE method	2DE	F (44-88)[65] M (50-102)[65]
Renal screening in patients with normal or abnormal eGFR	Albuminuria	Albumin: creatinine ratio (ACR) mg/mmol	Urine ACR	F 3.5mg/mmol M 2.5mg/mmol
Retina	Microvascular remodelling	HTN induced retinopathy	Retinal Screening	Grade I-IV
Aortic compliance	Conduit arterial remodelling	Surrogate for central high blood pressure	CF PWV	5.4 - 9.9m/s [79, 115]
			PP	<60mmHg [79]
			AAD	8.9 ± 3.6 (10^{-3} $mmHg^{-1}$) [115]
Exercise induced arterial HTN (EIAH)	Masked HTN	Sub-clinical HTN	Peak systolic BP response to moderate exertion	≥ 200-230mmHg [76]
Endothelial function	Vascular remodelling	Endothelial dysfunction	Flow mediated vascular dilatation (FMD)	FMD 7-10% [88]

(AAD= ascending aorta distensibility, BP= blood pressure, BSA= body surface area, CF PWV= carotid-femoral pulse wave velocity, CMR= cardiac magnetic resonance imagining, 2DE=Doppler echocardiography, eGFR= estimated glomerular filtration rate, F= female, HTN= hypertension, LAA=left atrial appendage, M= male, PP=pulse pressure)

Chapter 2

Association of Pre-Hypertension and New-Onset of Atrial Fibrillation: A Systematic Review and Meta-Analysis

2.1 INTRODUCTION

A growing body of evidence is associating pre-hypertension, defined as BP range of 120-139/80-89 mmHg, with new-onset atrial fibrillation (AF). Pre-HTN is closely associated with stroke and cardiovascular (CV) morbidity (116, 117). Notably, the updated American Heart Association (AHA) guidelines acknowledged BP > 120/80mmHg as "elevated" and recommended robust lifestyle modification with prompt introduction of pharmacotherapy in patients with persistently high BP of more than 130/80mmHg with >1% annual risk of cardiovascular events. However, a consistent pattern of AF reduction or improved cardiovascular outcomes by intensive BP control is yet to be seen (7-11). With the increasing evidence base establishing a link between pre-hypertension and AF, we sought to perform a systematic review and meta-analysis to determine the strength of these associations in relation to the development of new-onset AF.

2.2 METHODS

2.2.1 Literature Search

The meta-analysis was registered with PROSPERO (149706). With the help of an experienced librarian, an online search of PubMed and EMBASE databases was performed from inception up to 31st August 2019, using the search terms: "pre-hypertension" or

"elevated blood pressure" or "blood pressure" AND "events", "atrial fibrillation", "atrial arrhythmia", "outcome". Duplicate citations were removed.

2.2.2 Inclusion and Exclusion Criteria

We included prospective longitudinal studies published in English with more than 50 participants and a minimum follow-up duration of 1 year that employed standardized methodology to assess blood pressure to quantify pre-HTN and its association with new-onset AF (Table-2.9.1). In addition, a manual search of the bibliographies of the retrieved articles was performed to identify all relevant studies. We excluded reviews, editorials, case reports, letters and conference abstracts associating AF incidence with blood pressure levels. However, their reference lists were manually searched for relevant publications.

2.2.3 Data Extrapolation

The literature search, study selection and extraction of the data set was performed by two authors (KBK and AM) independently. The quality of the studies was gauged by modified Newcastle-Ottawa scale by two independent reviewers (KBK and AM) as listed in Table 2.9.2. Divergent views were resolved by consensus. Data was collected on cardiovascular risk profiling of the participants, follow-up duration, and incidence of new-onset AF. The reported quantitative risk estimation for new-onset AF was used for statistical analysis to derive a cumulative hazard profile for pre-HTN.

2.2.4 Statistical Analysis

Our search resulted in a list of studies with comparable populations and acceptable distribution of reported BP range. Adjusted hazard ratios (HR) were used to report risk comparison in the studies. Pooled HR and 95% confidence intervals were calculated by random effects meta-analysis technique. The most adjusted model in each study was utilised. The most common covariate adjusted for were age, gender, BP, BMI, history of

cardiovascular disease, smoking, diabetes and left ventricle hypertrophy. All the studies have adjusted for age, gender, BP, smoking and left ventricle hypertrophy as shown in table 2.9.1. A 2-tailed value of $p<0.05$ was considered statistically significant. Furthermore, heterogeneity across studies was assessed by using I^2 statistic. A Funnel plot was used to examine the heterogeneity in reported estimates and publication bias by illustrating effect size against standard error (Figure 2.8.1).

2.3 RESULTS

2.3.1 Literature Search and Study Selection

Initial online search of PubMed and EMBASE database retrieved 15,530 studies, which were narrowed down to 5 relevant articles as per eligibility criteria (Figure 2.8.2). Out of the above 5116 were found to be duplicate references. In total, 10,414 were screened for abstracts and titles. Out of those, 10,390 were excluded as the outcome of interest was not reported. The remaining 24 studies were accessed for full text review to confirm their eligibility as per reported criteria in section 2.2.2. We have to further exclude 19 studies as the pre-defined outcome was not reported by them. Finally, the 5 remaining articles were found to be eligible to include in the analysis.

2.3.2 Study Population

The five studies that reported on the association between pre-HTN and incident AF recruited 4,346,851 participants (48% male) with a mean age of 51$\pm$7.5 years over a median follow-up duration of 12.4 years (Interquartile Range [IQR] 6.1-14yrs.). The included studies were all community based. Only 14.6 % of the total participants were found to be hypertensive (BP >140/90mmHg) and 5.5% were diabetic. The average BMI of the cohort was 26 kg/m^2 and 29% were active smokers as shown in Table 2.9.1.

2.3.3 Outcomes

The association between pre-HTN and AF was reported by five prospective studies (49, 118-121). Adjusted for conventional CV risk factors, pre-HTN increased the risk of incident AF by 27% [Figure 2.8.3: HR 1.27 (95% CI 1.14-1.41), p<0.0001]. The population of the included studies were comparable with I^2 of 38%, p=0.08. The individuals with pre-HTN were older with a relatively increased burden of metabolic risks including a higher incidence of dyslipidaemia, as compared to normotensive cohort (Table 2.9.3). The overall burden of pre-HTN increased by three-fold during the follow up. Further, one-third of participants with pre-HTN developed HTN (BP of >140/90 mmHg) during the follow up. Because of the variable burden of the cardiovascular risks and diverse methodologies adapted by the selected studies for meta-analysis, the reported incidence range of AF was 2.43 to 18 events/1000 person-years.

2.4 DISCUSSIONS

This systematic review and meta-analysis present a pooled analysis of prospective longitudinal studies associating pre-HTN with incident AF. Pre-HTN as an independent predictor was associated with an adjusted 27% increased risk of new-onset AF. Hypertension is identified as the most prevalent risk leading to AF (70, 122). A number of risk models have incorporated HTN as their integral component to predict AF incidence based on a single time point evaluation (123-128).

Our meta-analysis presents the adjusted risk posed by pre-HTN for the development of new-onset AF. Individuals with pre-HTN are likely to develop sustained HTN associated with electro-anatomical remodelling of left atrium and a greater risk of future AF.

Although the precise mechanism associating pre-HTN and AF is not fully understood,

conduit arterial stiffness due to sustained central high BP along with endothelial dysfunction resulting in left atrial remodelling could be a plausible patho-physiological link (16, 35, 37, 39, 129). Aortic stiffness is recognised as a surrogate for central high blood pressure and studies have revealed a 30% incidence of increased aortic stiffness in middle age cohorts categorised as pre-HTN by brachial BP recordings (129). Aortic stiffness assessment by pulse pressure evaluation can provide incremental risk estimation concerning new-onset AF, independent of brachial BP values (79, 118).

Another important observation of our meta-analysis was that the patients with pre-HTN had a relative co-existence of cardiovascular risks. This indicates that patients with pre-HTN require more extensive cardiovascular profiling to recognise sub-clinical end organ injury. Conventionally, HTN induced end organ injury is characterised by diastolic LV assessment, retinal examination, urinary albumin: creatinine ratio and LA volume assessment. However, incorporation of central blood pressure indices and aortic stiffness appraisal (including their response to exercise) can be of incremental value to un-mask early CV remodelling with prompt introduction of preventative strategies potentially leading to improve CV outcomes. As a modifiable factor, pre-HTN associated with other risks can result in structural left atrial changes and increases the risk of new-onset atrial fibrillation.

The current guidelines do not specify blood pressure targets for AF patients. The SMAC AF study recorded no significant difference concerning short term AF free survival in patients offered aggressive BP control post ablation (46). However, recent work on aggressive risk factor modification has shown superior rates of sinus rhythm maintenance with strict blood pressure control (target of <130/80mmHg) along with weight loss in overweight individuals with AF (26, 101, 130). This reflects the importance of a holistic approach to modify underlying cardiovascular risks rather targeting BP in isolation. Pre-HTN can represent an

early sub-clinical phase of cardiovascular remodelling in individuals at increased risk of hypertension-induced end organ injury. Further studies are required to quantify how intensive risk profiling and aggressively targeting pre-HTN can improve AF outcomes.

2.5 CLINICAL IMPLICATIONS

Our review and meta-analysis have significant clinical implications. Despite being recognised as the most common modifiable CV risk in AF, BP targets to prevent the arrhythmia are not fully defined. Importantly, individuals with pre-HTN can have central arterial stiffness as a possible mechanistic link associating HTN with AF.

Ongoing aggressive CV risk factor modification in individuals with pre-HTN can provide us with a window of opportunity to prevent accelerated CV and left atrial remodelling, resulting in reduced AF burden. Further trials identifying pre-HTN patients with a focus on defining treatment targets in at-risk individuals will strengthen both primary and secondary prevention strategies in AF.

2.6 STUDY LIMITATIONS

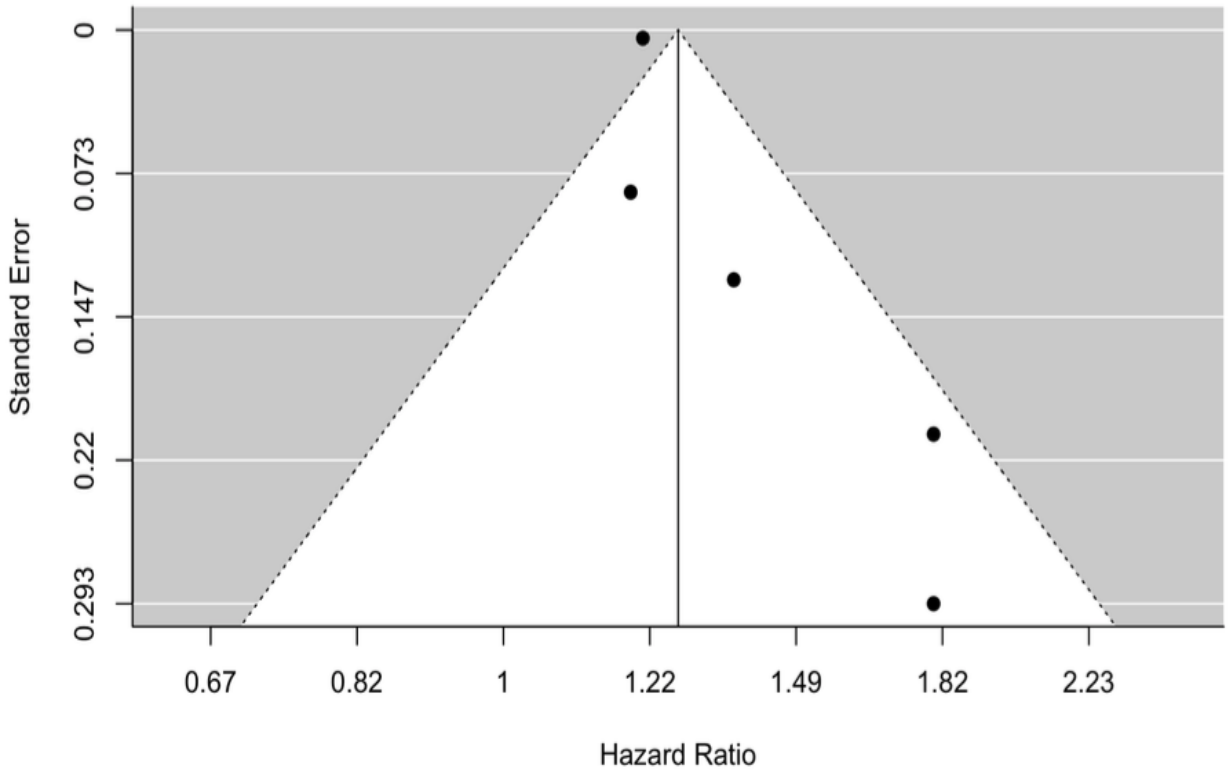
Our review has the following limitations. Due to the nature of the included studies, we could only perform an aggregated data analysis of range of cut-offs used to define pre-HTN. Most of the included studies characterise the incidence of pre-hypertension and HTN based on single point evaluation during follow-up. Additionally, an exhaustive conventional cardiovascular risk adjustment was not performed in all the studies selected for analysis as listed in Table 2.9.1. However, the incidence of AF is likely to be under-estimated as the diagnosis was based on symptoms or pre-defined time points for screening during follow up. This meta-analysis is not able to tease out the impact of medications on BP assessment

and AF outcomes. Arrhythmia burden was not quantified by the included studies nor was it further differentiated into AF or atrial flutter**.** Finally, the cohort selected for analysis predominantly consisted of middle-aged Caucasians. It remains unclear whether the meta-analysis results can be generalized for younger, elderly or non-Caucasian individuals.

2.7 CONCLUSIONS

Pre-hypertension is found to be independently associated with new-onset AF. Further trials are required for better understanding of this association and defining the role of targeting pre-HTN as a part of an aggressive CV risk factor modification programme for the prevention of AF.

Figure 2.8.1: Funnel Plot Showing Publication Bias



Rank Correlation Test for Funnel Plot Asymmetry

Kendall's tau = 0.8000, p = 0.0833

Egger's Regression Test for Funnel Plot Asymmetry

Model: mixed-effects meta-regression model

Test of funnel plot asymmetry: Z = 2.041; p-value = 0.041

Figure 2.8.2: Study Selection Flow Diagram

Search Engine: EMbase and PUBMED for English literature until 31st August 2019. Search terms "pre-hypertension" or "elevated blood pressure" or "blood pressure" **AND** "events", "atrial fibrillation", "atrial arrhythmia", "outcome" were used to enlist the studies.

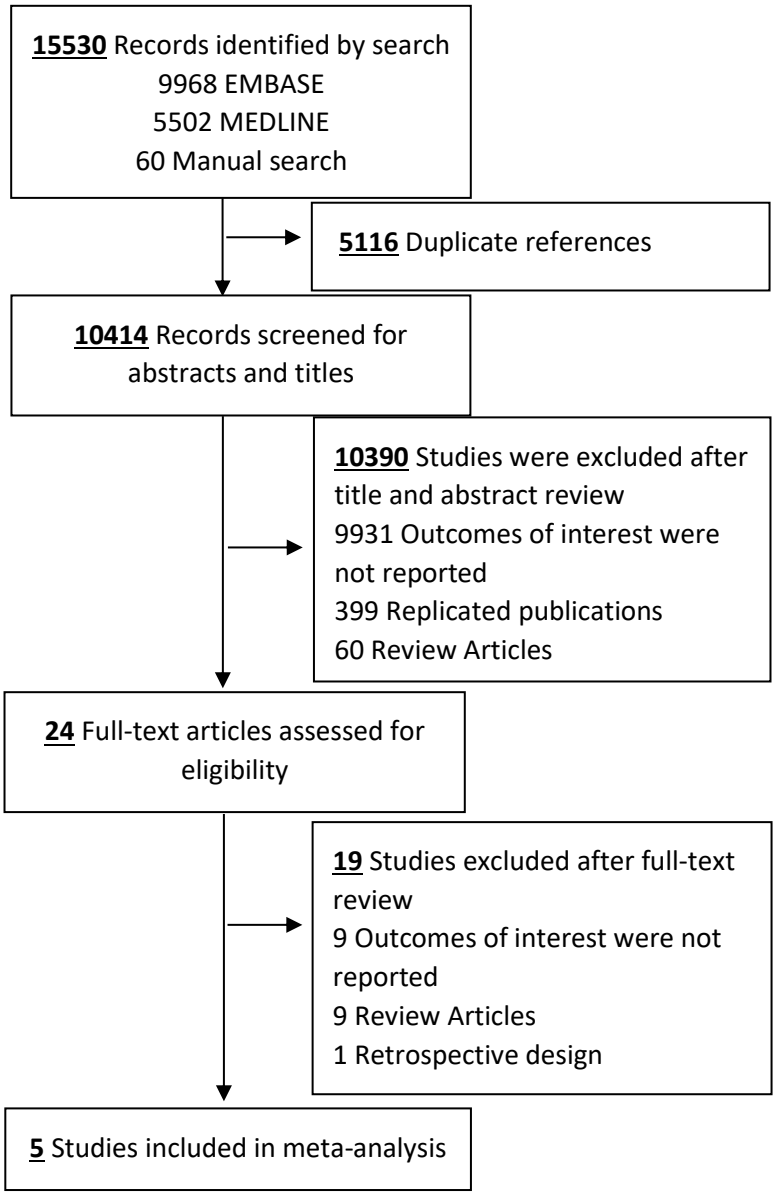
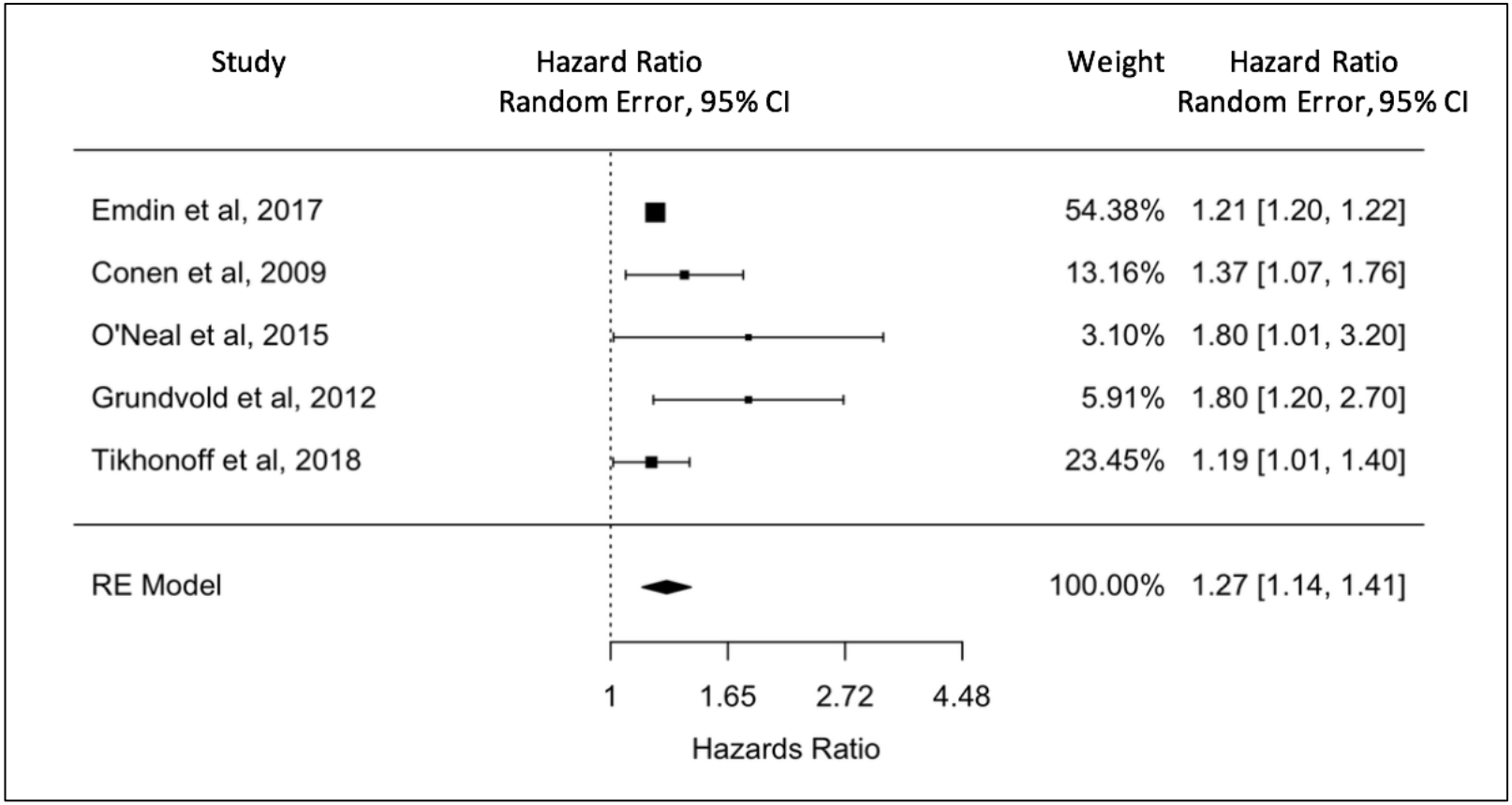


Figure 2.8.3: Association of Pre-Hypertension and Incident AF



Heterogeneity: Tau^2 = 0.005, df=4 (0.165), I^2 = 38.5%, Test for Effects size = 0.2388, SE= 0.053, p-value <0.0001

Table 2.9.1: Overall Characteristics of the Study Participants

First author, publication year	Study population, (n)	Mean Age (yrs.)	Male (%)	Follow up (yrs.)	DM (%)	HTN (%)	Cholesterol mg/dl	BMI kg/m^2	Smokers (%)	HR (95% CI)	Covariates adjusted for
Valérie Tikhonoff et al. Heart 2018 (131)	3956	42±15	48	14	1	11	5.4 ± 1.2	25±4	19	1.19 (1.0-1.4)	Gender, Age, smoking, BMI, serum cholesterol, DM, h/o CVD
Emdin Connor et al. Int J Epidemiol 2017 (54)	4301349	46±13	45	6.9	3.2	10	5.5±0.8	26±3	10	1.21 (1.9-1.22)	Age, BMI, Gender, DM, Smoker
Wesley O'Neal et al. J Am Soc Hypertens 2015(10)	5311	62±10	47	5.3	14	22	5±0.9	27±5	42	1.8 (1.0-3.2)	Age, Gender, Race, BP, DM, BMI, smoking, cholesterol, HDL, statins, aspirin, LVH
Irene Grundvold et al. Hypertension-AHA 2012 (53)	2014	50±5	100	30	NR	13	6.6±1.2	25±3	44	1.81 (1.2-2.7)	Age, LVH, BMI, SBP and DBP
David Conen et al. Circulation 2009 (52)	34221	55±7	0	12.4	2.8	17	NR	26±5	12	1.37 (1.1-1.76)	Age, CVE
5 Studies	**4346851**	**51 ± 10**	**48**	**14**	**5.5**	**14.6**	**5.6 ± 1**	**26 ± 4**	**29**	**1.27 (1.14-1.4)**	

(BMI= basal metabolic index, BP= blood pressure, CVD= cardio-vascular disease, CVE= cardio-vascular events, DBP= diastolic blood pressure, DM= diabetes mellitus, HDL= high density lipoproteins, h/o= history of, HR= hazard ratio, HTN= hypertension, LVH= left ventricle hypertrophy, SBP= systolic blood pressure, yrs. = years)

Table 2.9.2: Quality Assessment of Studies Included in Meta-analysis by Modified Newcastle-Ottawa Scale

First Author, Year (Ref. #)	Selection		Comparability			Outcome A		Total
	participants representative of population	Adequate sample size	Appropriate Stat. Method	Reproducibility	Adjusted for risk factors	Follow up	Outcome	
Valérie Tikhonoff et al. Heart 2018 (131)	*	*	*	*	*	*	*	7
Emdin Connor et al. Int J Epidemiol 2017 (54)	*	*	*	*	*	*	*	7
Wesley O'Neal et al. J Am Soc Hypertens 2015(10)	*	*	*	*	*	*	*	7
Irene Grundvold et al. Hypertension-AHA 2012 (53)	*	*	*	*		*	*	6
David Conen et al. Circulation 2009 (52)	*	*	*	*		*	*	6

Table 2.9.3: Characteristics of the Study Participants as per their BP Classification

First author, publication year	Study population (n)			Mean Age (yrs.)			Male (%)			PP (mmHg)			DM (%)			Anti-HTN Rx			BMI kg/m²		
	Overall	Pre-H	HTN	Optimal BP	Pre-H	HTN	Optimal BP	Pre-H	HTN	Optimal BP	Pre-H	HTN	Optimal BP	Pre-H	HTN	Optimal BP	Pre-H	HTN	Optimal BP	Pre-H	HTN
Valérie Tikhonoff et al. Heart 2018 (129)	3956	971	996	42±15	43±16	48±15	48	46	57	41±5	49±6	55±8	1	3	6	11	28	60	25	26	27
Emdin Connor et al. Int J Epidemiol 2017 (52)	430,1349	159,5134	117,3307	39±7	47±9	59±11	34	51	51	NR	NR	NR	2	3.4	5	4	9	20	24	26	27
Wesley O'Neal et al. J Am Soc Hypertens 2015(10)	5311	1122	2577	57±9	61±10	65±9	47	53	46	NR	NR	NR	5	9	21	6	16	22	26	28	29
Irene Grundvold et al. Hypertension-AHA 2012 (51)	2014	518	526	48±5	50±5	52±5	100	100	100	33±6	44±6	56±11	NR	NR	NR	3	12	NR	25	25	25
David Conen et al. Circulation 2009 (50)	34221	NR	NR	NR	NR	NR	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5 Studies	**4346851**	**1597745**	**1177406**	**46±8**	**50±8***	**56±7***	**43±8**	**50±3**	**51±5**	**37±5**	**46±3***	**55±1***	**2.7**	**5.1***	**10.6***	**6±3**	**16±4***	**34±11***	**25**	**26***	**27***

(*= statistically significant comparison p-value ($p<0.05$), BMI= basal metabolic index, BP= blood pressure, DM= diabetes mellitus, HTN= hypertension, Pre-H= pre-hypertension, PP= pulse pressure, Rx= treatment, yrs.= years)

Chapter 3:

Association of Increased Aortic Stiffness with New Onset Atrial Fibrillation and Mortality: A Systematic Review and Meta-Analysis

3.1 INTRODUCTION

A number of studies have alluded to the predictive value of central arterial stiffness on adverse cardiovascular outcomes and increased mortality (132, 133). Likewise, the evidence base on the association between aortic stiffness and atrial fibrillation (AF) is on the rise (61, 134). Specifically, aortic stiffness as determined by pulse pressure has been shown to be associated with increased risk of developing AF independent of established cardiovascular risk factors and mean arterial blood pressure in a large population-based cohort (118).

Ageing and hypertension (HTN) are the predominant factors leading to aortic stiffness. In addition, the co-existence of HTN with uncontrolled conventional cardiovascular risks result in premature conduit vascular remodelling and aortic stiffness (129). Importantly, epidemiological studies have revealed that up to 15-20% of middle-aged adults can have "sub-clinical" central arterial stiffness (135) as the central high blood pressure is not timely diagnosed, in these individuals especially with normal brachial blood pressure measurements (80).

Although several non-invasive methods are currently available for evaluation of aortic stiffness by employing central pulse wave morphology or velocity assessment (136) its integration in routine clinical care and cardiovascular risk profiling remains poor. This may be due to the lack of established reference values and standardised measurement methodology.

Furthermore, several studies have reported high pulse pressure (PP) as a marker of aortic stiffness and associated it with poor cardiovascular outcomes including new-onset AF (118, 119). However, aortic pulse wave velocity (PWV) represents the "gold standard" method in aortic stiffness assessment with a cut off value of 10 m/s, due to the evidence base associating escalated aortic PWV with cardio-vascular and mortality outcomes (137). Interestingly, compared to increased PP, the independent association of amplified aortic PWV with new onset AF has not been recognised after adjusting for age and HTN (121).

