Morphological and electrophysiological differences between the Caucasian and South Asian Atrium

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Papers

1. **O'Neill, J**, Tayebjee, MH. Why are South Asians seemingly protected against the development of atrial fibrillation? A review of current evidence. Trends Cardiovasc Med. 2017; 27: 249- 257.

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4. **O'Neill, J**, Tayebjee, MH. Electrophysiological properties of the South Asian heart. Heart Asia. 2018; 10: e011079.

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Abstracts

1. **O'Neill, J**, Jegodzinski, L, Tayebjee, MH. Incidence of subclinical atrial fibrillation in a South Asian population. Europace. 2018; 20:Suppl 4 iv37-iv38.

2. **O'Neill, J**, Swoboda, PP, Plein, S, Tayebjee, MH. Left atrial size and function in a South Asian population and their potential influence on the risk of atrial fibrillation. Europace. 2018; 20:Suppl 4 iv37.

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Abstract

Introduction: South Asians (SAs) have a low prevalence of atrial fibrillation (AF) compared with Caucasians despite a higher prevalence of hypertension, diabetes mellitus and coronary artery disease. The aim of this thesis was to determine whether this was related to an under-detection of the arrhythmia and if not, whether differences in left atrial (LA) size, electrophysiological properties or autonomic function in SAs might help to explain this disparity.

Methods: Retrospective and prospective cohort studies were performed on SA and Caucasian participants using data from implantable cardiac devices, cardiac magnetic resonance imaging scans, invasive electrophysiology studies and a range of non-invasive cardiac investigations.

Results: The cumulative incidence of subclinical AF was significantly lower in SAs compared with Caucasians (log rank p=0.002) with an annual event rate of 6.9% versus 13.9%. In comparison with Caucasians, SAs were of a smaller height with lower lean body mass and higher waist:hip ratio; had lower minimum (27.7±11.1 ml vs 34.9±12.3 ml, p=0.002) and maximum LA volumes (64.7±21.1 ml vs 80.9±22.5 ml, p<0.001) even after matching for body surface area; lower P wave dispersion (males 28.0(12)ms vs 25.0(12)ms, p=0.039; females 24.0(12)ms vs 22.0(12)ms, p=0.004) and P wave terminal force in lead V1 (males 0.031(0.04)mm•s vs 0.021(0.03) mm•s, p=0.023; females 0.036(0.04)mm•s vs 0.034(0.04)mm•s, p=0.030), electrophysiological variations related to the inhomogeneity of LA conduction and LA size respectively; increased heart rate (82.5(18)bpm vs 78.0(18)bpm, p=0.024), lower atrioventricular (280(50)ms vs 300(60)ms, p=0.001) and ventriculoatrial (300(60)ms vs 320(93)ms, p=0.013) effective refractory periods

and lower heart rate variability (in SA males), suggestive of sympathetic predominance.

Conclusions: SAs have reduced LA size and evidence of increased sympathetic tone and reduced inhomogeneity in LA conduction. The morphological, electrophysiological and autonomic differences identified in SAs may help to explain why this ethnic group has a lower prevalence of AF.

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Abbreviations

ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
AHRE	Atrial high rate episode
ANP	Atrial natriuretic peptide
ANS	Autonomic nervous system
APD	Action potential duration
ARB	Angiotensin II receptor blocker
AV	Atrioventricular
AVNRT	Atrioventricular nodal reentry tachycardia
AVW	Atrioventricular Wenckebach
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
BSA	Body surface area
CI	Confidence interval
CIED	Cardiac implantable electronic device
DC	Direct current
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ERP	Effective refractory period
GP	General practice
GWAS	Genome-wide association study
HDL	High-density lipoprotein
HF	High frequency
HR	Hazard ratio