With the increasing evidence base on the link between aortic stiffness and cardiovascular events including AF, we sought to perform a systematic review and meta-analysis to determine the strength of these associations in relation to development of new-onset AF along with cardiovascular and all-cause mortality. PRISMA guidelines were followed to perform literature search and report the results.

3.2 METHODS

3.2.1 Literature Search

The meta-analysis was registered with PROSPERO (CRD42018102267). With the help of an experienced librarian, an online search of PubMed and EMBASE databases was performed from inception up to 30th December 2018, using the search terms: "stiffness", "aortic

distensibility," "aortic stiffness," "arterial compliance" or "central blood pressure", "pulse pressure", "pulse wave velocity," AND "events", "atrial fibrillation", "mortality", "cardiovascular mortality" "outcome". Duplicate citations were removed.

3.2.2 Inclusion and Exclusion Criteria

Prospective longitudinal studies with more than 50 participants and a minimum follow-up duration of 1 year that employed standardised methodology to assess aortic PWV, ascending aorta distensibility (AAD) or pulse pressure (PP) to quantify aortic compliance and its association with all-cause or cardiovascular mortality or new-onset AF were included. We included studies published in English language only. In addition, a manual search of the bibliographies of the retrieved articles was performed to identify all relevant studies.

We excluded reviews, editorials, case reports, letters and conference abstracts in addition to the studies that employed non-standardised methods to measure aortic stiffness and those that did not adjust cardiovascular outcomes with blood pressure levels. However, their reference lists were manually searched for relevant publications.

3.3.3 Methods of Aortic Stiffness Assessment in Included Studies

The aortic stiffness in the selected studies was characterised by aortic PWV, AAD or PP evaluation. PP is recorded as the difference between systolic and diastolic blood pressure. In contrast, the aortic PWV is determined by the distance covered by the central pressure wave between two discrete vascular points and dividing it by the transit time. The AAD is derived by comparing the maximum and minimal aortic cross-sectional area determined on axial and coronal planes at the level of ascending, arch and descending aorta (129).

Majority of the studies included in our meta-analysis employed aortic PWV to evaluate aortic stiffness by using the following technology: Doppler ultrasound, applanation tonometry or oscillometric analysis of pulsatile pressure wave along the vascular wall usually at the level of carotid and femoral arteries (118, 133, 138-155). In addition, five studies (49, 118-121) examined the association of PP with incidental AF and two citations used AAD as a marker of increased aortic stiffness (83, 156).

3.3.4 Data Extrapolation

The literature search, study selection and extraction of the data set was performed by two authors (KBK and AT) independently. The quality of the studies was gauged by modified Newcastle-Ottawa scale by two independent reviewers (KBK and AT) as listed in Table 3.10.1. Divergent views were resolved by consensus. Data was collected on cardiovascular risk profiling of the participants, follow-up duration, methodology used to assess aortic stiffness and cardiovascular outcomes. Aortic PWV was generally reported as a categorical or continuous variable. Reported quantitative risk estimation for cardiovascular outcomes was used for statistical analysis to derive a cumulative hazard profile for each aortic stiffness index.

3.3.5 Statistical Analysis

Our search resulted in a list of studies with heterogeneous populations and widely distributed aortic PWV range. Adjusted odds ratio (OR) or hazard ratios (HR) were used to report risk comparison in the studies. To address the widely described range of aortic stiffness indices in the included studies, reported data of low and high PWV group for each study was extracted to calculate pooled OR and 95% confidence intervals by random effects meta-analysis technique. The most adjusted model in each study was utilized. A 2-tailed

value of $p<0.05$ was considered statistically significant. Funnel plots were used to examine the heterogeneity in reported estimates and publication bias by illustrating effect size against standard error (Figures 3.9.1-3.9.7). Furthermore, heterogeneity across studies was assessed by using I^2 statistic. In addition, where risk was reported per unit of PWV, OR were manually adjusted to estimate the risk associated with a 1m/s increase in PWV. Meta-analysis of studies evaluating aortic PWV was performed to report the pooled OR for cardiovascular and all-cause mortality separately. In addition, cumulative OR was derived to illustrate the association of high pulse pressure with new onset of AF.

The terms "predictors" and "impact" are used to describe the association of baseline aortic stiffness with defined outcomes including new-onset AF during follow up of selected longitudinal studies.

3.4 RESULTS

3.4.1 Literature Search and Study Selection

Initial online search of PubMed and EMBASE database retrieved 3,583 studies, which were narrowed down to 37 relevant articles as per eligibility criteria (Figure 3.9.8). A further 10 studies were excluded because of cross-sectional study design, use of non-standardised methodology to evaluate aortic stiffness and non-reporting of relevant outcomes. One study reporting pulse pressure and new onset AF using 24-hr ambulatory BP monitoring was excluded because of its retrospective design (157). Another study was excluded due to statistical limitations as it did not report association of pulse pressure with new onset AF (158). This meta-analysis included 25 studies: Twenty of these reported on the association of aortic stiffness and mortality (83, 133, 138-141, 143-147, 150-155, 159-161) while five

longitudinal studies explored the association between aortic stiffness and new onset AF (49, 118-120, 149).

3.4.2 Study Population

3.4.2.1 Aortic stiffness and mortality

The 20 studies that reported on the association between aortic stiffness and mortality recruited 26,614 participants (54% male) with a mean age of 60±10 years over a median follow-up duration of 7.8 years (Interquartile Range [IQR] 3.3-12.2 yrs.). Though majority of the included studies were community based, distinct populations including diabetes, end stage renal failure (ESRF) and HTN were represented by two (141, 159), five (138, 140, 150, 151, 155) and three studies (139, 152, 162) respectively (See Table 3.10.2). Forty percent of the total participants were found to be hypertensive with a mean systolic blood pressure (SBP) of 143±11 mmHg and 23% were diabetic. The average BMI of the cohort was 25 kg/m^2 and 12% were active smokers. A significant difference in average brachial BP between general and HTN participants (135.5 +/- 6 vs 143 +/- 7, p= 0.04) was recorded.

The mean PWV of the cohort was 10.8±1.8 m/s with no significant differences seen between the general, hypertensive, diabetic or ESRF populations (10.8±1.8, 10.9±1.8, 11.1±2.6 or 10.4±1.2 m/s respectively; p=NS).

3.4.2.2 Aortic stiffness and atrial fibrillation

The five longitudinal studies that described the association of aortic stiffness with new-onset AF have 26,868 participants with a mean age of 62±4 years (48% male) and a mean follow-up of 8.7±3 years (49, 118-121). Majority (60%) of the studies included in the

analysis were community based (118, 119, 121). Discrete population of hypertensive and diabetic participants were represented by one study each (49, 120). Although 46.5% of the participants included in the pooled analysis were known to have HTN, the mean BP for the cohort was 128 $\pm$ 14mmHg. The average BMI of the participants was 27.6±1.4 kg/m^2 with 28% incidence of diabetes (See Table 3.10.3). The mean pulse pressure for the selected cohort was 60±16 mmHg with a mean HR of 66$\pm$6 bpm.

3.4.3 Outcomes

3.4.4 Cardiovascular mortality

The association between aortic stiffness and CV mortality was reported by 19 studies (83, 133, 138-140, 143-147, 150-155, 159-161). Twelve of these studies (138-140, 143, 146, 148, 150-152, 154, 159, 160) including a sub-study (148) reported PWV as a continuous variable while seven reported it as categorical (83, 133, 144-147, 155). Three studies reported PWV as both categorical and continuous variable concomitantly (138, 143, 153). Every metre per second (m/s) increase in PWV was associated with an independent 25% increase in CV mortality [Figure 3.9.9: OR 1.25 (95% CI: 1.16-1.34), p<0.00001]. An adjusted pooled high PWV (>10.7 ± 0.5 m/s) was associated with more than two-fold increase in CV mortality [Figure 3.9.10: OR 2.34 (95% CI 1.81-3.02), p=0.0001]. Moderate to high heterogeneity was seen in the studies that reported PWV as categorical (I^2=41%, p=0.00001) or continuous variable (I^2=78%, p<0.00001) in association with CV mortality.

3.4.5 All-cause mortality

All-cause mortality was reported by 10 studies (83, 141-144, 147, 148, 152, 155, 160). The pooled analysis of five studies (141, 148, 152, 155, 160) revealed a 16% increase in all-cause mortality with each m/s increase in PWV adjusted for conventional cardiovascular risk

factors including ageing [Figure 3.9.11: OR 1.16 (95% CI: 1.08-1.25), p<0.00001]. On the other hand, meta-analysis of six studies (83, 138, 142-144, 147) reported a 57% increased risk of all-cause mortality with adjusted high versus low PWV with a cut off of 10.3±2 m/s [Figure 3.9.12: OR 1.57 (95% CI: 1.2-2.1), p=0.0010]. Significant heterogeneity was seen in the studies that reported PWV as categorical (I^2=57%, p=0.04) or continuous PWV variable (I^2=88%, p=0.00001) in association with all-cause mortality.

3.4.6 Pulse pressure and atrial fibrillation (AF)

The association between pulse pressure (PP) and AF was reported by five prospective studies (49, 118-121). Adjusted for conventional CV risk factors, high PP (60 ± 16 mmHg) increased the risk of developing new-onset AF by 38% [Figure 3.9.13: OR 1.38 (95% CI 1.15-1.64), p=0.0004]. Significant heterogeneity was seen amongst these five studies (I^2=75%, p=0.003). Interestingly, none of the studies reported adjusted aortic PWV as an independent predictor of new-onset AF. In addition, the selected studies did not differentiate atrial flutter from AF or different AF subtypes.

3.5 DISCUSSIONS

This systematic review and meta-analysis present a pooled analysis of prospective longitudinal studies associating aortic stiffness, defined as elevated PWV (>10.7± 1.7m/s), with CV and all-cause mortality. High PWV was associated with an adjusted two-fold and 57% increased risk of CV and all-cause mortality respectively. Furthermore, each m/s increase in PWV was also associated with an adjusted 25% and 16% increased risk of CV and all-cause mortality, respectively. Notably, the association between aortic stiffness with CV outcomes were seen across a variety of subjects including general population cohorts

and specific ESRF, hypertensive and diabetic populations. Furthermore, increased PP was found to be an independent predictor of new-onset AF. High PP (>60mmHg) was independently associated with an adjusted 38% increased risk of new-onset AF.

3.5.1 Association of Aortic Stiffness with CV and All-cause Mortality

The association between increased aortic stiffness and mortality including CV outcomes is well described in community-based population studies as well as in diverse groups including elderly, ESRF, hypertensive and diabetics (83, 147, 148, 155, 159, 161, 163, 164). Importantly, our review further affirmed the independent predictive value of arterial stiffness beyond known cardiovascular risk factors including HTN. However, the clinical utility of aortic stiffness assessment is inadequate due to the lack of established reference values and standardised measurement methodology. Undeniably, numerous methods to appraise aortic stiffness by various modalities can add further confusion in the clinical settings. Majority of the studies included in our review employed aortic PWV to quantify arterial stiffness (Table 3.10.1). However, these studies employed four different non-invasive devices using oscillometric and applanation tonometry techniques (139, 140, 161). Furthermore, five studies (138, 141, 143, 144, 146) included in our analysis used Doppler to compute carotid-femoral PWV. Despite validation and reported correlation of different techniques and devices (129, 133, 136, 165, 166) disparities were reported during calculation of surface distance between carotid and femoral arteries for non-invasive PWV assessment (Table 3.10.1). Of note, these commercially available validated devices examine different aspect of ascending aortic response to ejected volume load to compute central blood pressure indices including central PP, AI, and AP. Hence these calculations

are not interchangeable due to the technical limitations posed by device software and characteristics of the population studied (136, 166, 167).

Nevertheless, aerobic exercises and weight loss with ongoing cardiovascular risk factors modification in addition to BP control is reported to improve arterial stiffness in observational settings (168). Treatment with angiotensin converting enzyme inhibitors have been found to improve vascular physiology by refining endothelial function through enhanced release of nitric oxide and inhibition of fibrosis on vascular layers, but the actual mechanism influencing the arterial stiffness beyond BP control is yet to be elucidated (169). Although, the moderate intensity aerobic exercise has been reported to be modestly effective in reducing aortic stiffness, the underlying mechanisms remain poorly understood (170). Further work is needed to evaluate other treatment options useful to reduce aortic stiffness that may improve clinical outcomes.

3.5.2 Aortic Stiffness and AF

Although the link between aortic stiffness and AF recurrences post cardioversion or catheter ablation has been reported previously (61), the current meta-analysis demonstrated that high PP (>60mmHg) is independently associated with the development of new-onset AF. The mechanisms by which aortic stiffness results in AF remain incompletely understood but are thought to involve left atrial stretch in the setting of left ventricular diastolic dysfunction that contributes to AF triggers, perpetuators and substrate (171).

3.5.2.1 Association of PWV with new-onset AF

Except augmented pulse pressure, other methods to characterise aortic stiffness were not found to be consistently predictive of new-onset AF. For example, MRI based measure of

AAD was not predictive of AF development in the Multi-Ethnic Study of Atherosclerosis (MESA) (119). Further, in contrast to central PP and augmentation index, PWV was not reported to be independently associated with incidental AF in the Framingham Heart Study offspring and third-generation cohorts (119, 149, 172).

These inconsistencies may in part be explained by the different populations studied and methods employed for aortic stiffness assessment. Central PP is defined as the difference between central systolic and diastolic blood pressure. It represents central pulsatile load, which determines the extent of atrial stretch and potentially influences the onset of AF (129, 173). In comparison, the aortic PWV is determined by the distance covered by the central pulsatile pressure wave between two distinct vascular points and dividing it by the transit time. The propagation velocity of the pressure wave is the major determinants of aortic PWV. In comparison to PP, the distal vascular segments significantly affect aortic PWV assessment during cross talk of ejected and reflective pulse (167).

3.5.2.2 Aortic stiffness, pre- HTN and AF

In general, the non-invasive measures of aortic stiffness indices provide incremental risk estimation independent of peripherally derived systolic BP readings. These central measures may be more patho-physiologically relevant than peripheral BP given the proximity to the heart. Therefore, these indices may be useful for identifying high-risk patients including 'pre-hypertension' (174) or those with persistent aortic stiffness despite optimal blood pressure control (175). However, these observations are not tested in a trail settings and further studies are required to explore the utility of "re-classification" of participants as per their aortic stiffness indices and the impact of targeting aortic stiffness on cardiovascular and AF outcomes. Of note, current guidelines do not specify blood

pressure targets in the care of AF patients while recent work on aggressive risk factor modification has shown superior rates of sinus rhythm maintenance with strict blood pressure control (target of <130/80mmHg) and weight loss in overweight and obese individuals with AF (26). However, none of the devices used to quantify aortic stiffness and central pressure indices non-invasively, is validated to be used during AF whereby the ventricular rates are irregularly irregular and often rapid. More work is needed to delineate how additional active monitoring and targeting of aortic stiffness indices can improve outcomes in AF patients.

3.6 CLINICAL IMPLICATIONS

The above observations have strong clinical implications, as aortic stiffness is a modifiable risk factor that can be evaluated non-invasively and with relative ease. Importantly, the risk associated with aortic stiffness is independent of HTN and other established CV risk factors. Further, recent evidence from the Framingham Heart Study illustrated 60% prevalence of aortic stiffness in hypertensive individuals with well-controlled blood pressure during monitoring. This finding may well explain the residual risk that requires further attention to improve CV outcomes (176). Aortic stiffness can be modified by aggressively targeting cardiovascular risk factors including hypertension, obstructive sleep apnea, increased pule pressure and obesity (168, 177). Further trials with a focus on methodological standardisation of central pressure indices with attention to the impact of reducing aortic stiffness on mortality and sinus rhythm maintenance will strengthen the case to assimilate central pressure estimation in conventional risk profiling of our patients. Taken together, integration of aortic stiffness evaluation in CV risk stratification of individuals should be

strongly considered in both primary and secondary prevention settings. However, further studies are needed to define optimal treatment targets in different sub-population of at-risk individuals, such as those with AF

3.7 STUDY LIMITATIONS

Our review has the following limitations. First, due to the nature of the included studies with heterogenous population, we could only perform an aggregated data analysis of the variable methodology and cut-offs for aortic stiffness indices. Second, the studies included in the meta-analysis span over two decades and the management of cardiovascular risks has significantly advanced during that period. We were unable to perform an exhaustive adjustment for all the known cardiovascular factors and accepted a pooled analysis adjusted for the conventional cardiovascular risks by these selected studies as listed in Table 1 and 2. Additionally the CHA_2DS_2VASC score and the anti-coagulation regime instigated during follow up was not reported. Third, this meta-analysis is not able to tease out the impact of medications on the measures of aortic stiffness or CV outcomes. Finally, the cohort selected for analysis was predominantly consisted of middle-aged and older Caucasians. It remains unclear whether the meta-analysis results can be generalized for younger or non-Caucasian individuals.

3.8 CONCLUSIONS

Aortic stiffness as a surrogate for central high blood pressure is independently associated with increased risk of new-onset AF, CV and all-cause mortality. Central pulsatile load

profiling by pulse pressure assessment can be of additional value in predicting new-onset AF. Further studies are required to explore this association of aortic stiffness to improve AF and cardiovascular outcomes.

Figure 3.9.1: Funnel Plot Illustrating Heterogeneity Amongst the Studies Associating High PP with AF

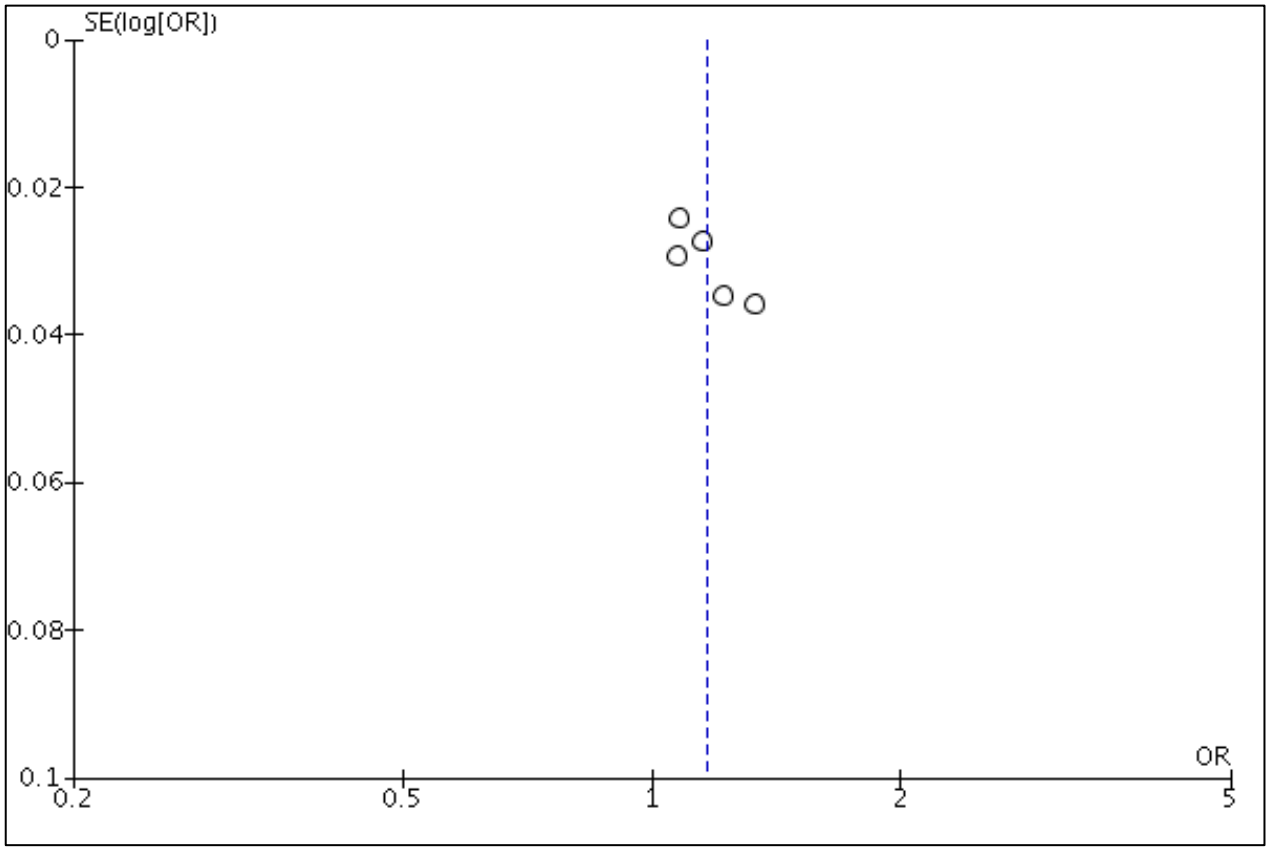


Figure 3.9.2: Funnel Plot Illustrating Heterogeneity Amongst the Studies Reporting All-Cause Mortality as Per 1 m/s Increase In Aortic PWV

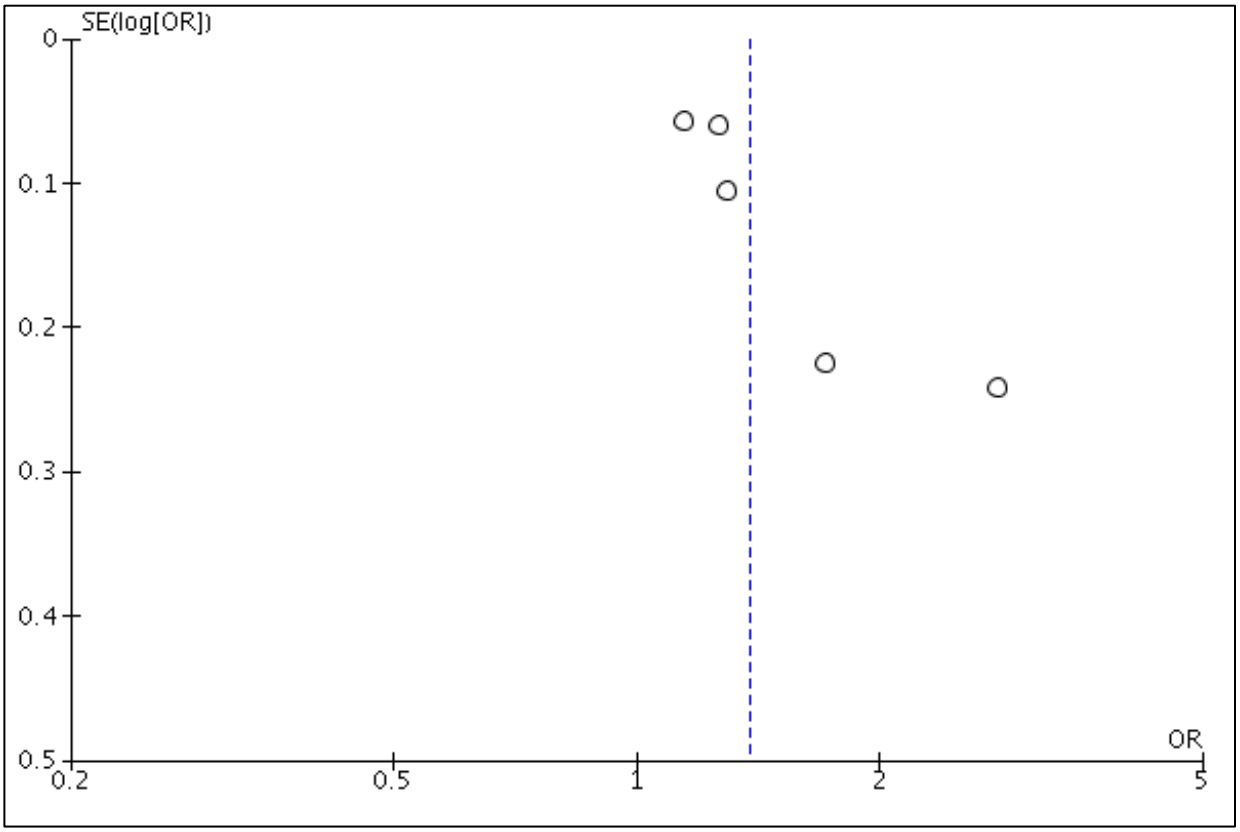


Figure 3.9.3: Funnel Plot Illustrating Heterogeneity Amongst the Studies Reporting All-Cause Mortality as Per High vs Low Aortic PWV

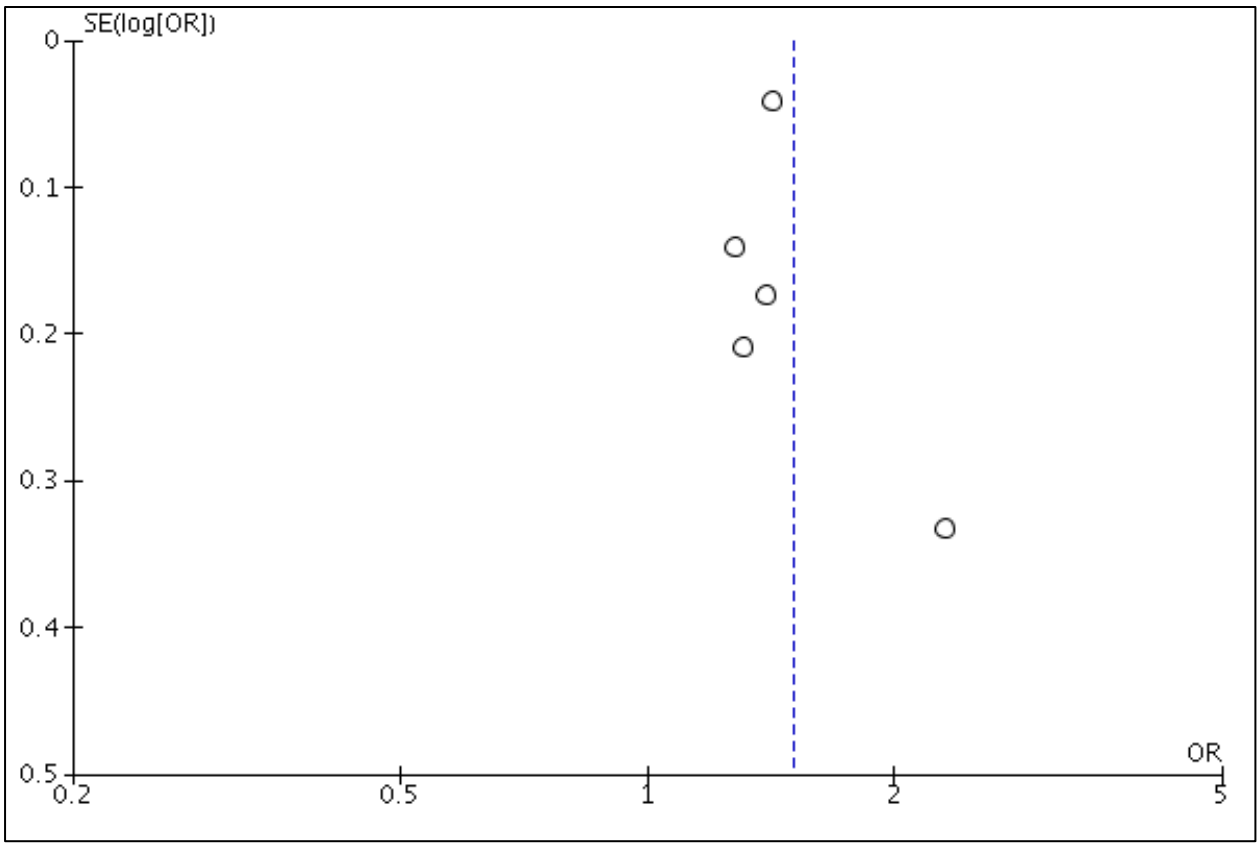


Figure 3.9.4: Funnel Plot Illustrating Heterogeneity Amongst the Studies Associating All-Cause Mortality with Increased Aortic PWV

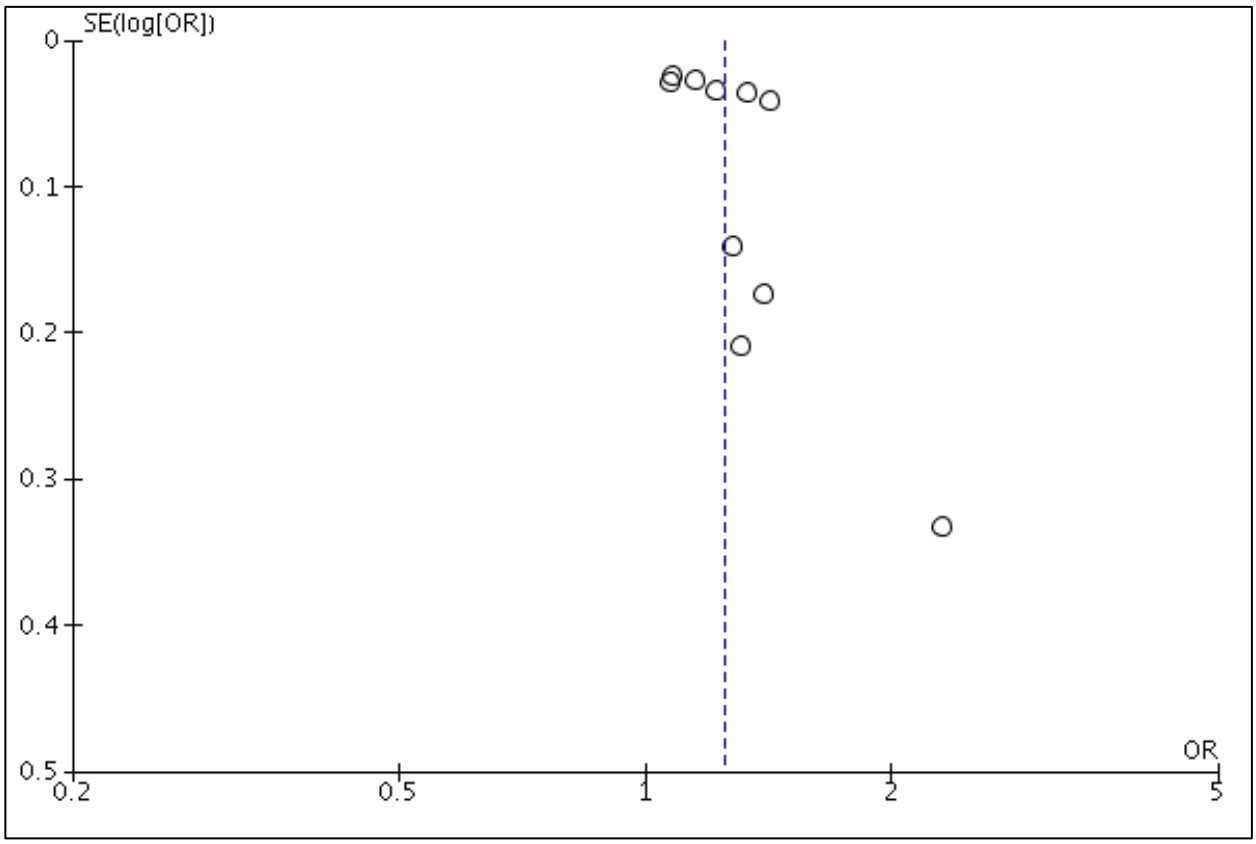


Figure 3.9.5: Funnel Plot illustrating Heterogeneity Amongst the Studies Reporting CV Mortality as Per 1m/s Increase in Aortic PWV

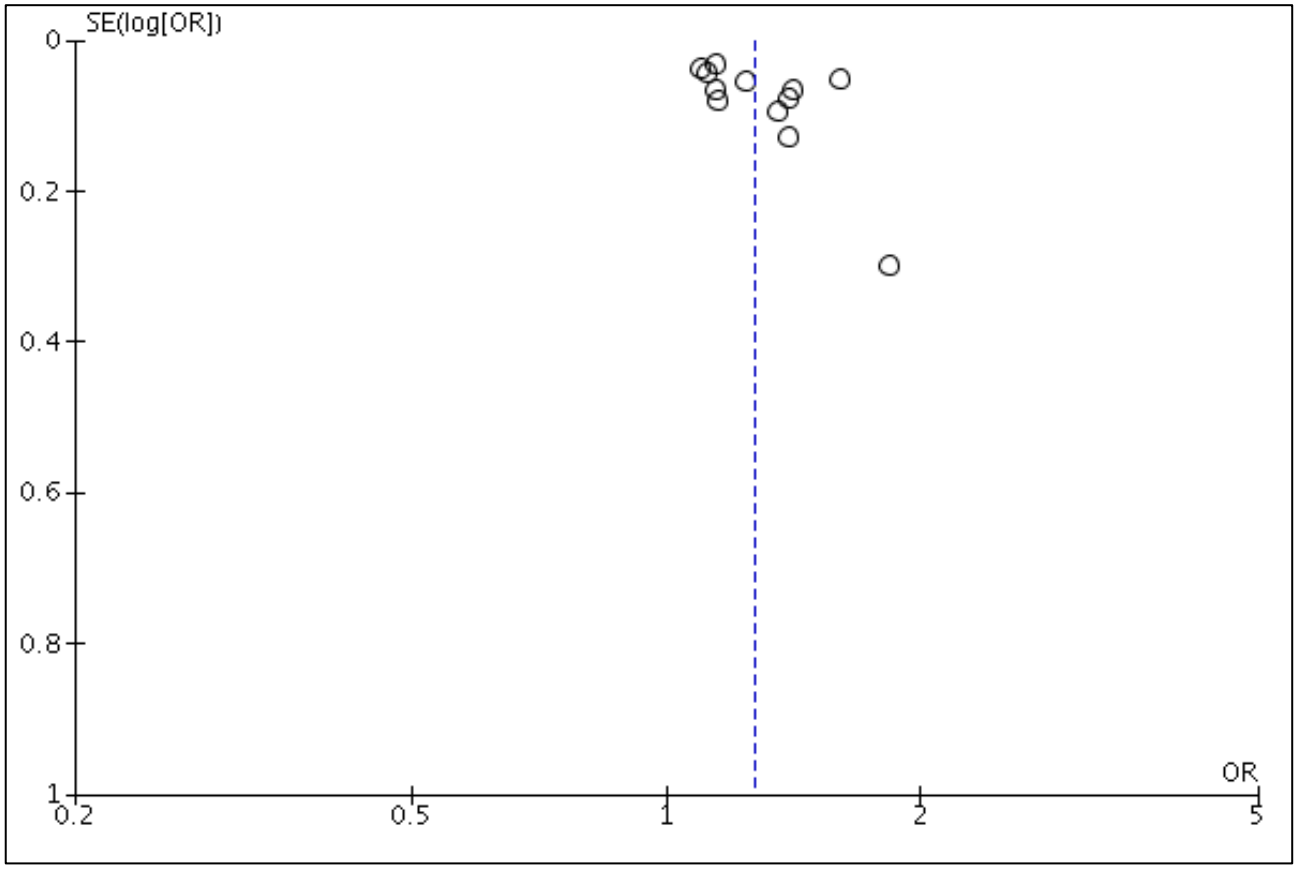


Figure 3.9.6: Funnel Plot Illustrating Heterogeneity Amongst the Studies Reporting CV Mortality as Per High vs Low Aortic PWV

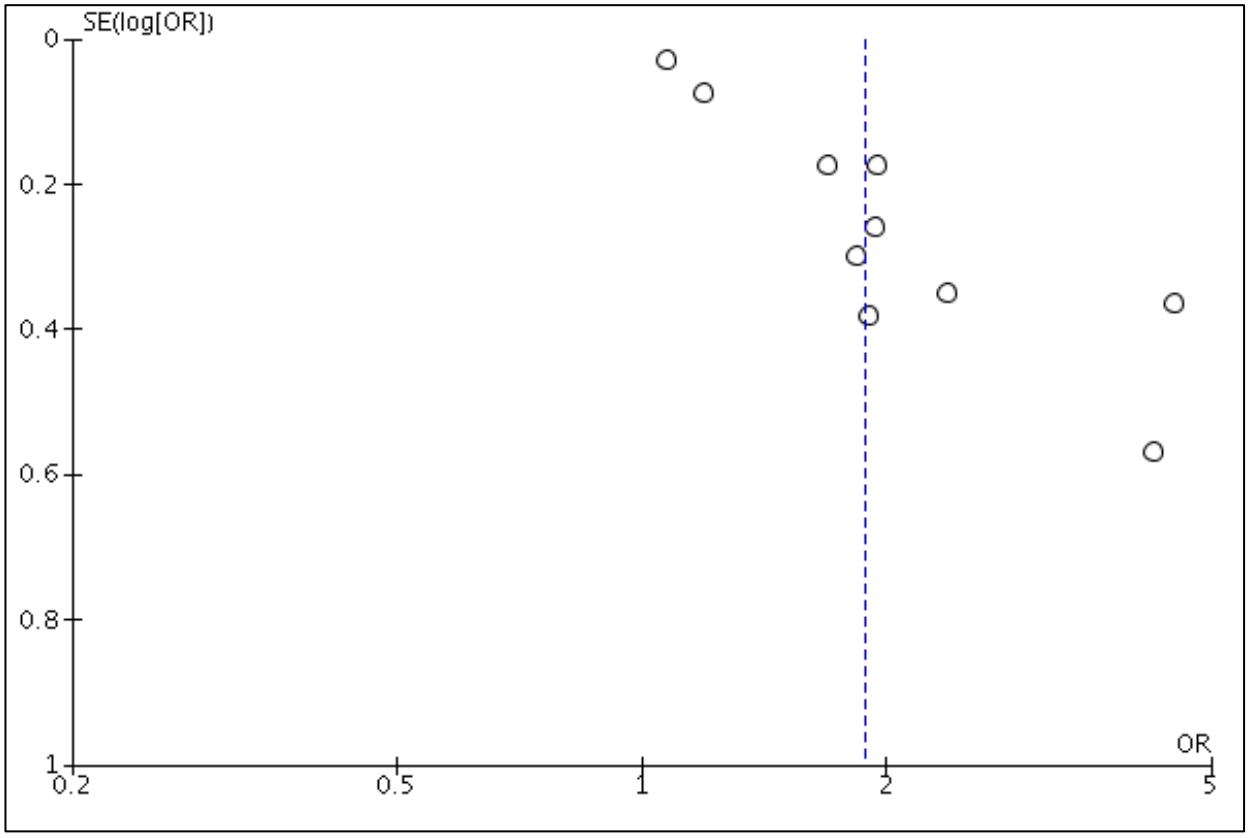


Figure 3.9.7: Funnel Plot Illustrating Heterogeneity Amongst the Studies Associating CV Mortality with Increased Aortic PWV

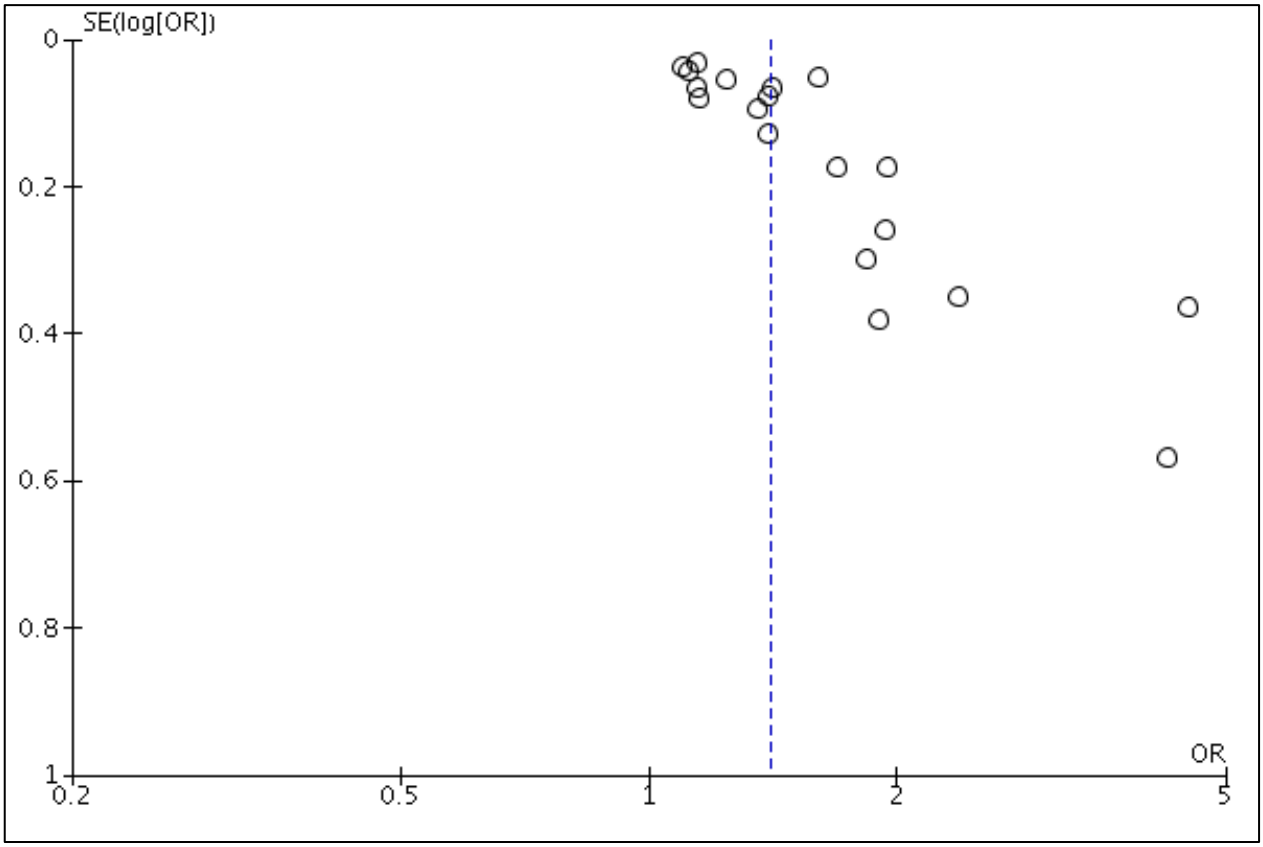


Figure 3.9.8: Literature Search and Studies Selection Criteria

Figure 3.9.9: Cardiovascular Mortality Association Per 1m/S Increase in Aortic PWV

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Blacher et al	0.3293	0.0793	7.5%	1.39 [1.19, 1.62]
Laurent et al	0.0953	0.0385	10.3%	1.10 [1.02, 1.19]
Laurent et al (b)	0.3293	0.1287	4.8%	1.39 [1.08, 1.79]
Meaume et al	0.174	0.0737	7.9%	1.19 [1.03, 1.37]
Pannier et al	0.1133	0.0427	10.0%	1.12 [1.03, 1.22]
Shoji et al	0.1398	0.0816	7.4%	1.15 [0.98, 1.35]
Shokawa et al	0.3001	0.0953	6.5%	1.35 [1.12, 1.63]
Wang et al (Female)	0.3436	0.0656	8.4%	1.41 [1.24, 1.60]
Wang et al (Male)	0.2151	0.0565	9.1%	1.24 [1.11, 1.39]
Wijkumen et al	0.131	0.0653	8.5%	1.14 [1.00, 1.30]
Willum-Hansen et al	0.4762	0.0569	9.1%	1.61 [1.44, 1.80]
Zoungas et al	0.131	0.0323	10.6%	1.14 [1.07, 1.21]
Total (95% CI)			**100.0%**	**1.25 [1.16, 1.34]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 50.39$, df = 11 ($P < 0.00001$); $I^2 = 78\%$

Test for overall effect: $Z = 6.06$ ($P < 0.00001$)

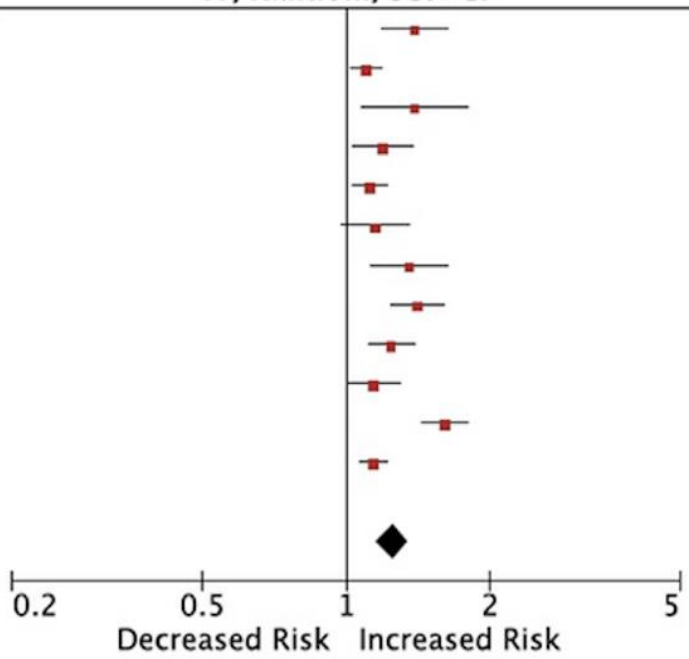


Figure 3.9.10: Cardiovascular Mortality Association for High Vs Low PWV

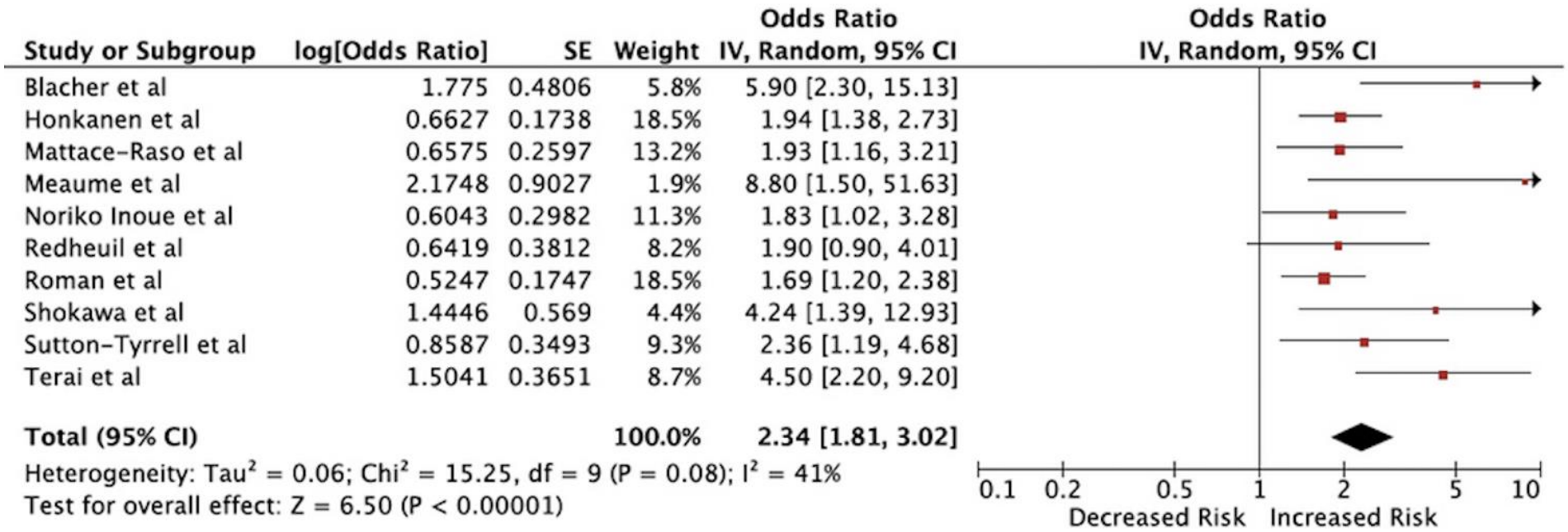


Figure 3.9.11: All-Cause Mortality Association Per 1m/S Increase in Aortic PWV

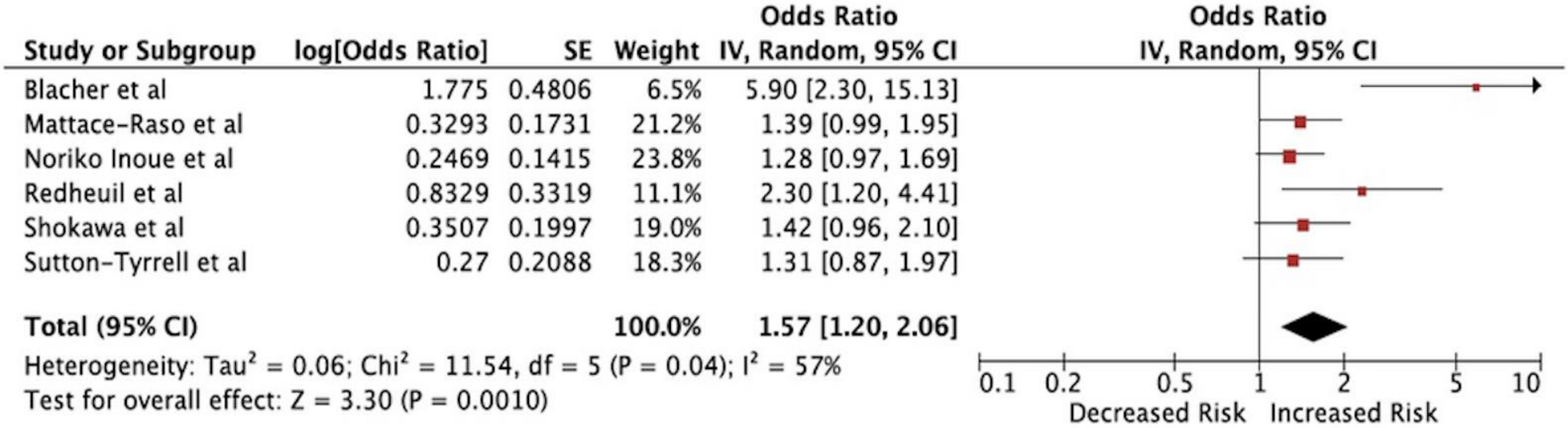


Figure 3.9.12: All-Cause Mortality Association for High vs Low PWV

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Blacher et al	1.775	0.4806	6.5%	5.90 [2.30, 15.13]
Mattace-Raso et al	0.3293	0.1731	21.2%	1.39 [0.99, 1.95]
Noriko Inoue et al	0.2469	0.1415	23.8%	1.28 [0.97, 1.69]
Redheuil et al	0.8329	0.3319	11.1%	2.30 [1.20, 4.41]
Shokawa et al	0.3507	0.1997	19.0%	1.42 [0.96, 2.10]
Sutton-Tyrrell et al	0.27	0.2088	18.3%	1.31 [0.87, 1.97]
Total (95% CI)			**100.0%**	**1.57 [1.20, 2.06]**

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 11.54$, df = 5 (P = 0.04); $I^2 = 57\%$

Test for overall effect: Z = 3.30 (P = 0.0010)

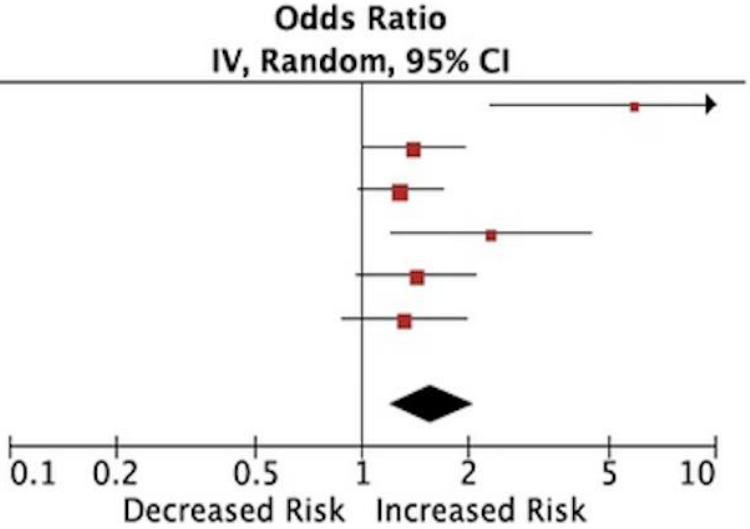


Figure 3.9.13: Association of Pulse Pressure with New-Onset AF

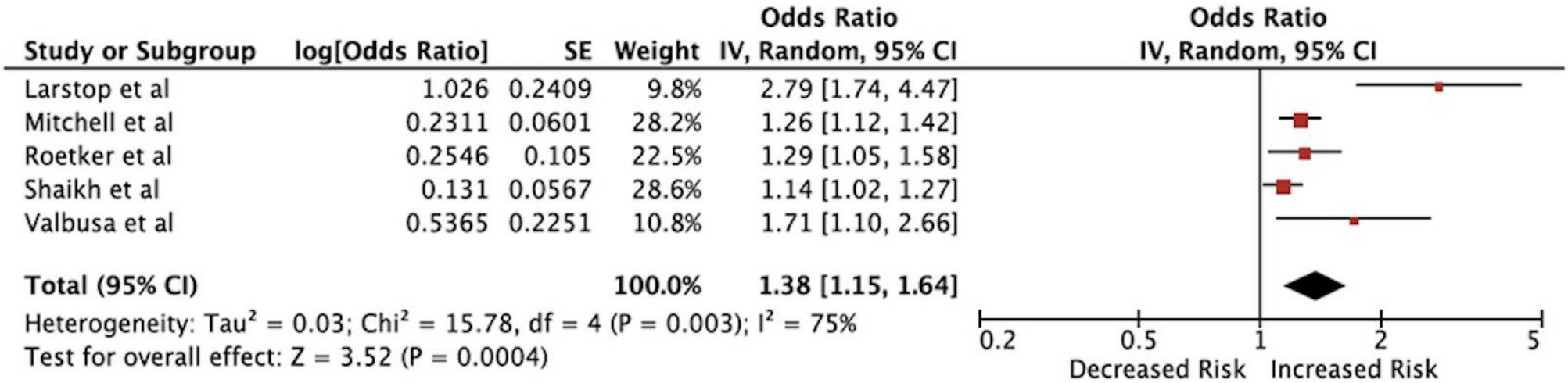


Table 3.10.1: Quality Assessment of Studies Included in Meta-analysis by Modified Newcastle-Ottawa Scale

First Author, Year (Ref. #)	Selection		Comparability			Outcome A		Total
	participants representative of population	Adequate sample size	Appropriate Stat. Method	Reproducibility	Adjusted for risk factors	Follow up	Outcome	
Alban Redheuil, JACC. 2014 Dec 23;64(24):2619-29. MESA Study	*	*	*	*	*	*	*	*******
Anderson et al., HTN 2009	*	*	*	*		*	*	******
Anne C K Larstop et al HTN 2012, 60; 347-353. LIFE study.	*	*	*		*	*	*	******
Blacher et al., 1999		*	*	*	*	*	*	******
Cruickshank et al., 2002	*	*	*	*	*	*	*	*******
Gary F. Mitchell, MD. JAMA. 2007;297:709-715"	*	*	*		*	*	*	******
Laurent et al., 2001	*	*	*	*	*	*	*	*******
Mattace-Raso et al., 2006	*	*	*		*	*	*	******
Meaume et al., 2001	*	*	*	*	*	*	*	*******
Nicholas S Roetker Am J Cardiol 2014;114:587-592	*	*	*		*	*	*	******
Noriko Inoue etal. Circ J 2009; 73: 549 – 553	*	*	*	*	*	*	*	*******
Pannier et al., 2005		*	*		*	*	*	*****
Roman et al. JACC 2009 Oct 27; 54(18): 1730–1734. The Strong Heart Study	*	*	*		*	*	*	******
Shaikh etal. Hypertension 2016 ;68:590-596	*	*	*	*	*	*	*	*******
Shoji et al., 2001		*	*	*	*	*	*	******
Shokawa et al., 2005	*	*	*		*	*	*	******
Stephane Laurent et al. Stroke. 2003;34:1203-1206	*	*	*		*	*	*	******
Sutton-Tyrrell et al., 2005	*	*	*	*	*	*	*	*******
Terai et al., 2008	*	*	*	*	*	*	*	******
Valbusa F, etal. Diabetes Care. 2012; 35:2337–2339.	*	*	*		*	*	*	******
Verbeke etal. CORD study. AJN, vol. 6, 2011		*	*		*	*	*	*****
Wang et al., 2010	*	*	*			*	*	*****
Wijkman M etal. J Diabetes Complications. 2016 Sep-Oct;30(7):1223-8	*	*	*		*	*	*	******
Willum-Hansen et al., 2006	*	*	*	*	*	*	*	*******
Zoungas et al., 2007		*	*	*	*	*	*	******