Abbreviations

HRV	Heart rate variability
IQR	Interquartile range
LA	Left atrial
LAEF	Left atrial ejection fraction
LF	Low frequency
LGE	Late gadolinium enhancement
LV	Left ventricular
LV EDV	Left ventricular end-diastolic volume
LV EF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVSD	Left ventricular systolic dysfunction
LV SV	Left ventricular stroke volume
METS	Metabolic equivalents
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging
NHS	National Health Service
N-N	Normal-to-normal
NYHA	New York Heart Association
OR	Odds ratio
OSA	Obstructive sleep apnoea
PWTF-V_1	P-wave terminal force in lead V_1
RMSSD	Root mean square of the sum of the squares of differences between adjacent NN intervals
SA	South Asian
SD	Standard deviation

Abbreviations

SDNN	Standard deviation of all NN intervals
SDANN	Standard deviation of averages of NN intervals
SFT	Skinfold thickness
SNP	Single-nucleotide polymorphisms
SSFP	Steady state free procession
SVE	Supraventricular ectopy
SVT	Supraventricular tachycardia
TIA	Transient ischaemic attack
UK	United Kingdom
ULF	Ultra low frequency
USA	United States of America
VA	Ventriculoatrial
VLF	Very low frequency
WPW	Wolff-Parkinson-White

Chapter 1. Introduction

1.1 Atrial fibrillation

Atrial fibrillation (AF) is a supraventricular arrhythmia characterised by irregular, rapid and uncoordinated atrial depolarisations resulting in atrial mechanical dysfunction[1]. It is the commonest sustained cardiac arrhythmia[2] with an estimated prevalence of 3% in adults aged 20 years or older[3]. This figure is expected to rise further, potentially more than doubling over the next 50 years[4]. It is associated with a five-fold risk of stroke, a three-fold incidence of heart failure[5] and a 1.5- to 1.9-fold increase in mortality[6] as well as having a significant impact on patients' quality of life. As a consequence, AF has become a major public health burden with current estimates suggesting that it accounts for around 1% of the total National Health Service budget in the United Kingdom (UK)[7] and between $6-26 billion of annual healthcare expenditure in the United States of America (USA)[8].

Observational studies have repeatedly shown that the South Asian population has a low prevalence of AF in comparison to Caucasians[9-13]. This finding is particularly surprising since South Asians have a high burden of established cardiovascular risk factors for the arrhythmia. The underlying mechanisms that seemingly protect South Asians against the development of AF remain uncertain.

In the following sections, an overview of the pathophysiology, aetiology and epidemiology of AF is provided. A comprehensive review of the literature relating to AF and South Asians is subsequently performed and areas of further investigation are proposed.

1.2 Pathophysiology

The exact mechanisms responsible for the initiation and maintenance of AF, one of the most complex heart rhythm disorders, are yet to be fully determined although multiple theories have been proposed (figure 1). At the beginning of the 20th Century, AF was believed to be related to either circus movement re-entry[14], in which an impulse propagated around an anatomical or functional obstacle leading to re-excitation of the heart, or ectopic focus re-entry[15], involving rapidly discharging ectopic atrial foci.

By the mid-20th Century, the multiple wavelet hypothesis had been proposed[16]. This theory suggested that AF was perpetuated by continuous conduction of several independent wavelets randomly propagating through the atria in a seemingly chaotic manner. In order for fibrillatory conduction to persist, the theory stated that a critical number of re-entrant wavefronts had to be present within a vulnerable atrial substrate. This theory was supported by experimental evidence in a canine model of AF induced by infusion of acetylcysteine and rapid pacing[17]. It was shown that just four to six independent wavelets propagating simultaneously were required to sustain arrhythmia. These findings were reproduced in subsequent studies[18]. The development of the surgical maze procedure[19], in which the atrium is compartmentalised to prevent the propagation of multiple wavelet re-entrant circuits, provided further support for the multiple wavelet hypothesis by preventing AF.