Table 3.10.2: Characteristics of CV and All-Cause Mortality Studies

First author, publication year	Population characteristics (n)	Mean Age (yrs.)	Male (%)	DM/ IGT (%)	HTN (%)	BMI (kg/ m²)	Mean SBP (mmHg)	Smoker (%)	Follow-up (yrs.)	PWV assessment			HR (95% CI)	Covariates adjusted for in addition to age, sex
										Modality, distance	*Mean PWV (m/s)*	*High vs. Low PWV cut-off (m/s)*		
Community-based general population														
Anderson, 2009 (144)	Non-DM (n=174)	60±10	51	27.5	20	25.5	136±4	52.5	19.6	Doppler; SCN to AA	10.2± 2.1	10.6	1.15(1.01 -1.30)	SBP
Inoue, 2009 (145)	Japanese (n=3960)	61±6	100	25	39	23.7	136.5±18	58	8.2	Pressure (FCP 4731) (SCN to FA) – (SCN to CCA)	8.3±1.2	9.0	1.83 (1.02-3.3)	PP, BMI, smoking, HDL, Glucose
Mattace-Raso, 2006 (159)	Low CV risk, (n=2835)	72±7	39	7	21	26.6	143±21	NR	5.4	Pressure (Compilor) CCA to FA	13.3±2.9	14.2	1.43 (1.06-2.00)	mean BP
Meaume, 2006 (151)	Elderly (n=141)	87±6	27	NR	NR	22.1	137±17	6	2.5	Pressure (Compilor) CCA to FA	14.2 ±3.1	17.7	1.19 (1.03-1.37)	SBP, glucose, CRP, anti HTN, CVD
Redheuil, 2014 (81)	General population (n=3675)	61±10	51	27	42	28.0	125±21	13	8.5	CMR NR	NR	NR	1.9 (0.9-3.8)	DM, SBP
Roman, 2009 (131)	Strong Heart Study (n=2405)	63±8	35	47	52	31.3	NR	28	5.6	Pressure (Sphygmocor) SCN to FA	PP	PP >50m mHg	1.23 (1.1-1.37)	Creatinine, DM, HTN, HR, BMI, smoking, cholesterol
Shokawa, 2005 (141)	Japan (n=492)	64 ±9	45	NR	NR	23.5	136±20	NR	10	Pressure (MCG400) CCA to FA	9.7±1.9	9.9	1.35 (1.12-1.57)	SBP, DM, cholesterol
Sutton-Tyrrell, 2005 (142)	Elderly (n=2488)	74±3	48	14.6	51	NR	136±21	10	4.6	Doppler CCA to FA	9.0 ±3.9	8.4 (M) 7.9 (F)	M: 1.6 (1.2-2.2) F: 1.8 (1.1-2.8)	SBP, CVD, creatinine, cholesterol, HR
Wang, 2010 (158)	General population (n=674)	52±13	100	NR	NR	NR	M-139±25	NR	15	Doppler NR	M: 9.5±2.3	M: 11.8	M: 1.5 (1.3-1.7)	SBP
Wang, 2010 Female Cohort (158)	General population (n=598)	52±13	NA	NR	NR	NR	F - 139±22	NR	15	Doppler NR	F: 9.5±2.5	F: 12	F: 1.7 (1.54-2)	SBP
Willum-Hansen, 2006 (152)	Danish (n=1678)	40-70	52	2.8	36.2	NR	125±13	44	9.4	Pressure CCA to FA	11.3±3.4	13.1	1.6 (1.4-1.8)	MBP, BMI, smoking, alcohol
	20,204	**62.6 ± 12.5**	**56.8**	**21.5**	**37.3**	**25.8**	**135.5 ± 6**	**30.2**	**9.5**		**10.6±2.0**	**12.2±2.8**		

First author, publication year	Population characteristics (n)	Mean Age (yrs.)	Male (%)	DM/ IGT (%)	HTN (%)	BMI (kg/ m²)	Mean SBP (mmHg)	Smoker (%)	Follow-up (yrs.)	PWV assessment			HR (95% CI)	Covariates adjusted for in addition to age, sex
										Modality, distance	*Mean PWV (m/s)*	*High vs. Low PWV cut-off (m/s)*		
Diabetic population														
Cruickshank, 2002 (139)	(n=394)	60±10	60	100	29	26.2	140±4	20	10.7	Doppler SCN to AA	11.6±3.8	NR	1.08(1.03-1.14)	BP, DM duration, anti HTN
Wijkman, 2016 (157)	(n=627)	60.5	64	100	61	30.3	138±12	NR	8	Pressure (Sphygmocor) SCN to FA	10.4± 1.4	10.8	1.14(1.0-1.3)	DM duration, SBP, HR, eGFR, smoking, HbA1c
	1021	**60.2**	**62**	**100**	**45**	**28.2**	**139±1.4**	**20**	**9.3**		**11.1**			
End-stage renal failure population														
Blacher, 1999 (136)	(n=241)	52±16	61	7.1	48	NR	157±28	NR	6	Doppler Aortic arch to FA	11±3.1	12	1.39 (1.1.9-1.62)	BP, HR, Hb, smoking,and LVH
Pannier, 2005 (149)	(n=305)	53±16	62	NR	NR	NR	155±28	NR	5.8	Pressure (Compilor) CCA to FA	11.1±3.1	10.75	1.12 (1.03-1.25)	PP, DM, CVD
Shoji, 2001 (138)	(n=265)	55±10	41	23	NR	21.5	153±27	23	5.3	Pressure (PWV-200) SCN to FA	8.6±2.2	8.2	1.15(0.98-1.35)	Smoking, SBP, DM, BMI, dialysis duration, CRP
Verbeke, 2011 (153)	(n=1084)	63.5	60	23	NR	25.1	148	17.5	2	Pressure (Sphygmocor) SCN to FA-SCN to CCA	10.65	8.8	1.15 (1.08-1.23)	DM, albumin
Zoungas, 2007 (148)	(n=207)	51±13	68	23	91	26.5	145±22	10	3.6	Pressure SCN to FA-SCN to CCA	9.9 ±3.5	9.9	1.14 (1.07-1.26	BP, CVD, carotid IMT, smoking, DM
	2102	**55.7± 4.6**	**58.4± 10**	**19**	**69.5**	**24.3**	**155±2.1**	**20.2**	**4.54± 1.7**		**10.15± 1.1**	**9.9 ± 1.5**	**1.2(1.1-1.32)**	
Hypertensive population														
Laurent, 2001 (137)	HTN (n=1980)	50±13	65	6	NR	25.2	148±22	25	9.3	Pressure (Compilor) CCA to FA	11.5±3.4	NR	1.5 (1.08-2.1)	CVD, DM, SBP, PP, cholesterol, HR
Laurent, 2003 (150)	HTN (n=1715)	51±13	59	8	100	25.1	148±22	15	7.9	Pressure CCA to FA	12.4±4	NR	1.4 (1.08-1.72)	MBP, PP, DM, smoking, cholesterol
Terai, 2008 (143)	HTN (n=676)	62±12	55	22	55	NR	135±17	NR	4.8	Pressure SCN to FA-SCN to CCA	9.0±0.6	8.8	3.82(1.32-11.0)	SBP, smoking, DM, creatinine, cholesterol
	4371	**54± 6.6**	**60± 5.3**	**12**	**77.5**	**25.1**	**143 ±7.5**	**20**	**7.3 ±2.3**		**10.7 ± 2.4**	**8.8**	**2.24 (1.1-3.5)**	

AA= abdominal aorta, BMI= body mass index, CCA= common carotid artery, CMR= cardiac MRI, CVD= cardiovascular disease, CRP= C- reactive protein, DM=diabetes mellitus, eGFR= estimated glomerular filtration rate, FA= femoral artery, Hb= haemoglobin, HbA1c= glycated haemoglobin, HDL= high density lipoprotein, HR= heart rate, HTN= hypertension, IGT=impaired glucose tolerance, IMT= intima- media thickness, MBP= mean BP, LVH= left ventricle hypertrophy, M=male, F=female, m/s = metre/second, NA= not applicable, NR = not reported, PP= pulse pressure, PTH= serum parathormone, SBP= systolic BP, SCN= sterno-clavicular notch.

Table 3.10.3: Characteristics of AF Studies

First author, publication year	Study population, (n)	Mean Age (yrs.)	Male (%)	DM/IGT (%)	HTN (%)	BMI (kg/m²)	Mean SBP (mmHg)	Smokers (%)	Pulse Rate (bpm)	Follow-up (yr)	Pulse pressure (PP) (mmHg)	HR (95% CI)	Covariates adjusted for
Larstop, 2012 (49)	Hypertensives (n= 8810)	66±7	46	13	100	28.4	123±8	NR	74	5	High vs. low PP (87 vs. 67)	1.67 (1.32-2.1)	Age, BMI, FRS, pulse rate, LVH
Mitchell, 2007 (118)	Community based study (n=5331)	57±11	45	7	23	26.2	133±13	28.5	NR	12	High vs. low PP (>60 vs <40)	1.17 (1.08-1.3)	Age, sex, CVD, DM, LVH, BMI, smoking, anti HTN
Roetker, 2014 (119)	Community based, (n=6630)	62±10	47	13	NR	28.5	126±21	NR	63	7.8	54±17	1.29 (1.05-1.6)	Sex, age, BMI, HTN, Race, smoking, Pulse rate, CVD, anti HTN
Shaikh, 2016 (149)	Community based study(n=5797)	61±9	45	10	37	27.5	128±18	12	63	7.1	Central PP High vs. low (>60)	1.14 (1.0-1.28)	Age, sex, FRS, HTN
Valbusa, 2012 (120)	Diabetics (n=350)	63±9	56	100	26	29.5	NR	25	NR	10	High vs low PP (61 vs. 53)	1.7 (1.1-2.7)	Age, sex, BMI, LVH, HTN, CVD
5 Studies	**n= 26918**	**62 ±4**	**47.8**	**28.6**	**46.5**	**28.2**	**128±14**	**21.7**	**66.7**	**8.4**		**1.38 (1.15-1.64)**	

BMI= basal metabolic index, CVD= cardiovascular disease, DM=diabetes mellitus, FRS= Framingham risk score, HTN= hypertension, IGT=impaired glucose tolerance, LVH= left ventricle hypertrophy, SBP= systolic BP

Chapter 4:

Non-Invasive Central Blood Pressure and Aortic Stiffness Indices Estimation and Technical Challenges

4.1 INTRODUCTION

Hypertension (HTN) is strongly associated with adverse cardiovascular (CV) outcomes and atrial fibrillation (AF) (14, 61). Despite the epidemiological studies associating pre-HTN with AF, uncertainties exist concerning intensive control of blood pressure in primary and secondary prevention of AF(46). The management of hypertension is driven by brachial blood pressure evaluation despite superior predictive relevance of aortic stiffness and central pulsatile load estimation (83, 178). Epidemiological data has suggested a 70% incidence of grade I central high blood pressure in individuals categorised as pre-hypertensive (120-139/80-89 mmHg) according to their brachial blood pressure assessment (80). Central blood pressure estimation can better characterise the pre-HTN group concerning risk of developing end organ injury and AF. However, the clinical applicability of central blood pressure (CBP) assessment is still limited as the methods of evaluation remain to be standardised and evidence targeting CBP to improve cardiovascular outcome is still evolving (80).

Majority of commercially available devices acquire central blood pressure waveform by calibrating peripheral blood pressure wave through applanation tonometry or automated cuff based sphygmomanometer (179). The accuracy of non-invasive CBP estimated by the

available non-invasive devices is considered “acceptable” with a mean difference of 5±8 mmHg, during comparative analysis with invasive ascending aortic pressure (180). However, some of these published studies lacked statistical power concerning validation, with a variable range of correlation and agreement values (181, 182). Further, application of various methodologies to estimate CBP indices resulted in inconsistent reporting of their predictive value independent to brachial BP (164, 183).

This review is aimed to critically appraise the methodology adopted by the commercially available devices to compute CBP and aortic stiffness. Delineating the strength and limitation of these devices will guide further application and validation of their use in AF patients.

4.2 CBP ASSESSMENT METHODS

In general, non-invasive CBP assessment is based on the indirect assessment of aortic compliance through estimation of central pulsatile load and waveforms. Overall, a 10mmHg amplification of pressure wave is recorded at the brachial arterial site compared to ascending aortic pressure (184). A number of non-invasive devices derive central pressure waveform by acquiring peripheral pressure wave that is further calibrated to the brachial BP. This calibrated peripheral pressure waveform is then used to form a central pressure wave through application of mathematical transfer function and wave analysis (Table 4.9.1). Invasive studies have validated these mathematical models used in non-invasive assessment of CBP with acceptable range of accuracy during sinus rhythm (185). However, standardisation of the available techniques to derive central pressure waveform is yet to be achieved. Consequently, the inconsistencies reported by the

outcome studies employing a range of devices to estimate CBP indices in a heterogeneous population may have limited the potential additional value of CBP assessment over traditional brachial BP readings (186). In addition, none of these non-invasive devices are validated to estimate CBP during AF.

4.2.1 Methods of Peripheral Pressure Wave Recording

In order to acquire CBP waveform, the non-invasive devices record peripheral pressure wave through applanation tonometry or by pulse volume plethysmography (PVP).

4.2.1.1 Applanation Tonometry

Applanation tonometry is one of the most common technique used by the non-invasive devices to acquire peripheral arterial pressure waveform as shown in Table 4.9.1. It is based on the principle that the external pressure applied to completely compress the artery is equal to the internal pressure, provided the applanation sensor is stable and completely in contact with the vascular wall. The pressure sensor used to applanate the artery can be single or arrayed. The pressure waveform acquisition by single sensor probe is operator dependent as one have to adjust the manual pressure application to acquire optimum pressure waveform. To ensure quality control, an inter-operator and intra-operator variability must be recorded for single sensor transducer. In comparison, an arrayed sensor is relatively operator independent and adjust its pressure application and acquisition of pressure wave automatically. Applanation of a superficial peripheral arterial segment is found to be more effective where the vascular wall is relatively fixed over a bone with stable sensor position during the cardiac cycle. The radial artery satisfies all these conditions (82). In contrast, carotid and brachial arteries applanation can be

demanding because of the presence of soft tissue and risk of atherosclerotic plaque rupture along with relative mobility of surrounding structures during respiration (179).

4.2.1.2 Pulse Volume Plethysmography (PVP)

Pulse volume plethysmography (PVP) is another method to acquire peripheral pressure waveform by estimating the volume shift at brachial arterial site evaluated by a pressure cuff equipped with a specialised sensor at the time of brachial BP assessment. A number of devices are commercially available to perform CBP assessment by acquiring pulse volume through peripheral oscillometric cuff as listed in Table 4.9.1. In general, these devices record volume shift at peripheral arterial site and conform a peripheral pressure waveform (187, 188). This recorded pressure waveform is then calibrated as per acquired brachial BP. This calibrated waveform is then utilised to acquire central pressure wave to estimate CBP and its indices. Some of these devices using PVP to estimate CBP indices offer ambulatory CBP estimation because of their automated design. However, not all of these devices are validated against invasive CBP assessment and hence not an ideal screening tool to perform ambulatory CBP (189). In addition, the use of these devices is not validated during AF because of significant variation in heart rate (HR) resulting in erratic peripheral pressure wave amplitude.

4.2.2 Calibration of Peripheral Pressure Waveform

The non-invasive estimation of CBP requires accurate calibration of the peripheral pressure waveform. The assumption of a relatively stable diastolic and mean blood pressure throughout the circulation provides the basis to use these indices for calibration of peripheral pressure waveform to derive aortic pressure wave (180). In general, brachial

systolic, diastolic and mean BP, derived from an automated cuff based device are used to calibrate peripheral pressure wave (179). Calibration algorithms can be different, depending on the peripheral site of assessment to compensate for the peripheral amplification of the pressure wave. In case of carotid artery tonometry, the pressure waveform is calibrated to brachial mean and diastolic pressure (179). In contrast, peripheral pressure waveform acquired by radial artery tonometry is calibrated to brachial systolic and diastolic blood pressure as from a practical point of view, there is no significant pressure amplification between the two sites.

In addition to tonometry, a new generation of automated cuff based devices are acquiring peripheral pressure waveform at brachial site by estimation of the volume displacement over time and further auto-calibrating it to the mean, systolic or diastolic brachial BP by applying principles of pulse volume plethysmography (PVP) (190). However, we know that peripheral amplification of systolic and mean BP (MBP) can be inconsistent depending on HR variability. Further, cuff based non-invasive assessment of brachial BP is not entirely accurate (180). The calibration errors introduced by the variable brachial BP indices are recognised as a major source of inaccuracy (191). Non-invasive CBP estimation during AF can be inaccurate by adapting current techniques because of their dependence on heart rate and peripheral blood pressure to calibrate pressure waveforms before subjecting it to mathematical algorithms to compute CBP and its indices.

4.2.3 CBP Estimation Algorithms

4.2.3.1 Generalized transfer function (GTF)

The transfer function is a mathematical algorithm to depict the relation between the input (peripheral pressure wave) and output (central pressure wave) signals in a frequency domain. There are no significant differences between the pressure pulse transduction properties of aorta and upper limb peripheral arterial tree concerning lower frequency. These lower frequencies (3 Hertz) constitutes 90% of the aortic pressure waveform. The GTF is essentially a low-pass frequency filter applied to the calibrated peripheral arterial pressure waveform acquired during inflation of the brachial cuff to constitute aortic pressure wave. (179, 188, 191) The acquired central pressure waveform is then subsequently used to calculate CBP and its indices (Figure 4.8.1). The GTF showed strong correlation with invasive CBP assessment, as a result, it was one of the first methodology approved by (Food and Drug Administration (FDA) to estimate CBP with multiple clinical validation publications (181, 192, 193). However, GTF has certain limitations including reduced precision in assessment of CBP indices requiring high frequency components like augmentation index (AI) (179). Additionally, input errors due to erratic HR during AF and erroneous brachial pressure readings can lead to inaccurate CBP assessment.

4.2.3.2 CBP assessment based on the second systolic pressure peak (SBP2)

This cuff based CBP estimation method is clinically more convenient. It is based on the observation that the second systolic pressure peak (SBP-2, Figure 4.8.1) at the peripheral site is strongly correlated with central systolic blood pressure (192) . The pressure

gradient in arterial tree during late systole is relatively small and it mainly comprises of low frequency components. Additionally, the reflective component of CBP wave (P2) is the dominant systolic peak recorded in an adult population. The CBP assessment based on peripheral pressure systolic peaks can be performed non-invasively. However, its reliance on peak of reflective pressure wave (P2) limits its use during AF and in elderly patients with advanced vascular remodelling because of the significant variability in wave amplitude (179).

4.2.3.3 CBP assessment based on physics model

This technique calculates CBP indices by estimating the pressure fluctuations recorded by sphygmomanometer cuff applied at the brachial arterial site. As a first step, the device determines brachial BP indices by sphygmomanometer cuff. The device then re-inflates the cuff to hold the pressure at 30mmHg above the estimated brachial systolic BP for >10 seconds to record the small intra-arterial pressure fluctuations. These recorded small pressure fluctuation at brachial artery are used to estimate aortic pressure by application of a physics model. The model estimates pressure wave reflection between the open (aortic) and closed (brachial) end in a time domain by assuming a uniform tube model between the two vascular sites. This technique is validated and mainly used by Pulsecor R 6.5 (Pulsecor Ltd. Auckland, New Zealand) to estimate CBP indices (194). The physics-based model is of limited value in patients with peripheral vascular disease involving sub-clavian artery. In addition, precise calibration of central aortic pressure waveform through this technique is also dependent on accurate brachial BP assessment.

4.2.3.4 N-Point moving average (NPMA)

NPMA is a mathematical low pass filter applied to the acquired radial or brachial pressure waveform to exclude high frequency signals and estimate peak of central aortic pressure waveform (195). Here "N" represents acquisition of sampling frequency. Each frequency signal point is summed up with its neighbours and divided by the number of data points. The pressure wave uniformity improves with the increase in number of data points. Therefore, the common denominator of the filter is imperative and strongly related to sample frequency. In general, the NPMA method with a common denominator of 4 (a quarter of the acquired sampling frequency= N/4) is reported to record the CBP with relative accuracy (195). However, the NPMA is dependent on peripheral pressure wave calibration. Further, accurate range of optimal frequency denominator can vary from N/4 to N/6 (179). Despite illustrating a strong correlation with invasive CBP assessment, NPMA based non-invasive central pressure valuation under-estimates central systolic BP by a mean of 7.6mmHg (195). Moreover, acquisition of central pressure waveform is not possible through this method, further limiting its clinical utility as a screening tool in CBP assessment (179).

4.2.3.5 Direct Method to Assess CBP waveform

This technique uses carotid artery applanation tonometry to record the central pressure waveform. Both PulsePen (Dia Tecne, Milan, Italy) and Compilor Analyse (ALAM Medical, Vincennes, France) are validated devices that record central pressure waveform at carotid arterial site with relative accuracy (196, 197). One of the major limitations is that the tonometer can only record pressure waveform and this has to be calibrated to the mean

arterial and diastolic pressure values obtained by conventional sphygmomanometer application at brachial artery.

4.2.4 ACCURACY OF AVAILABLE DEVICES TO ESTIMATE CBP NON-INVASIVELY

To date, there is no perfect method to estimate CBP non-invasively. A considerable variation is reported concerning the methodology, accuracy and validation of different devices used to estimate central pressure waveform and CBP indices (82, 129, 166, 179, 180, 189, 191, 198-200). Several limitations need to be addressed to improve precision in acquisition of central pressure waveform and calculation of CBP indices to better incorporate CBP assessment in clinical practice.

As compared to invasive central systolic BP, the commercially available devices under-estimate the systolic CBP by a mean of 5 mmHg (Table 4.9.1). In general, non-invasive devices over-estimate central diastolic BP (CDBP). As compared to invasive aortic pressure assessment, Sphygmocor XCEL was reported to over-estimate CDBP by a mean of 13 ± 6 mmHg with under-estimation of pulse pressure by a mean of 18 ± 10 mmHg (190). There are inherent limitations in the current available techniques to estimate CBP indices. Applanation tonometry has been around the longest and hence has more evidence base as compared to cuff-based sphygmomanometer (189, 201, 202) in recording peripheral pressure waveform as shown in (Table 4.9.1). These approaches are not equal in their estimates of peripheral pressure waveforms. The non-invasive devices used cuff sphygmomanometer to calibrate the acquired pressure waveform as per brachial BP

indices. Because of the inconsistencies in brachial BP evaluation, this step was found to be the major source of introducing error in CBP wave formation to derive CBP indices (203).

As a first step, a standardised and a relatively operator independent cuff base methodology has to be adopted to improve CBP indices assessment. At times, the new CBP assessment devices are validated against established non-invasive CBP evaluation techniques to confirm their accuracy and reliability. However, the majority of these evidence base and old non-invasive CBP assessment devices use brachial BP indices to calibrate peripheral pressure waveform and have the same inherent limitations as discussed above. Further, these methodologies are highly sensitive to heart rate variability and peripheral pressure wave amplitude, limiting their utility to appraise CBP during AF. For validation, adequately powered studies with invasive operator independent measures and strict quality control criteria for acquiring and calibrating peripheral pressure waveform can help reduce the inconsistencies reported by various devices during CBP indices assessment.

4.3 AORTIC STIFFNESS AND ITS ASSESSMENT

A compliant aorta is a conduit that acts as a buffer to LV ejection pressure and help maintain a steady flow to the end organs during diastole. Ageing and HTN are the major risks related to premature aortic stiffness. Aortic stiffness is recognized as a surrogate for persistently high CBP. Non-invasive assessment of aortic stiffness is performed by aortic pulse wave velocity (aPWV) appraisal, central pulsatile load recording or ascending aortic distensibility estimation. The aforementioned methods estimate aortic response to

central pulsatile pressure and volume load during ventricular-arterial coupling. As the conduit artery remodels, the aPWV increased with amplification of pulse pressure and reduced distensibility of proximal aorta (83). However, aortic PWV is accepted as a standard method to quantify aortic stiffness because of the published evidence base and its reproducibility (146-148, 155, 164). A variety of devices can be employed to estimate aortic pulse wave velocity (aPWV) to calculate aortic stiffness, non-invasively (82). Aortic PWV is calculated from the distance travelled by the pulsatile wave between two vascular sites and dividing it by transit time. The carotid and femoral arteries are the most common vascular points used to determine aPWV and is recognized as a "gold standard" to calculate the aortic stiffness (Figure 4.8.2) (30). The association between increased aortic stiffness and CV as well as all-cause mortality is well described. (133, 144, 155, 159, 161) as shown in Table 4.9.2. Central aortic compliance can also be estimated by central pulse pressure (CPP) and augmentation index (CAIx) calculation. CAIx is derived as a ratio between central augmentation pressure and central pulse pressure (CAIx=CAP/CPP x100). Increased pulse pressure (>60mmHg) with reduce diastolic BP (<70mmHg) is a strong indicator of conduit vascular remodelling (178). Increased pulse pressure (PP) is found to be independently associated with increased CV events including incidence of AF (61). However, evidence correlating increased CAIx with hard CV outcomes is limited (199). Carotid-Ankle pulse wave index (CAVI) is a recent addition in the available techniques to estimate vascular stiffness but its dependence on baseline arterial tone and limited applicability in patients with peripheral vascular disease (Ankle-brachial index <0.9) preclude its clinical utility (204). In recent years, cardiac MRI is being used to calculate aortic distensibility as a marker of persistently high CBP and aortic stiffness. Aortic

distensibility is calculated by the following equation: Change in aortic area (systole-diastole)/ PP x minimum aortic area (83, 165). The PP is estimated by deducing diastolic brachial pressure from its systolic counterpart, recorded by a cuff-based sphygmomanometer conventionally at the time of aortic distensibility assessment. CMR can also be used for aortic PWV velocity assessment. Reduced aortic distensibility and increased aortic PWV recorded by CMR is found to be significantly associated with adverse CV and AF outcomes (83, 119, 205). Despite the reproducible and consistent methodology of aortic distensibility assessment by CMR, its cost and relatively limited access are significantly limiting its widespread clinical use. However, aortic distensibility assessment can reliably performed in sinus rhythm and its validation during AF is yet to be reported.

4.5 CLINICAL RELEVANCE OF CBP INDICES AND AORTIC STIFFNESS

Aortic stiffness is a modifiable risk factor that can be evaluated non-invasively and with relative ease. Importantly, the adverse outcome associated with aortic stiffness is independent of HTN and other established CV risk factors. Recent evidence from the Framingham Heart Study demonstrated 60% prevalence of aortic stiffness in hypertensive individuals with well-controlled blood pressure. CBP assessment is of independent value over and above brachial BP in predicting CV events. This finding may well explain the residual risk associated with increased aortic stiffness that requires further attention to improve CV outcomes (176). Specifically, CBP appraisal is particularly relevant in the following clinical scenarios:

4.5.1 Characterising Systolic HTN in the Young

In younger and healthy individuals, central systolic BP is found to be lower than peripheral BP. A peripheral amplification of systolic BP is recorded in approximately 5 % of young males with an overall prevalence of 2.7% (206) . An isolated systolic hypertension is incidentally found in these individuals with normal diastolic BP (207). In general, HTN work up excludes any underlying secondary cause and these young individuals exhibit hypotensive response to treatment. They have normal CBP indices including pulse pressure (PP). In comparison to central pressure, the morphology of peripheral pressure waveform demonstrates a relatively increased systolic amplification. The isolated systolic peripheral amplification in young (<40 years) is not associated with any adverse cardiovascular outcomes. Hence, the CBP assessment in younger individuals with amplified brachial BP is strongly advocated to avoid unnecessary therapy and anxieties associated with diagnosis of HTN.

4.5.2 Aortic Stiffness and Pre-HTN

Ageing and Increased central pulsatile load can lead to premature stiffness of aorta. The causality of aortic stiffness and HTN is not fully established. However, studies have reported accelerated conduit vascular remodelling preceding diagnosis of HTN (208) . Aortic stiffness is one of the possible mechanism associating HTN with end organ injury (209). Moreover, amplified pulse pressure as a marker of increased aortic stiffness is independently associated with increased incidence of AF (118). Concerning CV outcomes, HTN with stiffened aorta incurred a higher prognostic risk as compare to HTN alone. Importantly, aortic stiffness is modifiable and reversible in relatively early stages by

addressing vascular risk factors including obesity (169). These findings further support the important role of aortic stiffness assessment and its integration in ongoing risk factor modification model to improve AF and CV outcomes. Compared to carotid-femoral PWV, targeting high CPP and Aix to improve CV morbidity is yet to be reported as these indices has to be adjusted for multiple factors including ageing, gender, heart rate, height and blood pressure (129, 169).

4.5.3 Ageing Related Arterial Stiffness and Cardiovascular Events

Ageing transforms conduit arterial compliance resulting in aortic stiffness. A stiffened aorta transfers its pulsatile load to the vital end organs without applying any buffering. In response to that, the resistance arterioles transform into an elastic reservoir resulting in reduced augmentation and diastolic BP with overall labile BP recordings. Uncontrolled cardio-vascular risks accelerate this physiological process of vascular ageing leading to premature conduit vascular remodelling, eventually resulting in irreversible end organ injury. In general, a steady rise in systolic BP is recorded from the age of 45 years onwards. In contrast, the diastolic BP remains stable resulting in escalated pulse pressure (PP= systolic - diastolic BP). Hence, increased PP is associated with increased aortic stiffness and reported to be an independent predictor of CV and AF outcomes particularly in individuals with age range of 40-60 years (61, 164). An independent association between increased aortic stiffness, recorded as amplified carotid-femoral PWV, and mortality (including CV mortality) is well described in community-based population studies as well as in those with end stage renal disease and diabetes mellitus (83, 147, 148, 155, 159, 161, 163, 164). The advantages of targeting aortic stiffness beyond BP control have been confirmed in recent

studies (169, 210, 211). Treatment with angiotensin converting enzyme inhibitors can improve vascular physiology by enhancing endothelial function through enhanced release of nitric oxide and inhibition of fibrosis on vascular layers, in addition to BP control (169, 212). In addition, moderate intensity aerobic exercise has been found to be effective in reducing aortic stiffness although the underlying mechanisms remain poorly understood (170). Despite an independent and modifiable factor, the limited realisation of aortic stiffness assessment in ongoing robust CV risk factor management represents an unmet therapeutic target and future studies can help address this gap.

4.6 LIMITATIONS OF CURRENT METHODOLOGIES TO ASSESS AORTIC STIFFNESS and CBP INDICES

A lack of standardised methodology is a major factor limiting the clinical use of CBP indices and aortic stiffness assessment. The differing methods used to appraise CBP indices and aortic stiffness can add further confusion in the clinical setting. In general, majority of the non-invasive devices calibrate pressure waveform by brachial BP indices. The variable precision with the techniques adopted to assess brachial BP has been found to be the major source of error in central pressure wave assessment (190). Furthermore, as compared to brachial BP measurements, the additional time, cost, technical challenges and training requirements needed for CBP assessment may hinder its clinical applicability. Majority of the studies employed carotid-femoral PWV (cfPWV) to quantify aortic stiffness. However, these studies employed four different non-invasive devices using Doppler, oscillometric and applanation tonometry techniques (138-141, 143, 144, 146, 161). Despite validation and reported strong correlation of different techniques to

estimate aortic stiffness (129, 133, 136, 165, 166), disparities were also reported during calculation of surface distance between carotid and femoral arteries for non-invasive cfPWV assessment (129). Of note, the relative dependency of CBP and aortic stiffness assessment algorithms on baseline HR and peripheral pressure wave acquisition significantly restrict their use during AF. Despite a reported independent association of increased aortic stiffness with AF, none of the commercially available device is validated to access CBP and its indices during AF.

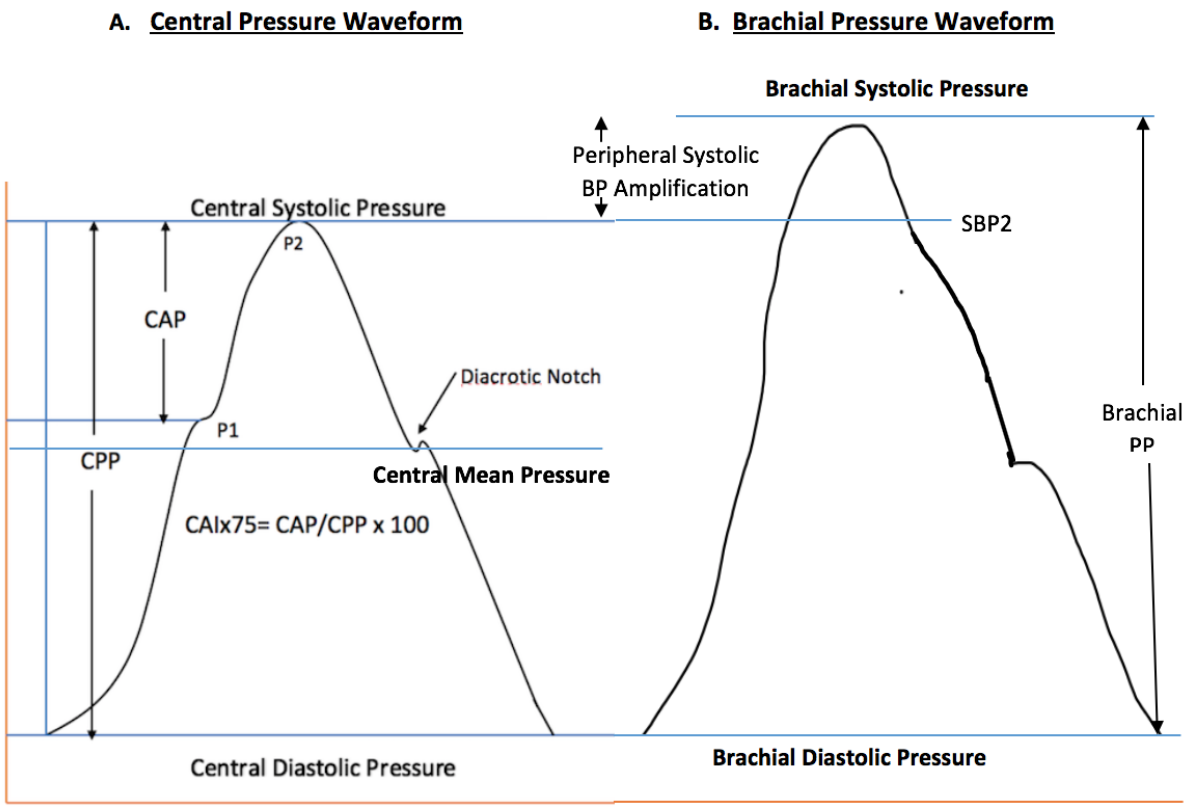
The commercially available devices to estimate CBP non-invasively, examine different aspect of ascending aortic response to ejected volume load to compute central blood pressure indices including central PP (CPP), CAIx75, and CAP. The CPP is an indirect estimate of central pulsatile load and found to be an independent predictor of AF in middle aged participants (121). In elderly or advanced aortic stiffness, the CPP is of limited value because of the reduced amplification of central systolic pressure wave (80). The CAP is calculated by the difference between the systolic summits as shown in Figure 4.8.1. It represents systolic amplification induced by the reflective pressure wave that can be amplified in aortic stiffness. CAIx75 is calculated as a ratio between CAP and CPP (CPP/CAP x100) and adjusted for HR 75bpm. Both CAP and CAIx75 are indirect measures of aortic stiffness and are dependent on multiple variables including gender, height and baseline heart rate (179). In addition, CAP and CAIx comprise of high frequency signals that are not adequately characterised by GTF based devices (179). These CBP indices are not interchangeable due to the technical limitations posed by device software and characteristics of the population studied (136, 166, 167). For example, standardised CBP assessment can help evolve a customised approach to HTN, as aggressive therapeutic

targets can be offered to the younger individuals with relatively increased aortic stiffness to prevent accelerated CV remodelling and AF.

4.7 CONCLUSION

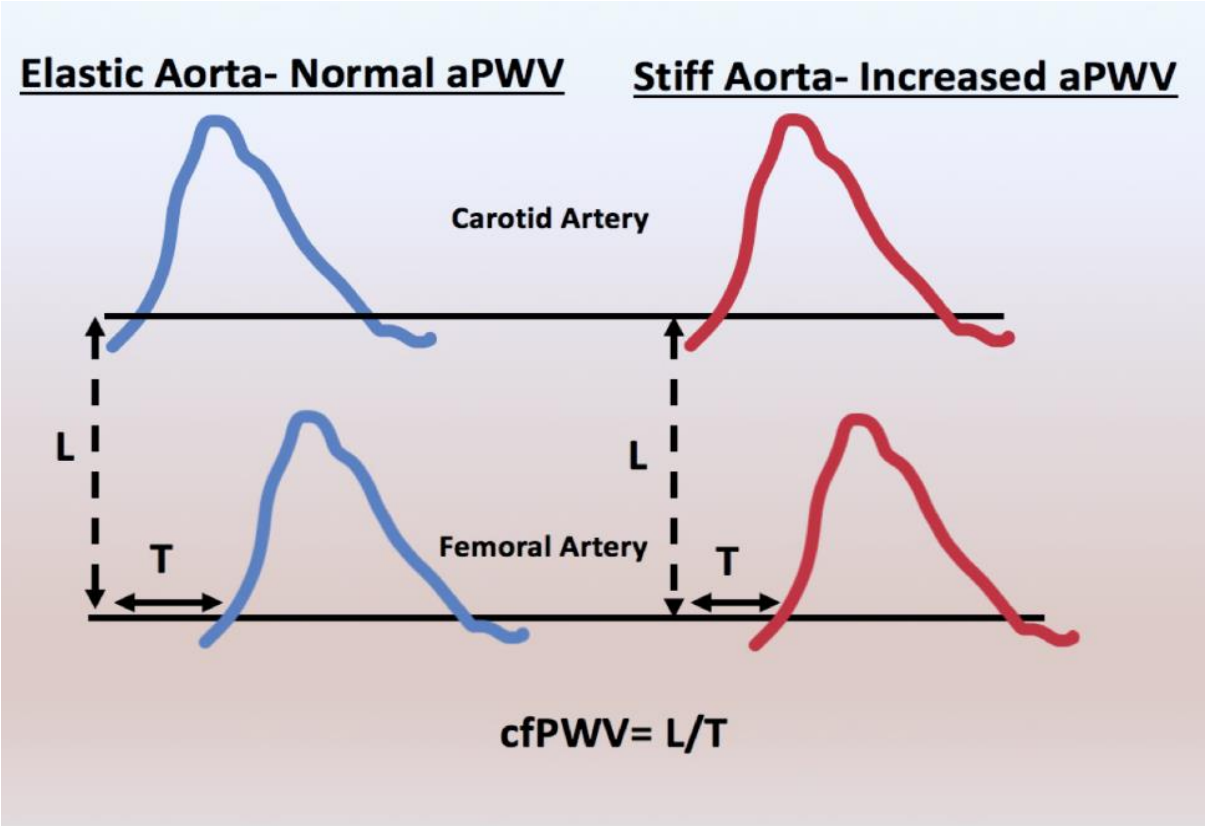
As a modifiable factor, aortic stiffness evaluation is clinically important for detection of premature conduit vascular remodelling consequent to the increased central pulsatile load. Non-invasive CBP assessment devices require a standardised methodology that is relatively time efficient, operator independent and user friendly to improve incorporation into routine clinical use to detect accelerated central arterial stiffness that can lead to subsequent end organ injury including AF. Further work is needed to define the treatment targets that will lead to improved CV outcomes.

Figure 4.8.1: Central and Brachial Pressure Waveform



CAIx75= Central Augmentation Index corrected for heart rate 75bpm, CAP= central augmentation pressure, CPP=central pulse pressure, P1=peak ejected pressure wave, P2=peak reflected pressure wave, SBP2= 2nd Systolic BP Peak

Figure 4.8.2: Carotid-Femoral PWV Assessment



aPWV= aortic pulse wave velocity, cf PWV= carotid-femoral pulse wave velocity, L= calculated distance between carotid and femoral artery, T= time taken by the pressure wave to reach from carotid to femoral artery

Table 4.9.1: Characteristics of Devices in Clinical Use to Estimate CBP and Its Indices

Device	Technique & peripheral site of recording of pulse wave	Calibration method of peripheral pressure waveform	Mathematical principle to derive central pressure waveform	Technique used for Invasive validation	Estimated CBP indices	Agreement with Invasive central SBP (mmHg)
SphygmoCor (198), (193), (192), (199), (213), (214), (215), (189), (201), (202)	Applanation tonometry of radial artery	Brachial SBP/DBP/MAP	GTF	MT or FF	CPW, CSBP, CDBP, CPP, CAIx, CAP	-5.4 (-7.6 to -3.2)
SphygmoCor XCEL (216)	Brachial Oscillometry	Brachial SBP/DBP	GTF	MT	CSBP, CDBP, CPP, CAIx	-4.6 (-11.2 to 3.8)
Omron HEM-9000AI (217), (218), (215),	Applanation tonometry of radial artery	Brachial SBP/DBP	WA (SBP2)	MT or FF	CSBP, CDBP, CPP, CAIx	-5.8 (-7.8 to -3.8)
Arteriograph (219), (220)	Brachial Oscillometry (35mmHg > SBP)	Brachial SBP/DBP	WA (SBP2)	FF	CSBP, CDBP, CPP, CAIx	-4.9 (-8.1 to -1.8)
Mobil-O-Graph (187)	Brachial Oscillometry	Brachial SBP/DBP	GTF	MT	CSBP, CDBP, CPP, CAIx	-6.2 (-14 to 2.2)
Vicorder (221)	Brachial Oscillometry	Brachial SBP/DBP	GTF	FF	CSBP, CDBP, CPP, CAIx	-6.4 (-13 to 1)
PulseCor R6.5 and R7 (222), (223)	Brachial Oscillometry	Brachial MBP/DBP	Physics Model	FF	CSBP, CDBP, CPP	-4.9 (-11 to 1.6)
BPro (189)	Applanation tonometry of radial artery	Brachial SBP/DBP	NPMA	FF	CSBP, CDBP, CPP	-0.9(-13.9 to 12)
PulsePen & Complior Analyse (224), (200)	Applanation tonometry of carotid artery	Carotid Artery waveform	Direct Method	FF	CSBP, CDBP	-3.6 (-9.6 to -2.4)

CAIx= central augmentation index, CAP= central augmentation pressure, CDBP= central diastolic BP, CPP= central pulse pressure CSBP= central systolic BP, CPW= central pulse wave velocity, FF= fluid filled, GTF= generalised transfer function, MT= micro tipped sensor, NPMA= N-point moving average, WA= wave analysis.

Table 4.9.2: Characteristics of Devices and Methodology Used to Estimate Aortic Stiffness

Device	Methodology	Technique Used	Clinical Utility	Increased CV and ACM Risk for High PWV cohort
SphygmoCor and SphygmoCor XCEL (133, 144, 155, 159, 161)	cf PWV	Tonometer and Sphygmomanometer	+++	HR 1.28 (1.16 to 1.47)
Compilor (20, 24, 25)	cf PWV	Mechano-transducer	++	HR 1.24 (1.04 to 1.54)
CAVI (225)	cf PWV	Sphygmomanometer	+++	NA
Arteriograph (51)	cf PWV	Sphygmomanometer	++	NA
MRI (83, 165)	Aortic PWV and Aortic distensibility	MRI	+	HR 1.9 (0.9 to 3.8)
Omron VP 1000 (226)	cf PWV	Sphygmomanometer	+++	HR 1.15 (0.98 to 1.3)
Doppler Echocardiography (138, 139, 141, 146)	Aortic PWV	Doppler USG	+	HR 1.28 (1.16 to 1.47)

CAVI= carotid-ankle vascular index, cf PWV= carotid-femoral pulse wave velocity, HR= hazard ratio, MRI=magnetic resonance imaging, NA= not applicable, USG= ultrasonography

Chapter 5:

Impact of Atrial Fibrillation on Assessment of Central Blood Pressure and Aortic Stiffness Indices

5.1 INTRODUCTION

Due to its high prevalence, hypertension (HTN) confers the highest population attributable risk for atrial fibrillation (AF) development (15). Several large epidemiological studies have also demonstrated both high-normal systolic blood pressure (<140 mmHg) and increasing pulse pressure, an indirect measure of aortic stiffness, to be independently associated with incident AF (10, 52, 118, 149). Further, both uncontrolled blood pressure and aortic stiffness have been shown to result in higher AF recurrences following catheter ablation (61, 227). Given the evidence of increased aortic stiffness even in subjects with high-normal systolic blood pressure, assessing aortic stiffness may be relevant towards comprehensive risk factor management in individuals with AF (34, 228). Despite been acknowledged as a precursor to HTN and an independent predictor of cardiovascular risk, aortic stiffness remains a largely unmet therapeutic target (229).

Of the many non-invasive methods used to quantify aortic stiffness, carotid-femoral pulse wave velocity (cfPWV) is considered the current reference method due to its standardized technique, reproducibility and ease of measurement (229, 230). An expanding range of devices is now available for assessing central blood pressure (CBP) indices and aortic stiffness, but the validity of these measurements during AF remains poorly defined (80,

185). Therefore, the present study is designed to evaluate the validity and reliability of non-invasive estimation of CBP indices and cfPWV (SphygmoCor XCEL, AtCor Medical, Australia) during AF as compared to during sinus rhythm (SR) with reference to invasive measures.

5.2 METHODS

5.2.1 Study Population

This study enrolled consecutive patients with symptomatic drug refractory paroxysmal or persistent AF referred for catheter ablation at our institution. Our inclusion criteria included AF patients with an age range of 20-80 years who were in SR and willing to provide informed consent for the study (Figure 5.8.1). Our exclusion criteria included patients with moderate to severe aortic root dilatation (>4.5cm) or moderate to severe aortic insufficiency, active malignancy, or recent (<4weeks) history of decompensated heart failure. The study protocol was prospectively registered (A prospective validation study to **I**nvestigate the role of **M**ulti-modality central **PULSE** wave evaluation and its impact on **A**trial **F**ibrillation outcome (IMPULSE AF) - Validation Study, ANZCTR, ACTRN12616001225404) with approval from the institutional ethics committee.

5.2.2 Patient Preparation

All patients provided informed consent and were studied in the fasting state under general anesthesia during their scheduled catheter ablation procedure prior to commencement of ablation protocol. All patients remained on uninterrupted oral anticoagulation while anti-arrhythmic drugs were ceased at least 5 days prior to the procedure. A transesophageal echocardiogram was undertaken to exclude left atrial thrombus. Simultaneous invasive and non-invasive CBP measurements were obtained

first in SR and subsequently during AF that was induced by rapid atrial burst pacing from a decapolar catheter positioned in the coronary sinus. Hemodynamic and aortic stiffness measurements during AF were performed only after stabilization of the arrhythmia at least 10 minutes post-induction.

5.2.3 Study Protocol

5.2.3.1 Invasive Central Blood Pressure Measurements

A 125 cm straight 4-Fr pigtail catheter with 4 side holes (SRD5287- Cordis, Miami, FL, USA) was placed in the aortic root through a 6F right radial arterial sheath (7cm Radiofocus, Terumo Medical, Tokyo, Japan). Invasive CBP was recorded by a fluid-filled manometer system (Sensis Vibe, Siemens Healthcare Germany). The transducer was zero calibrated at baseline and kept at the level of the mid-axillary line. The central pressure waveform was digitally recorded at 100Hz using the MacLab XT (GE Healthcare, Chicago, IL, USA) hemodynamic monitoring system. Central pressure indices were derived from averaging the pressure waveforms over 20 seconds. For each patient, an average of three central blood pressure readings were taken for comparison between invasive and non-invasive CBP indices.

5.2.3.2 Non-Invasive Central Blood Pressure Estimations

The SphygmoCor XCEL system was used to obtain non-invasive CBP estimates. It is an automated cuff based oscillometric device that acquires pressure waveform to assess brachial systolic and diastolic pressure. The central aortic pressure waveform is derived using proprietary transfer function, which is essentially a low-pass frequency filter applied to the acquired brachial arterial compression waveforms that has been validated for

assessment of CBP indices during SR (231, 232). The accuracy of automated oscillometric measures of blood pressure indices is known to be affected by the beat-to-beat variation during AF (233). To improve accuracy, we averaged three automated recordings to calculate CBP indices over 20 seconds each (234). Only the recordings fulfilling the waveform acquisition quality control criteria imposed by the device software were used. The acquired central pressure waveform was then used to quantify central systolic, diastolic, pulse and augmentation pressure. Central pulse pressure (CPP) was taken as the difference between central diastolic pressure and systolic peak. Central augmentation pressure (CAP) was derived by the difference between systolic peaks P1 and P2 of the central pressure waveform: P1 represents the ejected pressure wave, the amplitude of which is mainly determined by ventricular contraction and the PWV of the ascending aorta; P2 represents the reflected fraction of the ejected wave from peripheral segments of arterial tree. Central augmentation index was derived as a ratio between CAP and CPP that was automatically adjusted for heart rate (HR) of 75 beats per minutes (bpm) by the device software (Figure 5.8.2).

5.2.3.3 Carotid-femoral Pulse Wave Velocity (cfPWV) Assessment

The SphgmoCor XCEL estimates cfPWV by dividing the transit time expended by the ejected pressure wave to travel between carotid and femoral arteries over the surface distance between these two vascular points. The carotid and femoral pressure traces were averaged over 20 seconds to calculate the cfPWV in AF and during SR. These were repeated three times to minimize the impact of irregular heart rate during AF. A case

example to illustrate CBP waveform and aortic PWV assessment is shown in Figures 5.8.3A and 5.8.3B.

5.2.4 Statistical Analysis

Continuous variables were normally distributed and expressed as mean ± standard deviation. Pearson's correlation analysis and Bland Altman plots were used to compare the non-invasive estimates to invasive CBP indices. Assumptions of a linear regression were found to be upheld, using scatter plots and histograms to assess normality of residuals and random scatter of variance (Figure 5.8.4). The mean values of CBP indices were compared by the linear mixed-effect model to estimate the interaction of AF and SR. Additionally, to evaluate the impact of heart rate on the comparisons, the mean heart rate was taken as an arbitrary threshold. The p-value of ≤0.05 was regarded as statistically significant. All statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

5.3 RESULTS

Out of 58 individuals found suitable for the study, 33 were planned to have AF ablation and were approached to obtain informed consent. Two patients declined to participate in the study. The study cohort comprised of 31 patients with a mean age of 64±6 years (55% male) and mean CHA_2DS_2-VASc score of 1.9±0.7. Hypertension and dyslipidemia were highly prevalent amongst the study participants, who were overweight with preserved left ventricular systolic function and mild left atrial dilatation (Table 5.9.1). Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used in 65% and beta-blockers in 48% of the study cohort.

5.3.1 Non-invasive versus invasive CBP Indices during SR and AF

The estimated means of invasive and non-invasive CBP indices are listed in Table 5.9.2. The non-invasive appraisal of central systolic blood pressure (CSBP) was strongly correlated with the invasive measurements both in SR and during AF (Figure 5.8.5A: left and right panel respectively). Bland Altman analysis revealed that non-invasive method significantly overestimated CSBP by 3.2mmHg (Figure 5.8.5B: left panel) and 7.6mmHg (Figure 5.8.5B: right panel) during both SR and AF (mean heart rate 71±19 and 87±17 bpm respectively). Notably, invasive measure of CSBP was found to be significantly lower during AF as compared to SR (mean -5.6 mmHg, 95% CI, -13.7 to 2.48, p=0.03). However, this was not seen with the non-invasive CSBP method (mean -1.25mmHg, 95% CI -8.6 to 6.1, p=0.6). When analyzed according to low or high heart rate (taken as below or above the mean heart rate), there was no significant difference in CSBP estimates during SR. However over-estimation of CSBP was more noticeable during AF with higher ventricular rate (mean >87bpm) as shown in Figure 5.8.6B.

Moderate but statistically significant correlations were seen between non-invasive and invasive measurements of central diastolic blood pressure (CDBP) during SR and AF (Table 5.9.2). Similarly, the non-invasive method over-estimated CDBP during both SR and AF (+10.4 mmHg, p<0.004 and +9.0 mmHg, p<0.001 respectively, Table 5.9.2). Interestingly, a stronger correlation was found between non-invasive and invasive central pulse pressure (CPP) during AF than SR (R^2=0.70, p<0.001 vs. R^2=0.45, p= 0.043 respectively). Bland-Altman analysis of non-invasive estimation of CPP showed statistically significant underestimation during SR (-7.0 mmHg, p=0.026) and non-significant difference during AF (-1.3 mmHg, p=0.4). The mean central augmentation pressure (CAP) was comparable

during SR and AF (21.2±4 vs 18.1±3 mmHg, p=0.44) and showed moderate correlation (R^2=0.51, p<0.01). Central augmentation index (CAIx75) was also comparable during SR and AF (43±4 vs. 47±4 mmHg, p=0.05) with strong correlation (R^2 = 0.76, p<0.01). A significant correlation between brachial and central BP was reported (Figure 5.8.7A and 5.8.7B, left panels). However, as compare to invasive aortic assessment, significant amplification of pressure wave was recorded at brachial site. (Figure 5.8.7A, right panel).

5.3.2 cfPWV during SR and AF

Our cohort has a normal cfPWV for their age with a mean value of 5.9 ± 1.3 m/s and 6.5 ± 1.5 m/s during SR and AF respectively. A moderate but significant correlation was found between mean cfPWV during SR and AF (R^2=0.55, p=0.001; Figure 8A: left panel). Overall cfPWV was significantly higher during AF as compared to during SR (+0.58m/s, 95% CI 0.1 to 1.0 m/s, p=0.02; Figure 5.8.8A: right panel). At heart rate above mean of 87bpm, cfPWV was significantly higher during AF vs. SR (+0.93 m/s, 95% CI 0.20 to 1.66, p=0.0016; Figure 5.8.8B: left panel). However, this was not seen at heart rate below mean of 87bpm (+0.27m/s, 95% CI -0.13 to 0.68, p= 0.17; Figure 8B – right panel).

5.4 DISCUSSION

To the best of our knowledge, this is the first study evaluating the validity of non-invasive assessment of CBP indices and cfPWV in AF. Our key findings using the SphygmoCor XCEL are as follows: First, non-invasive CSBP & CDBP indices demonstrate moderate to strong correlation with invasive measures (R^2 0.48 to 0.93) and < 15% over-estimation during SR and AF. Second, non-invasive central aortic stiffness estimation of CPP demonstrates moderate correlation (R^2 0.45 to 0.70) with invasive measures and < 15% under-

estimation during SR and AF. Third, non-invasive aortic stiffness indices of CAP, CAIx75 & cfPWV when measured during AF and SR demonstrate moderately strong correlation (R^2 0.51 to 0.76). Last, CBP and aortic stiffness can be reliably assessed non-invasively during AF especially when ventricular rate is well-controlled.