More recently, it has become clear that the mechanisms underlying paroxysmal AF differ from persistent AF. It is now known that focal discharges from pulmonary veins are the main trigger for the initiation of paroxysmal AF[20]. This finding has led to pulmonary vein isolation becoming a first-line therapy in the treatment of paroxysmal AF. Although this technique is applied in patients with persistent AF, long-term success rates are significantly lower, highlighting the mechanistic

differences that exist[21]. It is currently believed that focal ectopic discharges initiate AF but multiple wavelet re-entry maintains the arrhythmia. Over time, due to abnormal atrial remodelling, episodes of AF can become increasingly frequent and prolonged until they no longer terminate spontaneously and the condition evolves from a paroxysmal to persistent form.

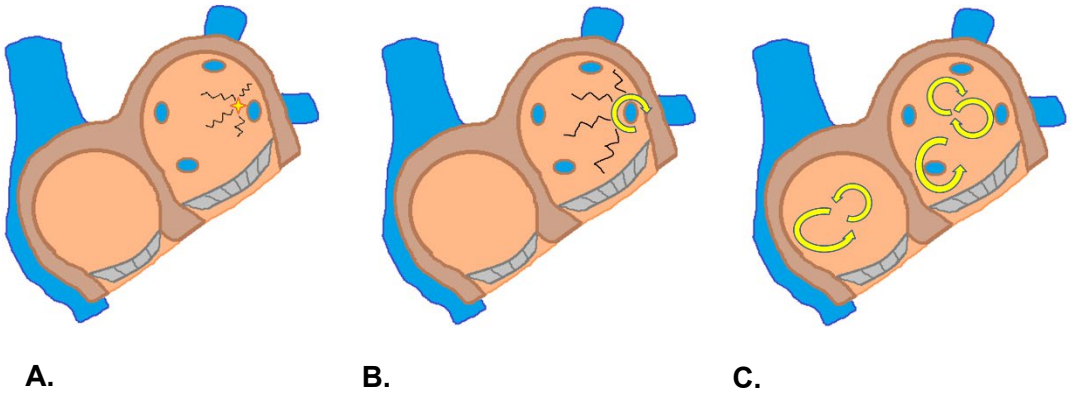

Figure 1. *Classical mechanisms for the initiation of atrial fibrillation[22].*

A. Ectopic focus; B. Single circuit re-entry; C. Multiple wavelet re-entry

1.2.1 Initiation of atrial fibrillation

Whilst the myocardial sleeves that surround the pulmonary veins are thought to be the primary source of ectopy triggering AF[20], other sites have been implicated including the superior vena cava, left atrial posterior free wall, crista terminalis, coronary sinus ostium, ligament of Marshall and interatrial septum[23]. The electrophysiological mechanism underlying the initiation of AF through ectopic triggers is not yet fully understood but it has been associated with enhanced automaticity[24] and triggered activity[25, 26] (figure 2).

Automaticity refers to the ability of cardiac cells to generate spontaneous action potentials. It is an intrinsic property of all myocardial cells but due to the natural hierarchy of pacemaker function, in normal cardiac conduction, spontaneous activity is usually restricted to pacemaker cells within the sino-atrial node. Normal

automaticity involves spontaneous diastolic depolarisation of the membrane potential, predominantly by the pacemaker current (I_f)[27], until a threshold potential is reached and an action potential is generated.