5.4.1 Effects of AF on CBP indices

The evaluation of BP during AF is challenging due to beat-to-beat variation of stroke volume and rapid change in diastolic ventricle filling, resulting in increased BP variability. The SphygmoCorXCEL is an automated oscillometry based BP device whereby abrupt changes in the pressure wave amplitude during AF can affect reading accuracy although it is well known that oscillometric estimation of systolic BP is reasonably accurate during AF as opposed to diastolic BP (233). To improve accuracy of measurements, we took a mean of three consecutively assessed CBP indices recorded over 20 seconds during AF with the SphygmoCorXCEL device. Reassuringly, we found moderate to strong correlations between non-invasive estimation of CSBP and CDBP with direct invasive measurements.

5.4.2 Effects of AF on Aortic Stiffness Assessment

Aortic stiffness was assessed by cfPWV evaluation with SphymoCor XCEL for our cohort. The baseline increase in HR and beat-to beat variability during cfPWV assessment can reduce the overall accuracy of central pulse wave velocity evaluation. To reduce the impact of HR variability during AF we recorded pressure waveforms for an average of 20seconds during cfPWV evaluation and took a mean of three consecutive assessments. Our cohort has normal cfPWV with a mean of 5.9 ± 1.3 m/s and 6.5 ± 1.5 m/s during SR and AF respectively. Overall cfPWV was over-estimated by a mean of 0.58m/s during AF,

which is within acceptable variance range for the mean age of our cohort and clinically non-significant.(235) Moreover, the mean difference in cfPWV estimation was even smaller at 0.2m/s, (95% CI -0.46 to 0.86, p=0.527) during controlled AF (HR of <87bpm).

5.4.3 Technical Considerations

None of the currently available devices used to estimate CBP indices and aortic stiffness have been validated against invasive ascending aortic pressure during AF. Majority of the devices including SphygmoCor XCEL acquire the peripheral pressure waveform and calibrate it to peripheral systolic and diastolic BP. A mean error of more than 10mmHg was reported during calibration of peripheral pressure waveform in irregular rhythm (203) resulting in over or under-estimation of non-invasive CBP indices (236, 237). The SphygmoCor XCEL uses brachial arterial oscillometry to record peripheral pressure waveform that is then adjusted to systolic and diastolic brachial BP. The calibrated brachial pressure wave is then subjected to Generalized Transfer Function to derive the central pressure wave form (231), (236). Hence, the error inducted during calibration of peripheral pressure wave can affect CBP estimates to an acceptable range of 5 ± 8mmHg during SR (186, 190, 191, 236). This observation is further supported by the strong association noted by the current study between non-invasive central and brachial blood pressure, suggesting that the accuracy of CBP is affected by the calibration error instituted during brachial artery oscillometry to determine systolic and diastolic BP (191). Previous validation studies reported under-estimation of CSBP and over-estimation of central diastolic BP by SphygmoCor XCEL (238). We recorded a non-significant over-estimation of the CSBP by SphygmoCorXCEL during sinus rhythm that appears contrary to

previous reports (190, 239). However, further analysis of previously published validation studies revealed over-estimation of CSBP by non-invasive devices when systolic BP ranged between 110-120 mmHg, which is similar to the mean CSBP of our cohort during AF and SR (238, 240). Additionally, the trend of over-estimation was consistent irrespective of underlying rhythm and the reported mean bias of the non-invasive CBP indices by the current study is within acceptable limits of <5mmHg (184, 232, 237).

5.5 STUDY LIMITATIONS

The size of our cohort was relatively small. However, our validation study has a normal distribution of variants with adequate statistical power to determine the impact of AF on CBP indices assessment (Figure 5.8.4). Most of our subjects (70%) were hypertensive and on blood pressure lowering medications that can affect CBP indices. Additionally, the CBP and aortic stiffness assessment was performed under general anesthetic in a cohort with a relatively lower burden of coronary artery disease as compared to previous validation studies, which were performed under light sedation in participants enlisted for coronary angiography with a relatively increased use of vasoactive drugs (185, 190). Nevertheless, comparisons of non-invasive to invasive measures were performed within the same patient and the effects of vasoactive and anti-hypertensive treatment are therefore minimized. Our cohort consisted of middle-aged Caucasians and it remains unclear whether the results can be generalized for non-Caucasian individuals in other age brackets.

5.6 CLINICAL IMPLICATIONS

Our key finding regarding the validity of non-invasive assessment of aortic stiffness during AF has important clinical implications. It has potential to extend the clinical applicability of aortic stiffness assessment in the AF population irrespective of the prevailing heart rhythm. Indeed, further studies are needed to delineate the association between aortic stiffness and AF outcomes in relation to targeting aortic stiffness as a modifiable risk factor. It is plausible that patients with sub-clinical central aortic stiffness carry heightened risk for progressive atrial remodeling despite 'normal' peripheral BP readings.

5.7 CONCLUSION

Central blood pressure and aortic stiffness indices can be reliably estimated non-invasively during AF especially when ventricular heart rate is adequately controlled.

Figure 5.8.1: Consort Diagram

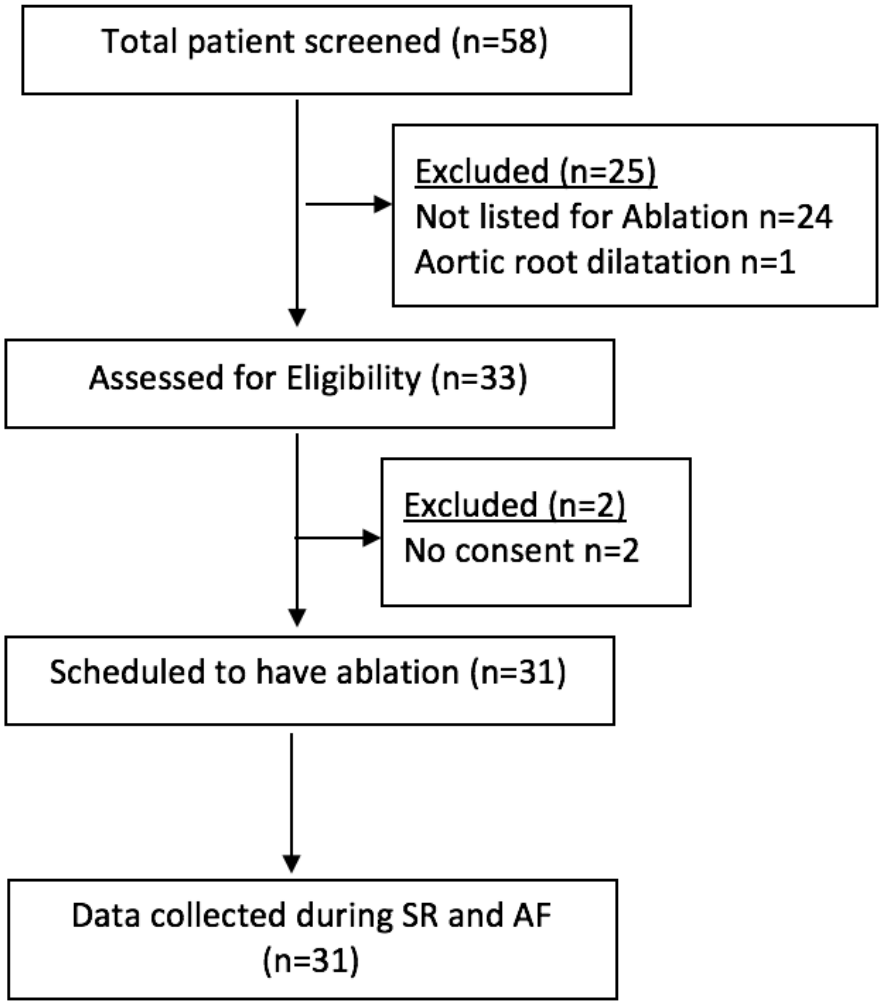
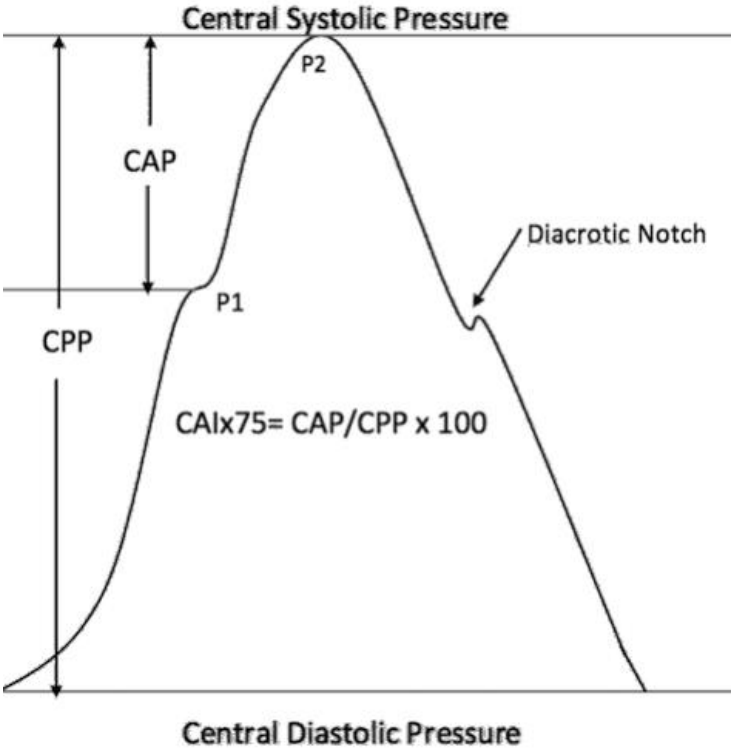
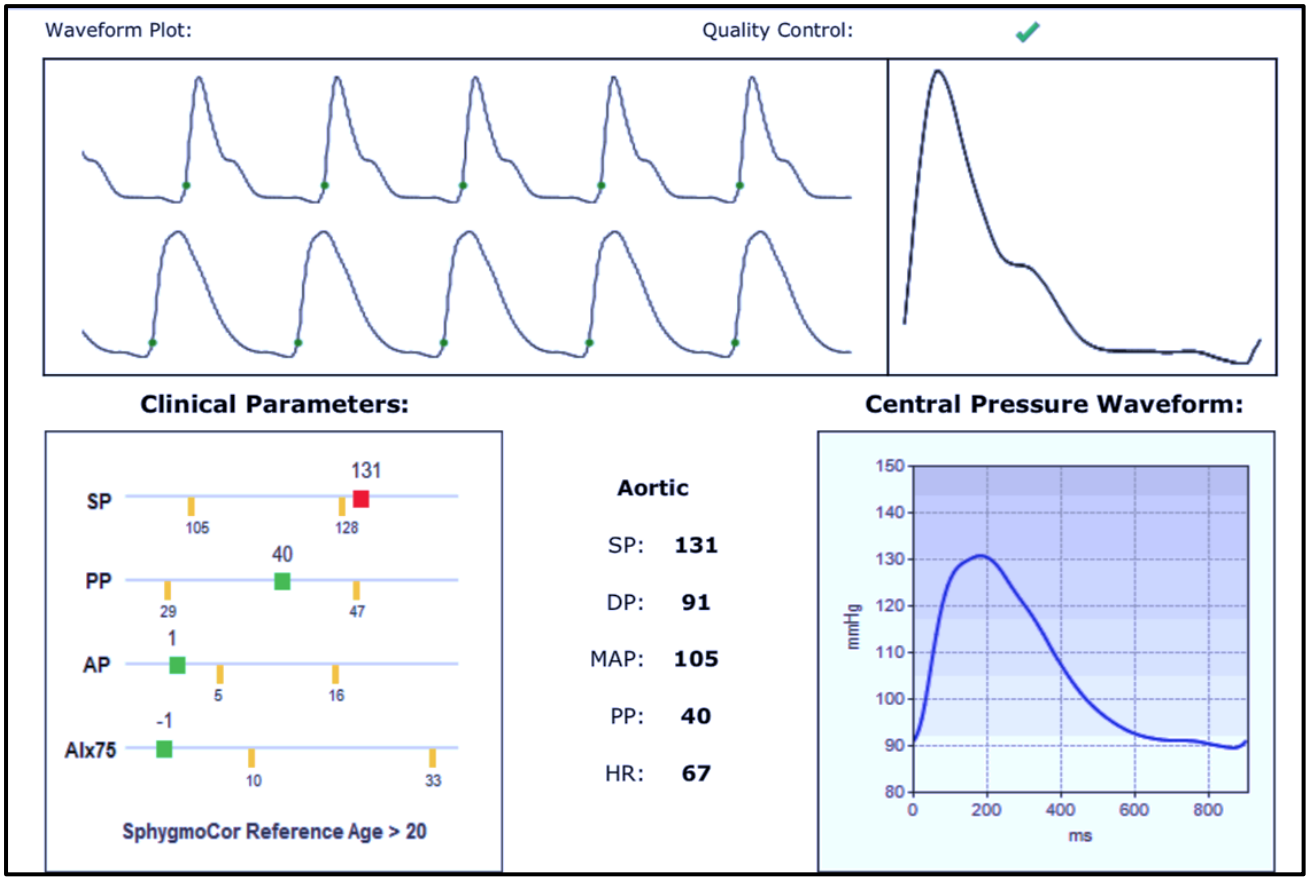


Figure 5.8.2: Central Aortic Pressure Waveform and Central Blood Pressure Indices



CAIx75= Central Augmentation Index corrected for heart rate 75bpm, CAP= central augmentation pressure, CPP=central pulse pressure, P1=peak ejected pressure wave, P2=peak reflected pressure wave

Figure 5.8.3A: Case Example Illustrating CBP Waveform Assessment



(Aix75= augmentation index, AP= augmentation pressure, DP= diastolic pressure, HR= heart rate, , MAP= mean arterial pressure, PP= pulse pressure, SP= systolic pressure)

Figure 5.8.3B: Case Example Illustrating Aortic PWV Waveform Assessment

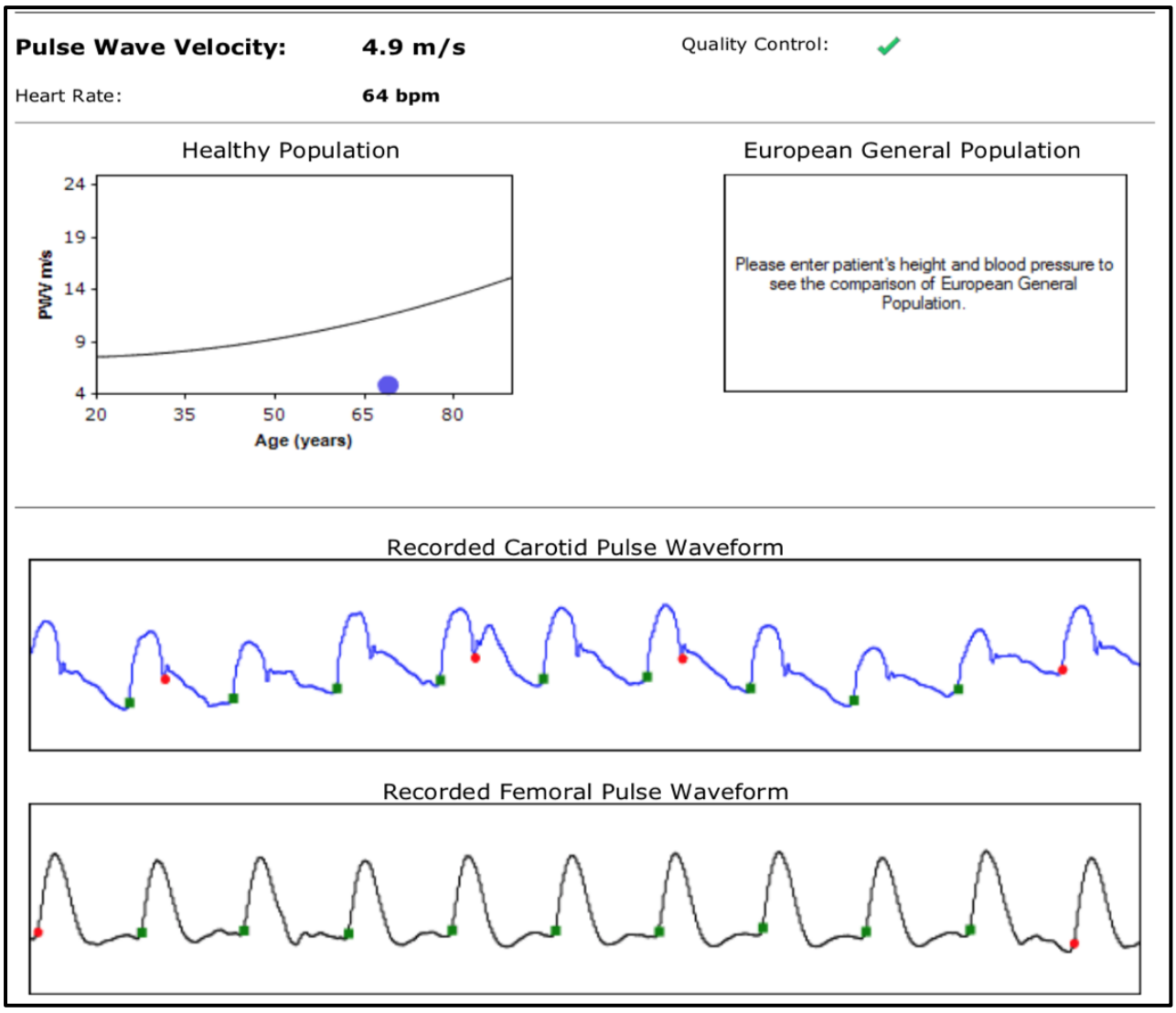


Figure 5.8.4: Scatter Plots and Histograms to Illustrate Normal Distribution of Blood Pressure Data during Sinus Rhythm and Atrial Fibrillation

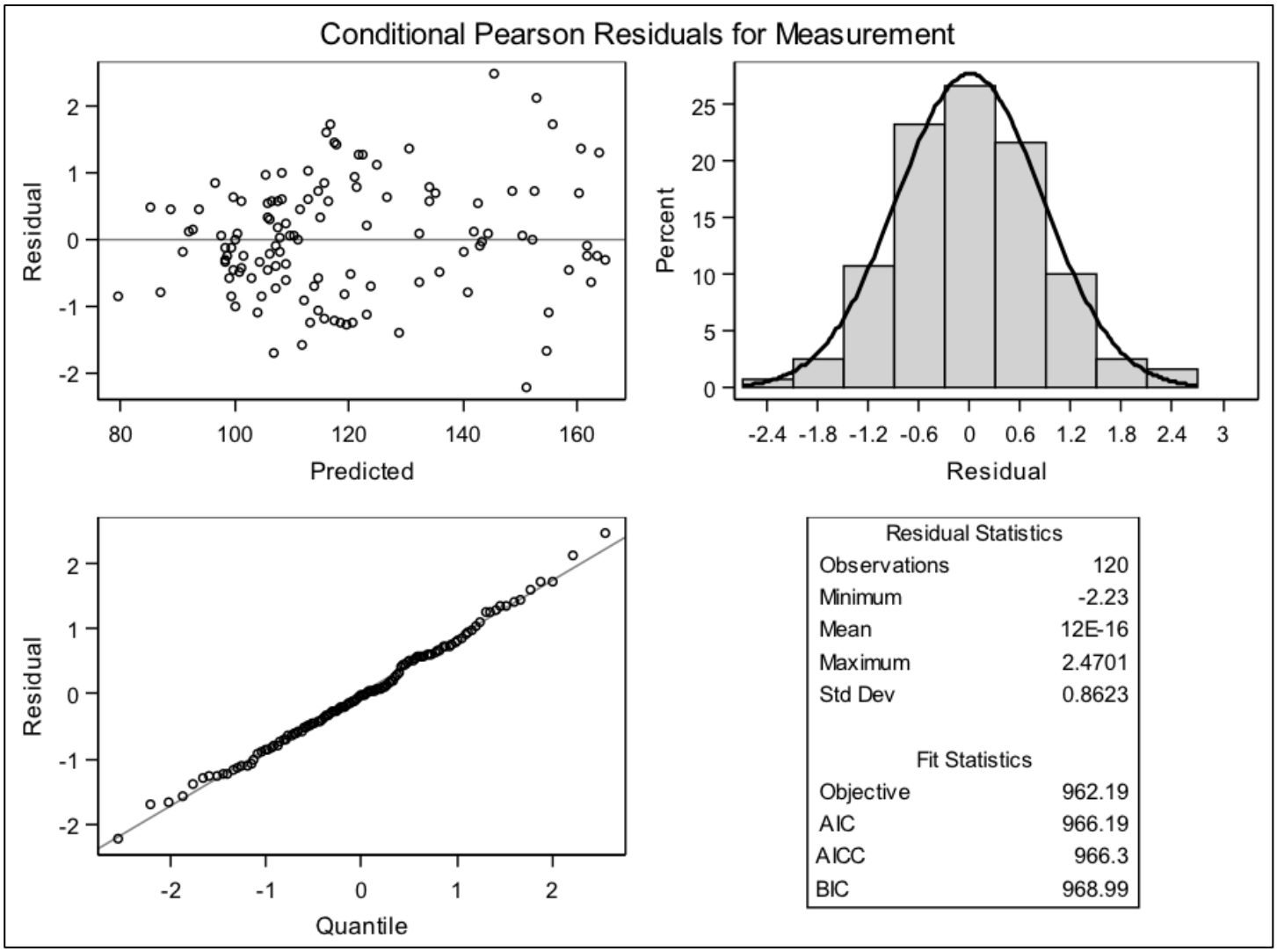


Figure 5.8.5: Central Systolic Blood Pressure during Sinus Rhythm and Atrial Fibrillation

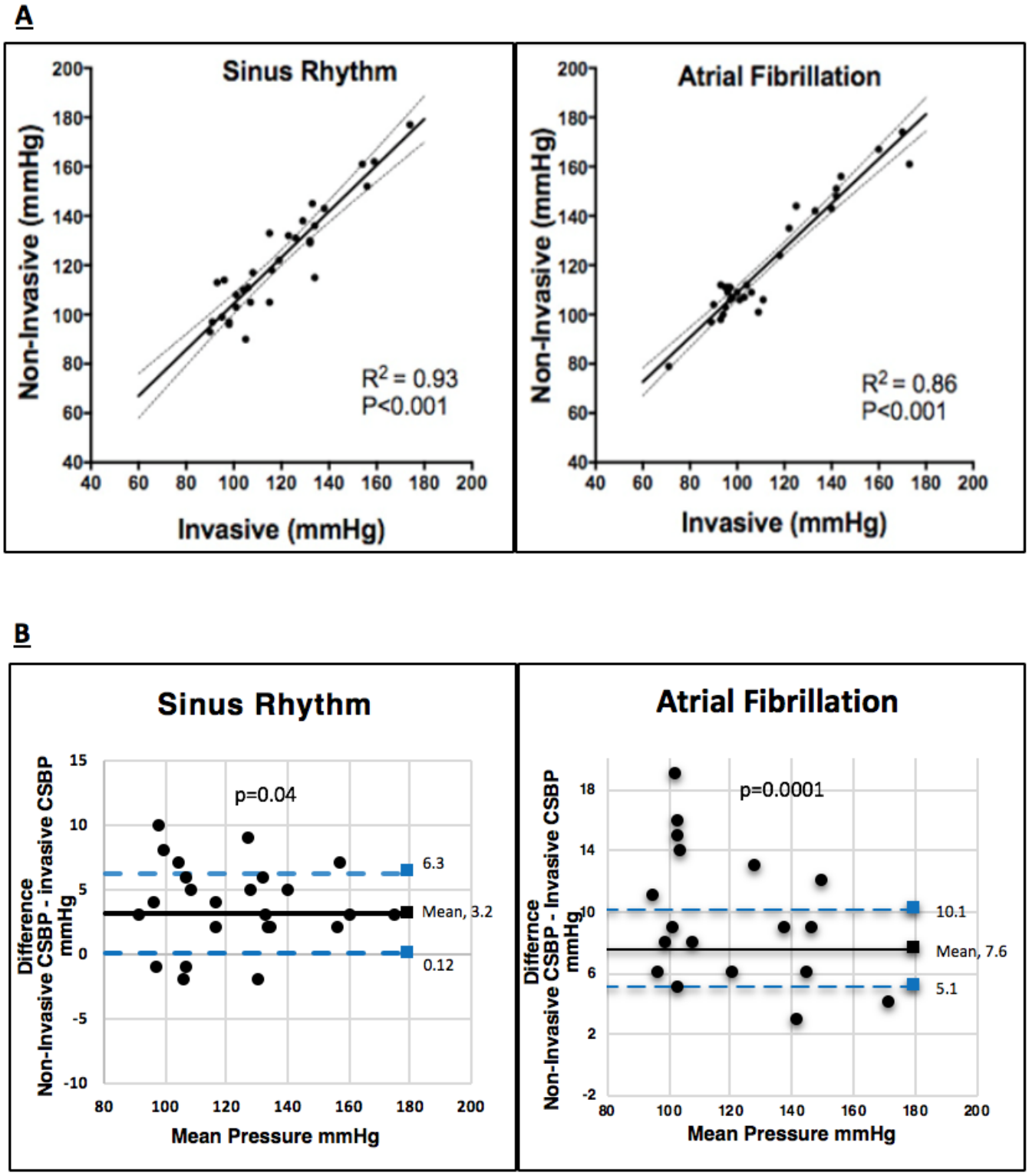
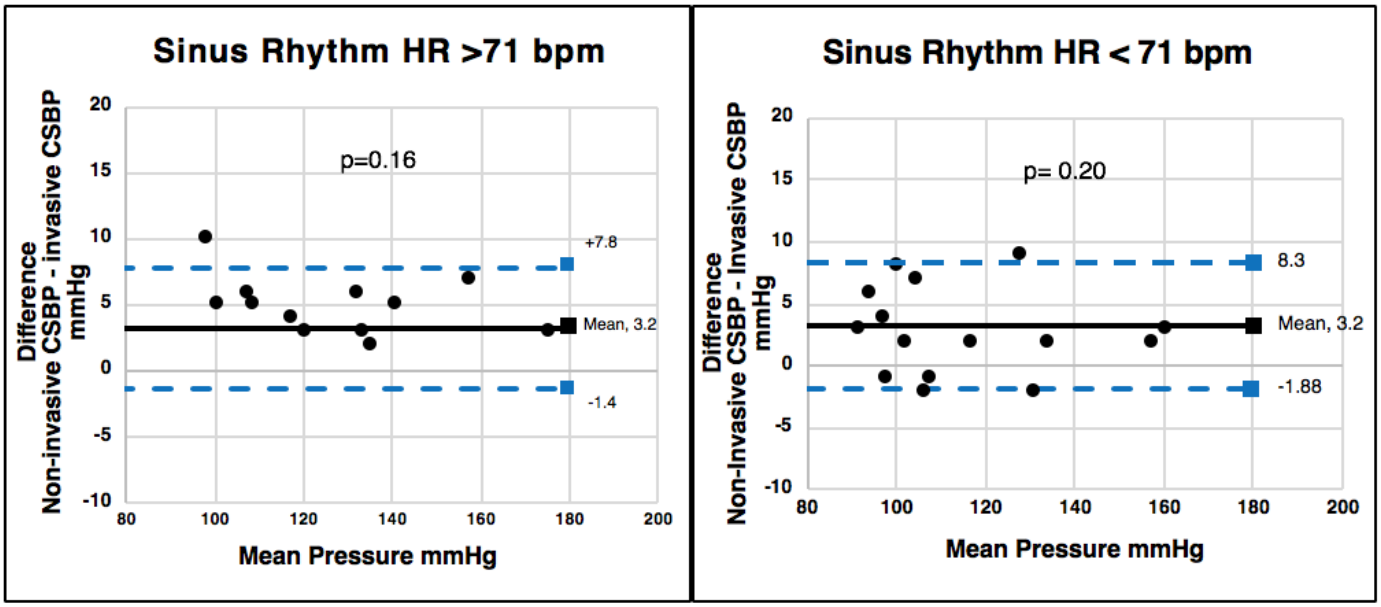


Figure 5.8.6: Bland- Altman Plots Illustrating the Agreement between Invasive and Non-Invasive CSBP during Sinus Rhythm and Atrial Fibrillation for High and Low HR

A



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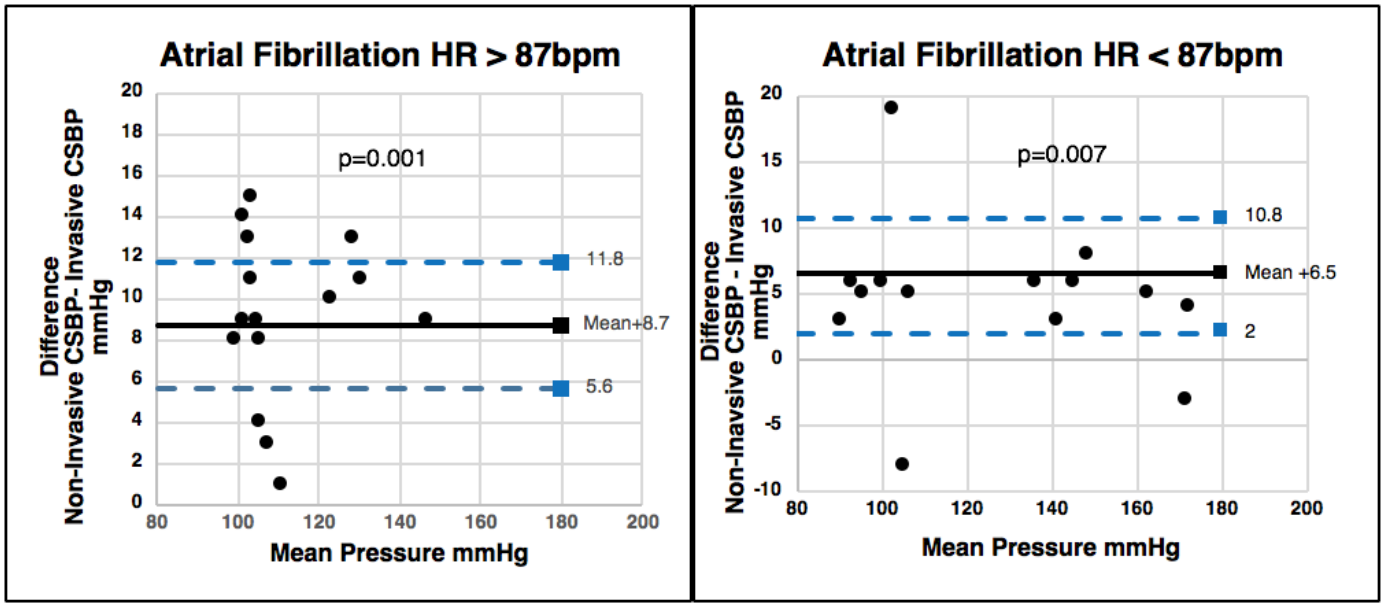


Figure 5.8.7A: Systolic Brachial and Invasive CSBP during Sinus Rhythm- Correlation and Agreement Analysis

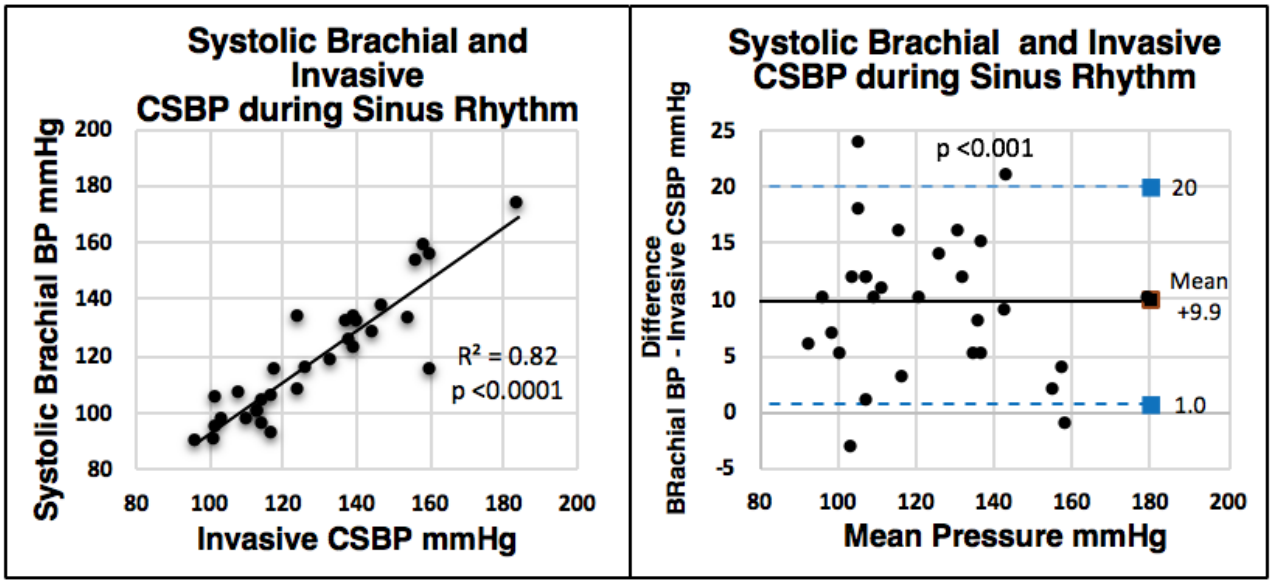


Figure 5.8.7B: Systolic Brachial and Non-Invasive CSBP during Sinus Rhythm- Correlation and Agreement Analysis

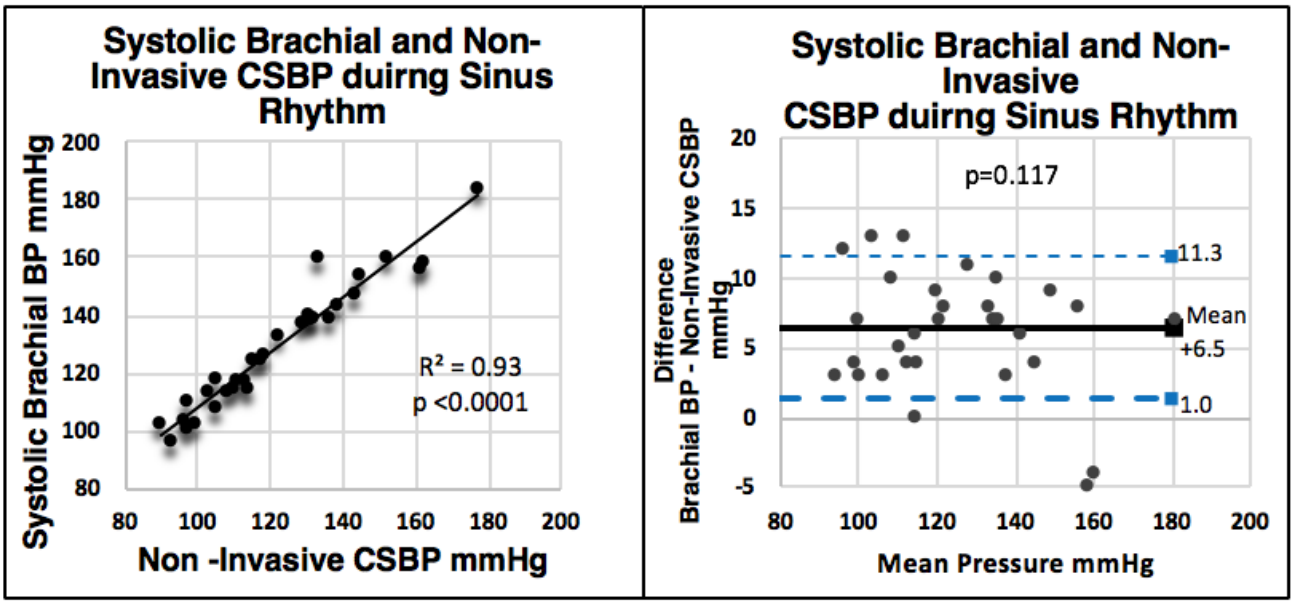
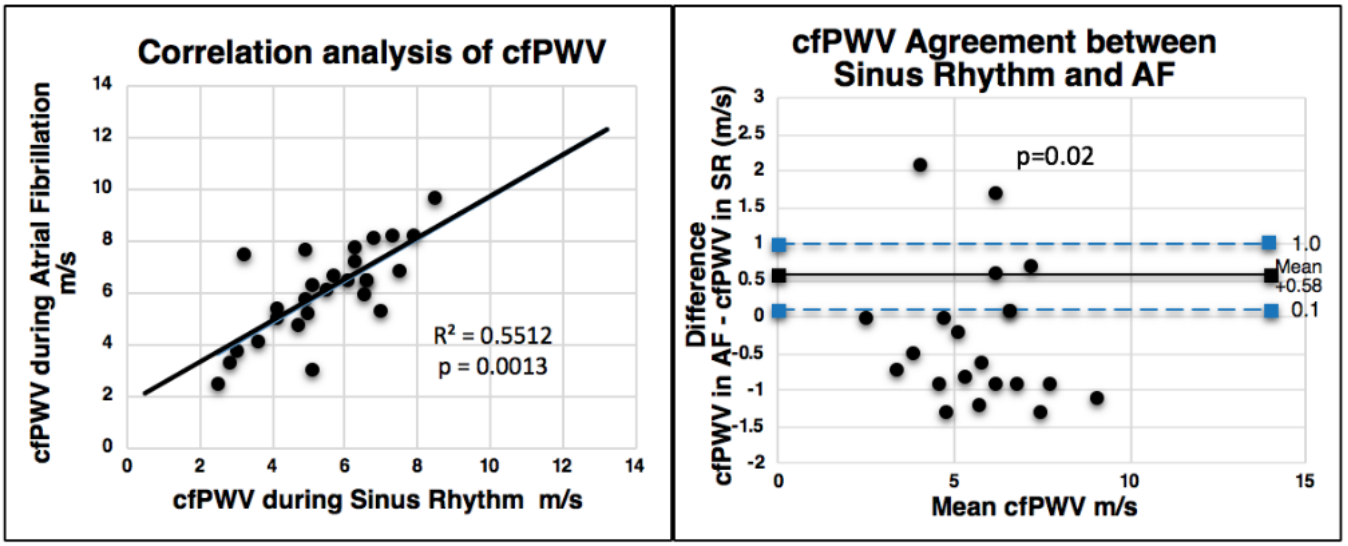


Figure 5.8.8: cfPWV Correlation and Agreement during Sinus Rhythm and Atrial Fibrillation

A



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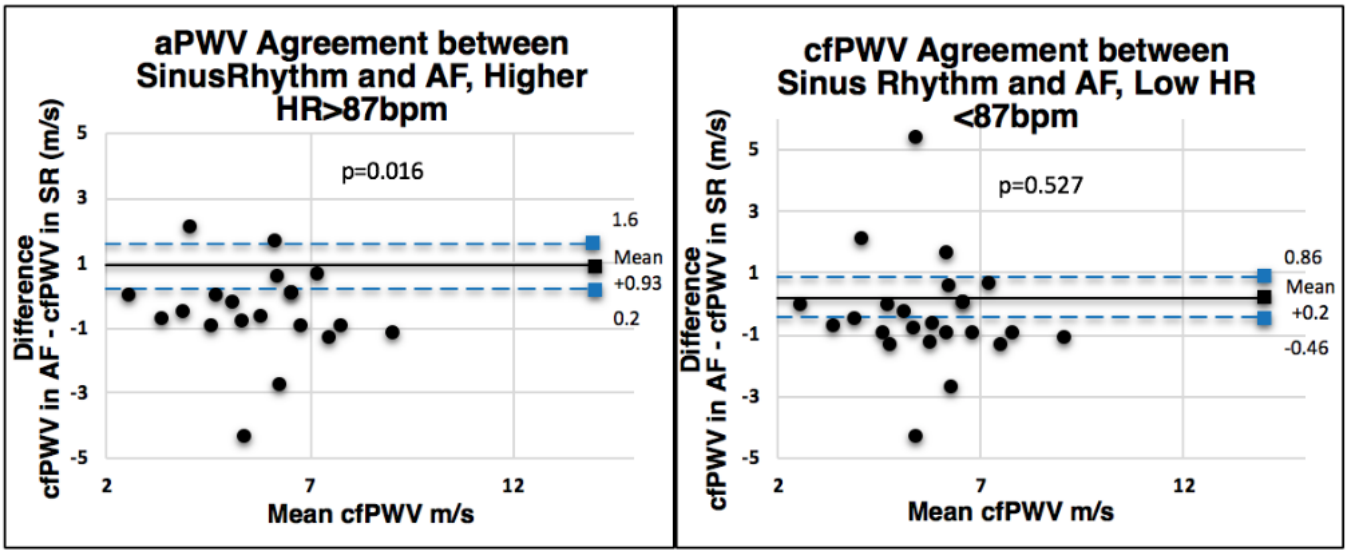


Table 5.9.1: Characteristics of the Study Cohort

Characteristics	**Total (n=31)**
Age (years)	64 ± 6
Male, n (%)	17 (55)
Body mass index (kg/m^2)	28 ± 5
Hypertension, n (%)	21 (68%)
Diabetes mellitus, n (%)	6 (19%)
Dyslipidemia, n (%)	24 (77%)
Coronary artery disease, n (%)	3 (9%)
Left ventricular ejection fraction (%)	62 ± 8
Left atrial volume indexed to BSA (ml/m^2)	30.5 ± 7.4
Diastolic function e/e' (septal)	10.5 ± 3.5
Ascending aortic diameter, anteroposterior (cm)	3.3 ± 0.4
*Persistent AF, n (%)	11 (35%)
CHA_2DS_2-VASc score	1.9 ± 0.7
HAS-BLED score	1.2 ± 0.6
Medications	
ACE-I/ARB, n (%)	20 (65%)
Beta-blockers, n (%)	15 (48%)
Calcium channel blockers, n (%)	6 (19%)
HMG-CoA reductase inhibitors, n (%)	24 (77%)
Anti-arrhythmic drugs, n (%)	12 (39%)

(ACE-I= Angiotensin-converting enzyme inhibitor, ARB= Angiotensin II receptor blocker, * = All persistent AF patients were cardioverted at least a few weeks pre ablation and were in sinus rhythm at the time of CBP assessment)

Table 5.9.2: Non-invasive versus invasive CBP indices during SR and AF

	Mean non-invasive pressure (mmHg)	Mean invasive pressure (mmHg)	Correlation Analysis		Bland-Altman Analysis	
			R^2	P-value	Mean Difference (95% confidence interval)	P-value
Central SBP during SR	122 ± 22	118 ± 22	0.93	<0.001	+3.2 (0.1 – 6.3)	0.04
Central SBP during AF	121 ± 24	113 ± 25	0.86	<0.001	+7.6 (5.1 – 10.1)	< 0.001
Central DBP during SR	81 ± 15	71 ± 12	0.48	<0.01	+10.4 (5.1 – 15.8)	< 0.004
Central DBP during AF	80 ± 13	71 ± 13	0.50	<0.01	+9.0 (5.4 – 12.5)	< 0.001
Central PP during SR	41 ± 15	48 ± 16	0.45	<0.04	-7.0 (-12.9 – -0.9)	0.026
Central PP during AF	41 ± 16	42 ± 15	0.70	<0.001	-1.3 (-5.0 – 1.9)	0.40

Mean heart rate during atrial fibrillation (AF) and sinus rhythm (SR) was 87±18 and 71±19 bpm respectively.
SBP= systolic blood Pressure, DBP= diastolic blood pressure, PP = pulse pressure.

Chapter 6:

Assessment of Residual Aortic Stiffness in AF: Exploring Central Haemodynamics Response to Exercise

6.1 INTRODUCTION

Exercise represents a physiological stress that can help expose sub-clinical cardiovascular (CV) remodelling to help predict increase risk of adverse events (241, 242).

A hypertensive response to exercise defined as brachial systolic BP of > 210mmHg in males and >190mmHg in females, is linked to future risk of hypertension and its related end organ injury including left ventricle hypertrophy (242). The precise mechanism of hypertensive response to exercise (HRE) is yet to be elucidated. However, endothelial dysfunction, conduit arterial stiffness, exaggerated sympathetic response and augmented neurohormonal response including angiotensin II are recognised as important contributors (243). Considering the significant difference in pulsatile load between central and brachial arterial tree (132), central haemodynamic assessment during exercise may better predict the CV outcomes. Further, aortic stiffness as a modifiable factor and marker of persistent high central blood pressure is acknowledged as a novel risk in atrial fibrillation (AF) (49, 61, 121, 244). Estimation of central blood pressure and its indices response to exercise can potentially unmask sub-clinical vascular remodelling in AF. This may improve AF management further by targeting the modifiable factors associating the arrhythmia with central arterial stiffness (121). Therefore, the aim of the current study was to characterise the central and peripheral blood pressure indices at rest and their response to exercise by history of AF (AF vs non-AF).

6.2 METHODS

6.2.1 Participants

The study enrolled 46 consecutive patients with history of paroxysmal and persistent AF being considered for ablation at Centre for Heart Rhythm Disorders, University of Adelaide, Adelaide, Australia. The Heart Rhythm Society Consensus definitions were used to define paroxysmal and persistent AF (245) . The study included patients with an age range of 20-80 years and willing to provide informed consent. All patients were found to be in sinus rhythm. Exclusion criteria were: moderate to severe aortic root dilatation (>4.5cm); moderate to severe aortic insufficiency; recent cardiac surgery; active malignancy; recent (<4weeks) history of decompensated heart failure; uncontrolled severe hypertension (resting BP > 180/120)(246); permanent AF; or inability to perform exercise stress test.

In addition, 31 consecutive patients with no documented history of AF, who were undergoing exercise stress test (EST) to exclude exertional angina or arrhythmia were recruited as controls.

All participants provided written informed consent to the study protocol that was reviewed and approved by the Clinical Research Ethics Committees of the Royal Adelaide Hospital, University of Adelaide. The study protocol was prospectively registered (ACTRN12618000074291).

6.2.2 Definitions

The following definitions were used to characterise the patient for the study:

- Hypertension was considered to be present if they were actively treated for the condition; Hypertension was well controlled on treatment in 55% (31/56) of the

patients with average systolic brachial BP of 127 ± 7 mmHg at rest. The rest of the 45% (25/56) patients had grade I-II HTN with a mean BP of 153 ± 10 mmHg despite ongoing anti-hypertensive treatment.

- Diabetes mellitus was classified as defined by the European guidelines (247) or if they were actively treated for the condition;
- Dyslipidemic as defined by the European guidelines (247);
- Coronary artery disease (CAD) if they had known stenosis of >50% of a major coronary artery or had undergone coronary revascularization.

6.2.3 Patient Preparation

All participants were advised to avoid heavy meal and refrain from coffee and smoking before evaluation of central blood pressure (CBP) indices at rest and early recovery (within 60 seconds post exercise).

6.2.4 Study Protocol

The SphygmoCor XCEL (AtCor Medical, Australia) system was used to record non-invasive CBP estimates. The SphygmoCor XCEL was chosen amongst the available devices as it is extensively validated and widely used in epidemiological as well as clinical settings to record CBP indices (132, 186). It is an automated oscillometric device that acquires pressure waveform by applying pressure cuff over the brachial artery approximately midway between the shoulder and elbow. This pressure waveform is further calibrated to brachial pressure indices and subjected to a proprietary generalized transfer function, which is essentially a low-pass frequency filter, to conform central pressure wave (179, 188, 191).

6.2.5 Data Collection

The baseline brachial and CBP was recorded following 10mins of rest during sitting. The participants then completed an exercise workload as per Bruce Protocol by using a treadmill during which 85% age predicted heart rate was targeted. The BP response to exercise was estimated within 60 seconds post exercise to ensure quality control of the recordings by avoiding motion artefacts.

6.2.6 Central Pulse Wave Analysis

We recorded oscillometric central pressure waveforms by applying pressure cuff from SphygmoCor XCEL device (AtCor Medical, Australia) over the right arm. Each measurement cycle consisted of a brachial blood pressure calculation followed by a sub-systolic pressure recording to generate a corresponding aortic waveform by using a validated transfer function (188, 191). We averaged two recordings to calculate CBP indices over 20 seconds. Only the recordings fulfilling the quality control criteria imposed by the device software were used to perform the analysis. The acquired aortic pressure waveforms were used to quantify central systolic, diastolic, pulse and augmentation pressure at rest and post exercise. Central pulse pressure (CPP) was derived by deducting diastolic pressure from systolic peak, Figure 6.9.1. Central augmentation pressure (CAP) is recorded by estimating the difference between systolic peaks (P2-P1). Here, P1 is the ejected pressure wave, the amplitude of which is mainly determined by ventricular contraction and the pulse wave velocity (PWV) of the ascending aorta. In contrast, P2 is the reflected fraction of the ejected wave from peripheral segments of arterial tree. Reflection index (RI) was derived by SphygmoCor XCEL software by dividing peak backward pressure wave (Pb) to peak forward pressure waveform (Pf), (RI= Pb/Pf). In

addition, augmentation index (AIx) was also calculated by the formula AP / PP x 100. The device software further corrected AIx for a heart rate at 75 beats per minute (AIx75) to avoid influence of fluctuating heart rate on AIx recordings (248). The comparison of the corresponding CBP indices at rest and post-exercise was performed and further adjusted to the co-variates to determine the change with exercise.

6.3 STATISTICAL ANALYSIS

The statistical software used was SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The continuous values for a range of brachial and CBP outcomes at rest and post exercise were expressed as mean ± SD for patient groups defined by history of AF. A mean change between resting and exercise index is calculated as change= (exercise value) – (resting value). The continuous variables were initially compared by using Student's t-test between AF and non-AF groups. The frequency distributions of the categorical variables amongst the two groups were compared by the Chi Square test. The difference in "change" in BP indices with exercise between the groups (AF vs non-AF) was analysed by using linear regression models. Robust standard errors were specified to account for the unequal variance in outcomes observed between the two groups. The mean estimates of differences were further adjusted for age, gender, resting heart rate (HR) and anti-hypertensives. The corresponding 95% confidence intervals were reported and p-values of <0.05 were considered as significant. The study had 80% power to detect a change of >7mmHg in CSP from rest to exercise with a large effect size of 0.7.

6.4 RESULTS

6.4.1 Characteristics of the Study Cohort

Figure 6.9.2 presents a CONSORT diagram of study recruitment, with none of patients declining to consent. The study cohort comprised of 77 patients with a mean age of 62 ± 14 years (69% male) and average CHA_2DS_2VASc score of 1.67 ± 0.4. The demographic details of the participants are listed in Table 6.10.1. The participants had a mean body mass index (BMI) of 27 ± 4kg/m^2 and a high prevalence of hypertension (72%). In terms of anti-HTN regime, majority of our participants (80%) were taking Angiotensin-converting enzyme inhibitors/Angiotensin receptor II blockers (ACE-I/ARB). Overall, the incidence of diabetes was 17%. Majority (95%) of the participants had normal LV systolic function with mean ejection fraction (EF) of 61 ± 7.3 % on echocardiography. Only 5% of the cohort had impaired LV systolic function with reported mean EF of 42 ± 11 %. Likewise, 83% of the patients had normal left atrial (LA) volume (<36mls/m^2) with an average LA size of 29 ± 4 mls/m^2. Only 17% of the participants had dilated LA with a mean of 42 ± 3.9 mls/m^2 on echocardiography.

6.4.1.1 Participants with History of AF

The mean age of the participants with history of AF was 67 ± 8 years and 69% were male. The average resting brachial and central BP was 136 ± 16 and 123 ± 13 mmHg respectively. Majority (80%) of patients with history of HTN and AF were on ACE-I/ARB based therapy. However, 52% of the AF cohort were taking regular beta-blockers with an average resting heart rate (HR) of 67 ± 12 bpm. The mean CHA_2DS_2VASC score for the AF group was 1.9 ± 0.6 as listed in Table 6.10.1.

6.4.1.2 The Controls

The mean age of the controls was 54.4 ± 11 years, 69% were males, as listed in Table6.10.1. The average resting brachial and central BP was 142 ± 15 and 128 ± 13 mmHg respectively. In controls, hypertension was found to be the most common cardiovascular risk and 80% of hypertensive patients were on ACE-I/ARB based therapy. Only 19% of the controls were on regular beta-blockers with a mean HR of 71.5 ± 12 bpm. The mean CHA_2DS_2VASC score for the control group was 1.5 ± 0.5.

Compared to controls, the participants with history of AF were older (mean age 67 ± 8 years vs 54.4 ± 11 years, p<0.001) and recorded to have lower resting brachial (136± 16 mmHg vs 142 ± 15 mmHg, p= 0.015) and central systolic blood pressure (123 ± 13 vs 128 ± 13 mmHg, p=0.006). However, as compare to controls, increased resting Aix75 (Aix75 >30) was more prevalent in AF group (41 vs 25%, p<0.001, Table 6.10.2). In terms of anti-HTN regime, 80% of total cohort was on ACE-I/ARB. However, beta-blockers were more frequently used in AF patients (AF 52% vs controls 19%, p=0.001) as listed in Table 6.10.2.

6.4.2 Exercise Stress Test

Participants were subjected to exercise on treadmill as per Bruce protocol to achieve 85% of age predicted target heart rate (220-Age). Their brachial and CBP indices response to exercise was characterised at rest and during early recovery. The participants with AF had reduced effort tolerance as compared to controls and managed to exercise for an average 7.4 ± 2.5 vs 9.5 ± 1.76 mins, p<0.001. The incidence of exercise induced HTN (peak brachial BP of >210mmHg) was comparable between the two groups (10% vs 7%, p=0.4). No sustained (>30 seconds) arrhythmia was inducible with exercise in our cohort.

Compared to patients with documented AF, the incidence of positive exercise stress test concerning ischemia was more commonly reported in the controls (19 vs 6%, p <0.001).

6.4.3 Brachial BP Indices at Rest

In patients with history of AF, the brachial BP was better controlled at rest (AF 136± 16 mmHg vs Control 142 ± 15 mmHg, p= 0.015). After adjusting for age, gender, resting HR and anti-hypertensives the resting brachial blood pressure remained significantly low in patients with history of AF than controls (difference 9.0mmHg, 95% CI -2.8 to 16, p=0.015) as shown in Table 6.10.3. However, no significant difference was recorded for adjusted resting brachial diastolic (4.7 mmHg, 95% CI 0 to 9.5, p=0.052) and pulse pressure (4.6 95% CI -1.9 to 11.1, p= 0.17) between the two groups.

6.4.4 Exercise Response of Brachial BP Indices

In response to moderate exercise, a comparable amplification in brachial systolic blood pressure was recorded between participants with history of AF and controls (166 ± 20 vs 174 ± 19 mmHg, 8.4mmHg, 95% CI -1.7 to 18.4, p= 0.09), Table 6.10.4. Furthermore, no significant difference was noted concerning exercise response to adjusted brachial diastolic (91 ± 15 vs 96 ± 12mmHg, 5 mmHg, 95% CI -1.7 to 11, p= 0.15) and PP (75 ± 17 vs 78 ± 15mmHg , 3mmHg , 95% CI -5.1 to 12, p=0.43) between the two groups, Table 6.10.4.

Additionally, we analysed the mean change in central and brachial BP indices in response to exercise between AF and controls. We found no difference in adjusted means between the two groups except a significant amplification in CAP in response to exercise in participants with known AF. (Tables 6.10.5 and 6.10.6).