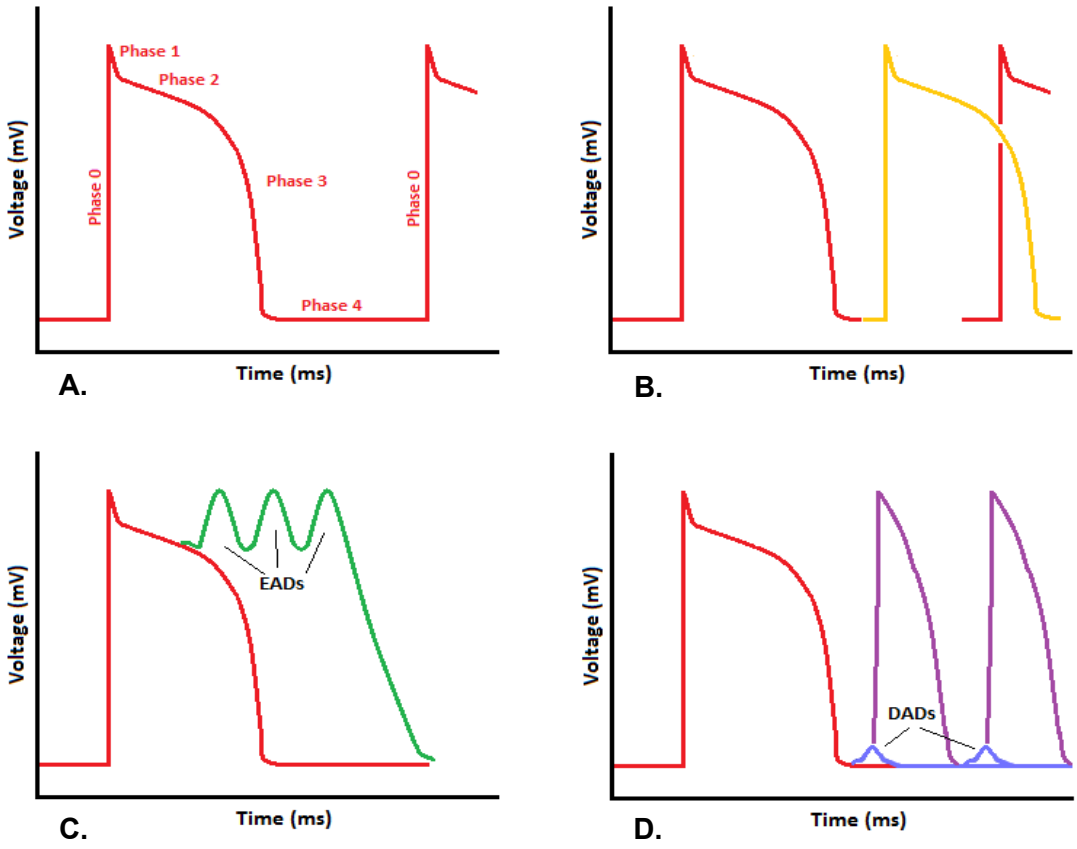

Figure 2. *Electrophysiological mechanisms underlying the initiation of atrial fibrillation in non-pacemaker atrial cells.*

A. Normal action potential; B. Enhanced automaticity;
C. Early afterdepolarisations; D. Delayed afterdepolarisations

Enhanced automaticity occurs if non-pacemaker atrial myocytes depolarise more rapidly (phase 4 of the action potential) than the sino-atrial node. This results in the formation of an atrial ectopic beat which overrides the sino-atrial node and can trigger AF[28]. The basic mechanism underlying enhanced automaticity relates to changes in the balance of ionic channels. Following repolarisation, the resting potential of atrial myocytes is maintained by high resting potassium permeability

through the inward rectifier potassium current (I_{K1})[29]. Although normal, non-pacemaker atrial cells also manifest I_f current, this is usually overwhelmed by the much larger I_{K1} and these cells do not manifest automaticity. However, enhanced automaticity can occur when there is a change in this balance, due to decreased I_{K1} and/or increased I_f [29].

Triggered activity results from the premature activation of myocytes by afterdepolarisations, membrane potential oscillations which follow the upstroke of an action potential. Early afterdepolarisations occur during the repolarisation phase of the cardiac action potential (phase 3). They are primarily a result of prolonged atrial cell action potential duration (APD) which allows L-type calcium currents (I_{CaL}) time to recover from inactivation. This leads to the inward movement of calcium ions, abnormally depolarising the membrane potential and, if the threshold potential is reached triggering ectopy[29].

Delayed afterdepolarisations occur following complete repolarisation (phase 4) of the action potential but prior to the next normal action potential. They are a consequence of intracellular calcium overload. This induces the abnormal release of calcium from the sarcoplasmic reticulum and leads to the activation of the transient inward current (I_{TI}) which regulates membrane depolarisation[30]. If the inward current produced by the delayed afterdepolarisation becomes large enough to reach threshold potential, an abnormal depolarisation occurs, triggering ectopy or tachycardia[28].