6.4.5 Resting Central BP Indices

The resting central systolic blood pressure was better controlled in patients with history of AF (mean CBP with AF 123 ± 13mmHg vs mean CBP in controls 128 ± 13mmHg, p=0.006). After adjusting for co-variates including age, gender, anti-hypertensives and resting heart rate the difference in resting central systolic blood pressure between patients with history of AF and controls remained significant (9.0mmHg, 95% CI 2.6 to 15.3, p=0.006) as shown in Table 6.10.3. There was no difference noted in adjusted CPP (4.4mmHg, 95% CI -1.1 to 10, p=0.12), CAP (1.8mmHg, 95% CI -2.4 to 6.1, p=0.40), RI (5.8, 95% CI -2.3 to 13.9, p= 0.16) and AIx75 (-2.0, 95% CI -9.8 to 5.9, p=0.62) at rest.

A significant amplification of systolic pressure wave was recorded at brachial arterial site for patients with history of AF (mean brachial BP 136 ± 16 mmHg vs mean CBP 123 ± 13mmHg, p<0.001) and controls (mean brachial BP 142 ± 15 vs mean CBP 128 ± 13 mmHg, p<0.001).

6.4.6 Exercise Response of CBP Indices

In addition to central systolic and diastolic pressure, CBP indices were recorded non-invasively to report central arterial response to exercise. A comparative analysis by using regression model was used to delineate variance in brachial and CBP indices between AF and non-AF groups. The recorded mean differences were further adjusted for age, gender, heart rate and anti-hypertensives. Overall, no significant difference was recorded in CBP response to exercise between participants with history of AF and controls (147 ± 16mmHg vs 150 ± 15mmHg, (difference 2mmHg 95% CI -3.7 to 12, p=0.29) as listed in Table 6. However, a significant increase in adjusted exercise CAP was noted for patients with history of AF (5.7mmHg, 95% CI 0.4 to 11.7, p=0.04) indicating impaired vascular compliance despite well controlled brachial and CBP. No significant difference was

recorded for CPP (0.8 mmHg, 95% CI -6.3 to 8.0, p=0.82), central Aix75 (-2.1, 95% CI -13.7 to 9.4, p= 0.72) and RI (0.8, 95% CI -8.5 to 9.9, p= 0.87) response to exercise between the two groups as shown in Table 6.10.6.

Additionally, we compared the mean change in the central and brachial BP indices of hypertensive and normotensive patients irrespective of AF history. No statistically significant difference was found between normotensive and hypertensive patients concerning CBP estimates at rest (123 ± 13 mmHg vs 121 ± 14mmHg, p= 0.54) or post exercise (146 ± 16mmHg vs 147 ± 16 mmHg, p=0.44).

6.5 DISCUSSION

6.5.1 Major Findings

Hypertension remains a dominant attributable risk for the development and progression of AF. Appropriate therapy to control BP is essential to improve AF outcomes. Here we evaluate the role of central blood pressure measurements. The current study illustrated an important finding of residual yet sub-clinical central arterial stiffness in patients with AF, suggested by increased prevalence of central AIx75 at rest and significantly amplified response of CAP to moderate exercise. The current study also highlighted the potential role of exercise stress testing to unmask residual aortic stiffness despite normal resting BP indices in AF. As a modifiable factor aortic stiffness is of independent value to predict AF outcomes (61, 119-121, 173).

6.5.2 Increased Incidence of Resting Central AIx75 in AF

Despite a relatively better controlled central systolic BP, we found increased incidence of resting central Aix75 in our AF group after adjusting for ageing. The central Aix75 is a ratio between CAP and CPP that is further adjusted for heart rate at 75bpm. The central Aix75

is derived by the formula Central AIx75= CAP/CPP x 100 (249). The distribution of central Aix75 can be variable due to age related central arterial stiffness and central Aix75 >30 is considered high for the age group of our cohort (249). However, no significant statistical difference was recorded in central AIx75 post exercise between the AF and control groups. Increased central Aix75 and CPP are the recognised but indirect CBP indices reflective of aortic stiffness (163, 250). Hence, the independent value of these indices to predict cardiovascular and AF outcomes is yet to be confirmed (61, 250). The CPP is derived by subtracting central diastolic from central systolic BP (Figure 6.9.1). We reported no change in CPP with exercise in our cohort. One of the possible explanation is that SphygmoCor XCEL under-estimates central systolic and over-estimates central diastolic pressure (80, 166). This leads to significant under-estimation of CPP. Likewise, central Aix75 is a ratio and dependent on multiple variables. Conceivably, an error introduced during estimation of CPP can impact on the reported central Aix 75 value and its overall difference between the two groups (248, 251).

6.5.3 The Potential Role of Characterising Exercise Response of CAP in AF Patients

In our study we reported increase CAP response to exercise in AF participants. The CAP is derived from aortic pressure waveform as the difference between the early and late systolic summits. The early systolic wave is predominantly formed by forward pressure wave generated by left ventricle ejection. On the other hand, the late systolic peak is influenced by the vascular compliance of the subject- a stiffer arterial tree leads to amplification of propagating wave at the infliction point ensuing increased CAP (252). A physiological increase in heart rate during exercise can unmask sub-clinical aortic stiffness by effecting ejection time of pressure wave (253). A rapidly propagating pressure wave in

a relatively stiffer vasculature results in amplification of late systolic peak recorded as exaggerated CAP during exercise in our AF cohort.

6.5.4 Role of Exercise Stress Test in Characterising Residual Aortic Stiffness in AF

We estimated BP response to exercise as this "physiological stress" has mechanistic relevance correlating HTN with AF. An exaggerated response of BP to moderate exercise reflects an overactive sympathetic response and/or endothelial dysfunction with vascular remodelling that prevent appropriate physiological vasodilation in response to exercise (242, 243). The above factors are associated with aortic stiffens and may explain its correlation with HTN and increased AF risk. However, studies reported conflicting data associating hypertensive response to exercise with ventricular and conduit arterial remodelling (243, 254). The difference in baseline characteristics of participants with variable intensities and modalities of exercise may help explain the inconsistencies in the reported data. In general, hypertensive response to exercise is observed in aortic stiffness (76). This may highlight the underlying mechanism associating exercise induced hypertension with aortic stiffness and CV remodelling including increased risk of AF. Nonetheless, a practical question is how to diagnose and manage a sub-clinical residual vascular remodelling to improve risk factor modification and CV outcomes. The revised HTN guidelines has reduced the thresholds to instigate pharmacotherapy and advocated aggressive risk factor management to achieve BP treatment targets (27). However, the role of exercise induced HTN and aortic stiffness as a surrogate for persistently high CBP in sub-clinical HTN was not explored. Even AF was not recognised as an index of target organ injury in HTN. The CBP indices response to exercise may help improve risk factors modification by revealing sub-clinical or pre- HTN in our AF patients.

6.6 CLINICAL IMPLICATIONS

Central arterial stiffness is an independent driver of AF. The body of literature defining BP targets to improve AF outcomes is evolving. Additionally, patients presenting with PAF and no identifiable conventional risk may benefit from assessment of sub-clinical aortic stiffness. Aortic stiffness can be estimated by a bedside recording of pulse pressure. Further, assessment of central hemodynamic response to exercise is clinically applicable and can help expose residual aortic stiffness as one of the possible mechanisms associating HTN with AF. The current study is very relevant in this regard. We explored the potential role of central hemodynamic response to exercise to further advance clinical application of risk factors modification in AF and to improve arrhythmia outcomes.

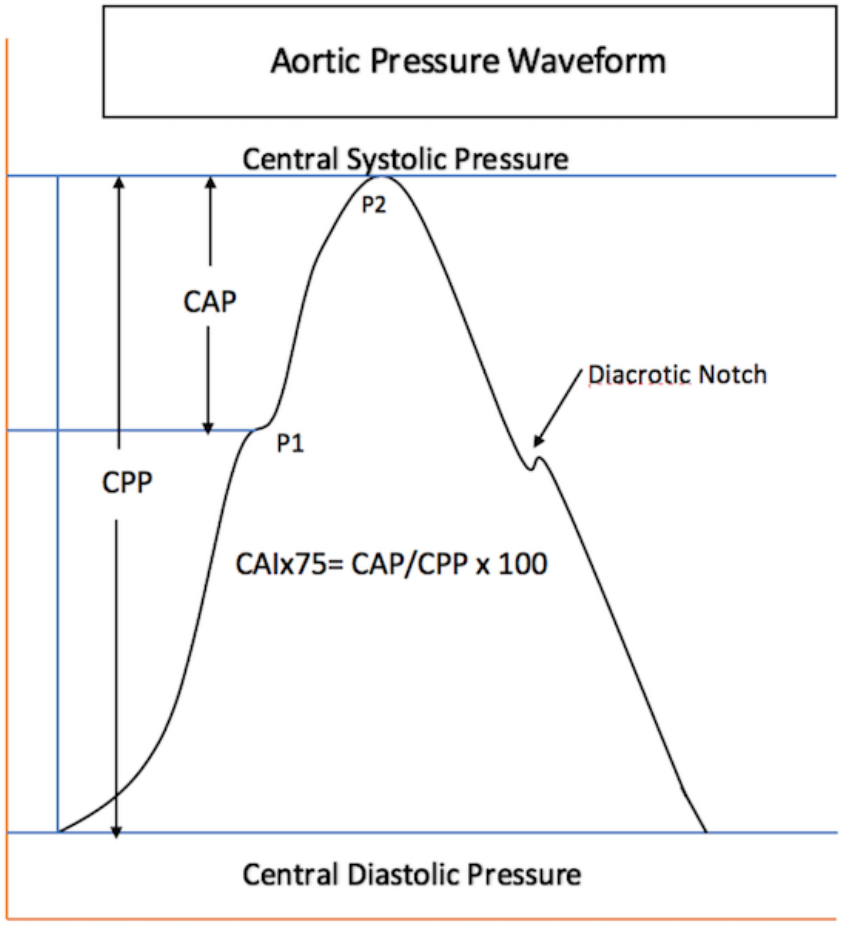
6.7 LIMITATIONS

Our study has the following limitations. First, it was an observational single centre study exploring the role of exercise stress testing to unmask central arterial remodelling in patients with AF. Second, majority of our subjects (80%) were hypertensive and taking active treatment that can potentially lower peripheral and CBP indices. In addition, the cohort selected for analysis was predominantly consisted of middle-aged Caucasians. It remains unclear whether the study results can be generalized for younger or older or non-Caucasian individuals. Finally, due to the existence of different exercise testing protocols, the results of our study pertain to the use of treadmill exercise according to the standardised Bruce protocol to achieve age predicted target HR of 85%. Despite the inherent limitations of an observational study our work has highlighted the association of aortic stiffness in AF and HTN.

6.8 CONCLUSION

As a modifiable factor, aortic stiffness associating HTN with AF, still represents an unmet clinical need. Central haemodynamics response to moderate exercise can potentially unmask residual aortic stiffness in patients with AF. Further confirmation of our findings in a large prospective multi-centre setting will help address the gap in evidence to improve ongoing risk factor modification and arrhythmia outcomes.

Figure 6.9.1: Central Aortic Pressure Waveform, Illustrating Central Blood Pressure Indices



(CAIx75= Central Augmentation Index corrected for heart rate 75bpm, CAP= central augmentation pressure, CPP=central pulse pressure, P1=peak ejected pressure wave, P2=peak reflected pressure wave)

Figure 6.9.2: CONSORT Diagram for the Study

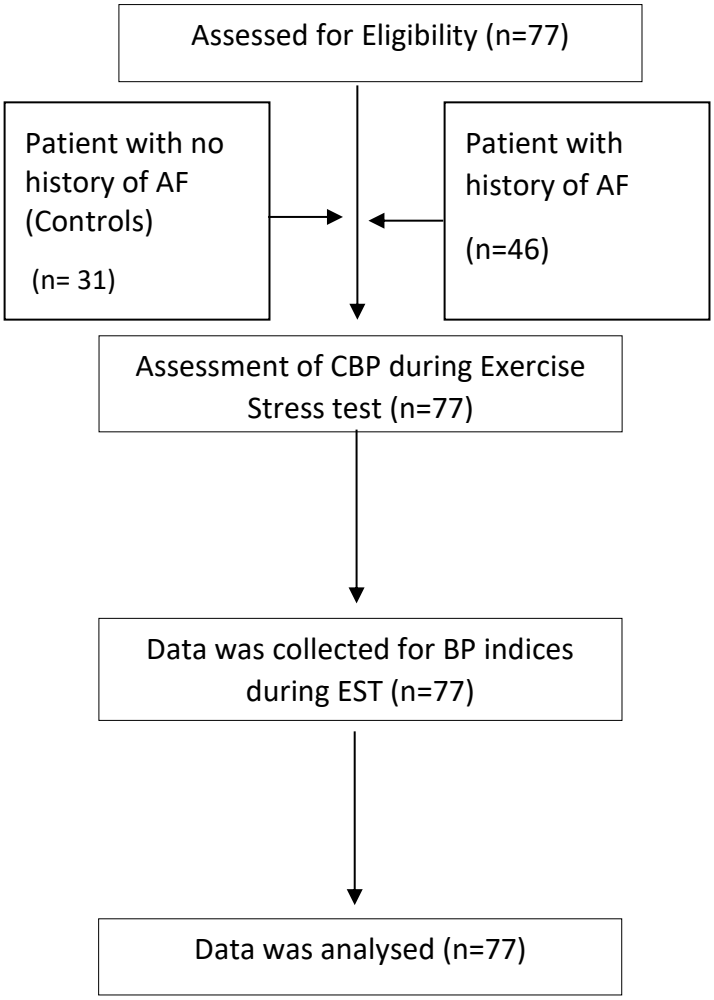


Table 6.10.1: Characteristics of the Study Cohort

Characteristic	All Patients (N=77)	History of AF (n=46)	No history of AF (n=31)	p-value
Age (years)	61.8 ± 13.7	66.8 ± 8.2	54.4 ± 16.7	*<0.001**
Male (n, %)	53 (68.8)	32 (69.6)	21 (67.7)	NS
BMI (kg/m^2)	27.5 ± 4.1	27.3 ± 3.8	27.7 ± 4.5	NS
Hypertension (n, %)	56 (72.7)	37 (80)	24 (80)	0.21
Diabetes Mellitus (n, %)	13 (16.9)	6 (13.0)	7 (22.6)	0.13
Central Systolic BP (mmHg)	125 ± 13	123 ± 13	128 ± 13	*0.006**
Brachial Systolic BP (mmHg)	124 ± 14	136 ± 16	142 ± 15	*0.015**
Left Ventricle Ejection Fraction (EF%)	61.3 ± 7	61±7	61 ± 7.3	NS
Left Atrial Volume (mL/m^2)	31.1 ± 6.6	31.5 ± 6.9	30.5 ± 6.3	NS
CHA_2S_2VASC score	1.67 ± 0.4	1.9 ± 0.6	1.5 ± 0.5	NS
Resting Heart Rate (bpm)	69.0 ± 12.6	67.3 ± 12.5	71.5 ± 12.5	NS
Medications				
ACE-I/ARB (n, %)	61 (80.3)	37 (80.4)	24 (80.0)	NS
Beta-Blockers (n, %)	30 (39.0)	24 (52.2)	6 (19.4)	*0.001**
Calcium Channel Blockers (n, %)	22 (28.6)	12 (26.1)	10 (32.3)	NS

(ACE-I/ARB= Angiotensin-converting enzyme inhibitors/Angiotensin receptor II blockers, BMI=Basal metabolic index, * = significant p-value)

Table 6.10.2: Prevalence of High BP Indices in our Cohort

Blood Pressure Index	All patients (N=77)		History of AF (n=46)		No history of AF (n=31)		p-value
	Freq	(%)	Freq	(%)	Freq	(%)	
High Resting CPP (CPP ≥ 45 mmHg)	26	(33.8)	14	(30.4)	12	(38.7)	NS
High Resting Central Augmentation Pressure (CAP ≥ 14 mmHg)	24	(33.0)	14	(32.0)	10	(33.0)	NS
High Resting Central Augmentation Index (CAIx 75 ≥ 30)	27	(35.1)	19	(41.3)	8	(25.8)	*0.001**
High Resting Brachial Pulse Pressure (Brachial PP ≥ 60 mmHg)	25	(32.5)	12	(26.1)	13	(41.9)	NS

(AF= atrial fibrillation, BP= blood pressure, Freq= frequency, NS = non-specific, P= p-value, * = significant P-value)

Table 6.10.3: Estimated Means for BP Indices at Rest

Blood Pressure Index	Mean Value for Total Cohort (n=71)	History of AF (n=46)	No history of AF (n=31)	Adjusted Difference in Means	Unadjusted p-value	Adjusted p-value
Central SBP (mmHg)	125±13	123±13	128±13	9 (2.6 to 15.3)	0.12	*0.006**
Central DBP (mmHg)	83±9	81±8	86±10	4.5 (0.5 to 8.6)	*0.023**	*0.03**
CPP (mmHg)	41±12	41±13	41±11	4.4 (-1.1 to 10)	0.9	0.12
CAP(mmHg)	12±9	12±8	11±11	1.8 (-2.4 to 6)	0.5	0.40
Aix75	23.6±16	43±25	31±21	-2 (-9.8 to 5.9)	0.25	0.62
RI	63±17	64±17	60±18	5.8 (-2.3 to 14)	0.38	0.16
Brachial SBP (mmHg)	138±16	136±16	141±15	9.3 (2.8 to 15.9)	0.10	*0.015**
Brachial DBP (mmHg)	83±10	81±8	86±12	4.7 (0 to 9.5)	*0.03**	0.05
Brachial PP(mmHg)	55±14	54±14	55±12	4.6 (-1.9 to 11)	0.79	0.17

*= statistically significant p-value, AF= Atrial fibrillation, Aix75= Adjusted augmentation index at heart rate of 75bpm, BP= Blood pressure, CAP= Central augmentation pressure, CPP= central pulse pressure, DBP= Diastolic blood pressure, PP= Pulse pressure, RI= reflection index, SBP= Systolic blood pressure

Table 6.10.4: Estimated Means for BP Indices Post Exercise

Blood Pressure Index	Mean Value for Total Cohort (n=71)	History of AF (n=46)	No History of AF (n=31)	Adjusted Difference in Means	Unadjusted p-value	Adjusted p-value
Central SBP (mmHg)	148±15	147±16	150±15	4.2 (-3.7 to 12)	0.44	0.30
Central DBP (mmHg)	92±12	89±11	97±13	5.0 (0.6 to 10.5)	*0.004**	0.08
CPP (mmHg)	55±15	58±14	52±15	-0.8 (-8.0 to 6.3)	0.9	0.12
CAP(mmHg)	14±13	18±12	9±12	5.7 (1 to 11.7)	0.06	*0.04**
Central Aix75	30±21	30±16	31±28	2.1 (-9.4 to 13.7)	0.25	0.7
RI	67±17	64±17	60±18	5.8 (-2.3 to 14)	0.38	0.16
Brachial SBP (mmHg)	169±20	165±20	174±19	8.4 (-1.7 to 18.4)	*0.04**	0.09
Brachial DBP (mmHg)	93±14	90±14	97±12	5.0 (-1.7 to 11)	*0.04**	0.15
Brachial PP(mmHg)	76±16	77±15	75±17	3.4 (-5.1 to 12)	0.5	0.43

*= statistically significant p-value, AF= Atrial fibrillation, Aix75= Adjusted augmentation index at heart rate of 75bpm, BP= Blood pressure, CAP= Central augmentation pressure, CPP= central pulse pressure, DBP= Diastolic blood pressure, PP= Pulse pressure, RI= reflection index, SBP= Systolic blood pressure

Table 6.10.5: Adjusted Mean Change in Brachial BP Indices in Response to Exercise

Brachial BP Indices	Resting	Exercise	Change	Unadjusted difference (95% CI)	p-value	#Adjusted difference (95% CI)	p-value
Brachial Systolic Pressure (mmHg)							
AF history	136 ± 16	165 ± 20	30± 17	-2.8 (-8.92 to 8.64)	0.974	3.91 (-5.24 to 13.07)	0.394
No AF history	141± 15	174± 19	33 ± 16				
Brachial Diastolic Pressure (mmHg)							
AF history	81± 8	86± 12	6±12	-0.8 (-6.49 to 6.09)	0.949	0.61 (-6.15 to 7.37)	0.856
No AF history	90± 14	97± 12	7±10				
Brachial Pulse Pressure (mmHg)							
AF history	54±14	77± 15	23 ± 17	2.9 (-8.12 to 8.23)	0.989	3.30 (-5.05 to 11.65)	0.431

(#Adjusted for age, gender, heart rate and anti- hypertensives)

Table 6.10.6: Adjusted Mean Change in Central BP Indices in Response to Exercise

Central BP Indices	Resting Values	Exercise Values	Change in Response to Exercise	Unadjusted difference (95% CI)	p-value	Adjusted difference (95% CI)	p-value
Central Systolic Pressure (mmHg)							
AF history	123 ±13	147 ±16	24 ±13.3	2.60 (-4.6 to 9.8)	0.473	5.19 (-2.95 to 13.33)	0.206
No AF history	131.10 (12.57)	152.10 (14.35)	21 ± 13				
Central DP (mmHg)							
AF history	81± 8	89±10	7±9	-3.13 (-9.5 to 3.2)	0.328	-0.73 (-6.53 to 5.07)	0.801
No AF history	89 ± 11	97±13	10 ±12				
Central PP (mmHg)							
AF history	41±13	58 ±14	17±11	5.73 (-3.7 to 15.2)	0.231	5.92 (-4.0 to 15.9)	0.240
No AF history	41 ±11	52±15	11 ±19				
Central Augmentation Pressure (mmHg)							
AF History	12±8	18±12	6.6 (2.5)	8.8 (3.75 to 12.8)	0.015*	8.39 (3.52 to 13.3)	*0.037**
No AF History	11±11	9±12	-2.1 (1.42)				
Central Augmentation Index (CAIx) AP/PP x100							
AF History	43±25	30±16	12± 15	11 (-4.1 to 15.8)	0.242	6.5 (-4.17 to 16.2)	0.276
No AF History	31 ± 21	31±28	0.5±25				
Reflection Index (Pb/Pf)							

AF History	67 ± 18	64± 17	2.8 (25.7)	5.2 (-3.1 to 21.9)	0.09	5.8 (-2.3 to 13.9)	0.16
No AF History	68±19	60±18	8.0 (20.2)				

(AF=atrial fibrillation, AP= augmentation pressure, BP= blood pressure, DP= diastolic pressure, P= p-value, Pb = backward pressure wave, Pf = forward pressure wave, PP= pulse pressure, * = significant p-value)

Chapter 7:

Summary

AF is the most common sustained arrhythmia and emerging data has elucidated the strong correlation of the arrhythmia with uncontrolled CV risks. Amongst these modifiable risks, HTN is the most common population attributable factor associated with AF. However, treatment goals for blood pressure in AF is still indistinct. This thesis evaluates the role of CBP indices and aortic stiffness to better characterise HTN in atrial fibrillation. Additionally, it describes the association of CBP and aortic stiffness with AF to improve ongoing risk factor management and to help device better preventative strategies in AF.

Chapter-1 provides a comprehensive review of the literature linking HTN and AF. HTN is the most common risk associated with AF and better definitions of treatment targets are required for escalating global burden of the disease to prevent AF. Further, the burden of HTN and the impact of revised AHA guidelines for diagnosis, classification and management of HTN was discussed. Additionally, the complex patho-physiological nexus relating AF with HTN was re-visited and an assessment tool is proposed to better characterise atrial remodelling and end organ injury due to HTN. Chapter-2 summarises the association of pre- HTN and new-onset AF by presenting the systematic review and meta-analysis of current published literature. Pre-HTN was defined as a BP range of 120-139/80-89mmHg by the selected studies. It was found to be independently associated with new-onset AF and increases the absolute risk of arrhythmia by 27%. Moreover, as compared to their normotensive counterparts, increased burden of the metabolic risks

was reported in pre-HTN resulting in escalated risk of HTN induced end organ injury and CV events.

As compared to brachial BP indices, central haemodynamic assessment was reported to be more relevant in predicting HTN induced end organ injury and AF outcomes. Population studies revealed that up to one fifth of the participants characterised as "normotensives" based on their brachial blood pressure had aortic stiffness due to persistently high central blood pressure. Chapter 3 presents the systematic review and meta-analysis of all the published prospective trials associating increased aortic stiffness independently to AF, cardiovascular and all-cause mortality. Increased aortic stiffness, as a surrogate marker for persistently high central blood pressure was independently associated with a 33% augmented risk of new-onset AF. The increased cardiovascular and mortality risk inflicted by raised aortic stiffness was also confirmed. Chapter 4 evaluates the non-invasive assessment of CBP indices and provides us with a clinical insight to better incorporate these tools in our routine cardiovascular risk factor management. However, these non-invasive devices were not validated to be used for CBP and aortic stiffness assessment during AF. In Chapter 5, we present our findings of IMPULSE AF validation study (Trial Id: ACTRN12616001225404). It was the first study to evaluate and validate CBP and aortic stiffness assessment during AF. Our results showed a significant and strong correlation between invasive and non-invasive CBP recordings during sinus rhythm and AF. Additionally, aortic stiffness assessment by carotid-femoral PWV can be reliably performed during AF especially when ventricular heart rate can be adequately controlled.

In addition to resting CBP and aortic stiffness assessment, exaggerated BP response to exercise can help unmask pre- HTN associated with reduced central arterial compliance.

Chapter 6 characterises the difference of central and peripheral blood pressure indices response to exercise in AF compared to non- AF “controls”. Despite a relatively normal resting BP, patients with AF were found to have a residual aortic stiffness, demonstrating an advanced central arterial remodelling.

Aggressive cardiovascular risk factor management has been recognised for its crucial role to improve AF outcomes. Hypertension is the most prevalent modifiable factor related to AF and needs to better defined. Our work highlighted the role of CBP indices and aortic stiffness assessment to better characterise hypertension induced CV remodelling in individuals labelled as pre-hypertensives based on conventional brachial BP estimation. Additionally, this work has expanded the scope of central pressure wave and velocity assessment in AF and during exercise. However, further work is needed to establish CBP and aortic stiffness as a treatment target to prevent hypertension induced premature CV morbidities and mortality.

Chapter 8:

Future Directions

This thesis focussed on CBP and aortic stiffness evaluation to improve clinical profiling and CV risk management in AF by examining sub-clinical HTN and its associated end organ injury. However, few questions remain unanswered, some of which are discussed below.

The actual prevalence of central high BP and aortic stiffness in AF population is not fully known. Specifically, the incidence of central high BP in AF cohort characterised as normotensives based on brachial BP assessment has not been explored to date. This requires further studies as it may be particularly relevant in younger patients with normal LA size and no apparent AF risk factors.

The correlation between high CBP indices and electro-anatomical left atrial remodelling is yet to be fully described. While aortic stiffness and endothelial dysfunction are the possible patho-physiological links, further studies are required to better understand the underlying mechanisms. This will help affirm AF as a marker of end organ injury in hypertensive cohort.

Early detection of central high BP can help prompt introduction of treatment to preclude accelerated cardiovascular and left atrial remodelling. Chapter 4 of this thesis provides a comprehensive review of the actual methodology with clinical relevance of non-invasive assessment of CBP and aortic stiffness to better incorporate CBP indices assessment in

routine clinical practice. Further, in chapter 5 we extended the scope of CBP indices assessment during AF by presenting our IMPULSE AF study results. However, this thesis did not set out to study the prognostic impact of treating HTN as per CBP targets as a primary and secondary preventative strategy in AF.

In addition, the impact of HTN treatment based on CBP indices on CV outcomes including stroke, myocardial infarction, heart failure hospitalisation and renal failure requires further evaluation. Similarly, further clinical trials are needed to examine the benefits of targeting sub-clinical central vascular remodelling in AF unmasked by CBP indices in response to exercise.

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