1.2.2 Maintenance of atrial fibrillation

Electrical and structural remodelling within atrial tissue plays a key role in the maintenance of AF and this is further enhanced through alterations in autonomic tone. AF is a self-perpetuating arrhythmia whereby an increase in its burden creates

suitable conditions for remodelling and this in turn facilitates more AF, a concept that has previously been termed *'AF begets AF'* [31].

Electrical remodelling alters ion channel expression and function and can occur within minutes of the onset of AF. Calcium enters atrial myocytes with every action potential and so during rapid atrial rates, like those seen in AF, excessive calcium loading can occur. To counteract this, autoprotective mechanisms are activated, leading to a downregulation in I_{CaL}, an increase in I_{K1} and a reduction in transient outward potassium currents (I_{to}) within atrial myocytes[31-35]. Although the overall effect of these changes is a reduction in calcium loading, there is also a shortening of the atrial cell APD. By reducing APD, atrial re-entry circuits are able to stabilise, increasing AF vulnerability and sustainability[36, 37].

Structural remodelling is a more gradual process characterised by atrial enlargement and tissue fibrosis. These changes are driven by sustained rapid atrial rates as well as volume and pressure changes within the atrium which occur as a result of left ventricular dysfunction or valvular disease. Atrial size has consistently been shown to be associated with AF. The Framingham Heart Study[38] showed that a 5mm increase in left atrial diameter increased the risk of AF by 39% whilst the Cardiovascular Health Study[39] showed that a left atrial diameter of more than 5cm was related to a 4-fold increase in the risk of AF. *Tsang et al* found that LA volume was an independent predictor of AF, that a 30% larger LA volume equated to a 43% greater risk of AF[40] and that a 5mm increase in LA dimension increased the risk of AF by 48%[41]. Mathematical models indicate that this may be due to increased local intra-atrial conduction block, creating smaller and more numerous re-entrant circuits which in turn, favour the persistence of AF[42].

Atrial fibrosis disrupts the propagation of electrical impulses through the atria, leading to inhomogeneity in atrial conduction. This can promote re-entry and ectopic

activity, thereby creating substrate for AF. Fibrosis occurs both as a result of atrial enlargement and as a consequence of rapid atrial rates through the upregulation and expression of pro-fibrotic factors such as transforming growth factor beta-1 and angiotensin-II and through the stimulation of oxidative stress and inflammation[43]. This inflammation can then lead to the over-expression of matrix metalloproteinases, substances involved in extracellular matrix homeostasis, which in turn increase collagen concentration within the myocardium and stimulate connective tissue synthesis[43].

The autonomic nervous system heavily influences heart rate, atrioventricular nodal conduction velocity and cardiac contractility through a complex interaction between sympathetic and parasympathetic innervation. Paroxysmal AF is commonly preceded by an increase in parasympathetic activity, particularly in those without structural heart disease[44]. Vagal stimulation causes heterogeneous shortening of atrial APD and atrial ERP through the activation of acetylcholine-dependent potassium channels (I_{KACh}) and suppression of I_{CaL}, stabilising re-entrant circuits and increasing AF vulnerability[45-47]. Increased sympathetic activity has also been linked to the development of AF through its effects on atrial refractoriness and increasing atrial automaticity although this appears to be primarily in patients with underlying structural heart disease[48-51].

1.3 Aetiology

Atrial fibrillation occurring in the apparent absence of structural or valvular heart disease has previously been termed idiopathic or lone AF[52]. They are terms which have become outdated and increasingly avoided as the understanding of the aetiology of AF improves[53]. There is evidence to suggest that many cases of *"lone AF"* are in fact related to either underlying inflammatory changes within the atria[54] or genetic mutations in transcription factors specifically involved in atrial

development[55, 56]. The vast majority of AF cases occur as a consequence of atrial remodelling caused by structural heart disease or a known cardiovascular risk factor.

1.3.1 Hypertension

Hypertension is the most prevalent, independent and potentially modifiable risk factor for AF[57]. Two mechanisms have been proposed to explain this. Firstly, uncontrolled hypertension triggers the development of left ventricular hypertrophy (LVH). Abnormal thickening of the myocardium increases ventricular stiffness, leading to elevated left ventricular diastolic filling pressures and, in turn, increased left atrial pressure, atrial stretch and atrial fibrosis[57]. Secondly, hypertension causes alterations in atrial electrophysiology. Studies involving animal and human models have found that a chronic elevation in blood pressure prolongs atrial conduction velocity and reduces atrial ERP[58-60], factors which promote re-entry and can trigger AF.

Hypertension is present in around half of all patients with AF[61] and, after adjustment for other risk factors, it has been shown to be associated with a 1.5-fold and 1.4-fold risk of AF for men and women respectively[62].

1.3.2 Diabetes mellitus

Diabetes mellitus was first shown to be an independent risk factor for in AF in the Framingham study with an odds ratio of 1.4 in males and 1.6 in females[63]. More recently, a large registry study with 845,748 patients found that AF occurred in 14.9% of diabetic patients versus 10.3% of control patients ($p<0.001$) and showed that it was associated 2.13-fold risk of AF[64].

Diabetes mellitus has been shown to increase left ventricular mass and wall thickness, reduce left ventricular function and increase arterial stiffness[65]. The

cumulative effects of these structural changes are an increase in left atrial pressure, left atrial enlargement and atrial fibrosis, all of which favour the development of AF.

1.3.3 Coronary artery disease

Acute myocardial infarction (MI) is an established risk factor for AF with one systematic review reporting an AF incidence rate of between 6 and 21% in patients suffering acute MI[66]. Additionally, patients who have a transient episode of AF during acute MI have a recurrence rate of around 20% at one year[67]. Atrial ischaemia and infarction are the dominant pathophysiological factors in the development of AF but left ventricular infarction and the resultant ventricular dysfunction, raised left atrial pressures and atrial stretch, also play a role.

In patients with established coronary artery disease, the long-term risk of AF is also higher. One study which followed-up air force pilots over a 44-year period found that those with a prior history of MI had a 3.62-fold risk of AF whilst those with a diagnosis of angina had a 2.84-fold risk of the arrhythmia[61]. In a large cross-sectional study of 15,406 individuals living in Scotland, myocardial ischaemia was associated with 4.5-fold risk of incident AF[68]. Once again, the mechanism underlying this is likely to be related to chronic atrial ischaemia[69].

1.3.4 Congestive heart failure

A close and complex relationship exists between AF and congestive heart failure. Indeed, at times, it can be a diagnostic challenge to determine which is cause and which is effect. More than half of all patients with a new diagnosis of heart failure have co-existent AF and over a third of patients with new-onset AF are found to have congestive heart failure[70]. In patients with heart failure, the prevalence of AF is closely correlated with the severity of the disease. Patients with New York Heart Association (NYHA) functional class I symptoms have an AF prevalence of less

than 5%, those with NYHA class II or III symptoms have an AF prevalence of around 25% whilst patients with NYHA class IV symptoms have an AF prevalence of almost 50%[71].

Though the pathophysiological mechanisms are not fully understood, the two conditions certainly share a number of common risk factors such as hypertension, diabetes mellitus, coronary artery disease and age and it is likely that each condition predisposes the heart to the development of the other. For instance, heart failure increases left ventricular end-diastolic pressure which in turn increases left atrial pressure. This leads to atrial enlargement and fibrosis, thereby creating an environment capable of sustaining AF[71]. Conversely, AF causes atrioventricular dyssynchrony and a loss of atrial contraction which can lead to impaired diastolic filling, reduced stroke volume and around a 20% reduction in cardiac output[72]. Additionally, an uncontrolled rapid ventricular rate which can accompany AF can lead to a phenomenon known as tachycardia-induced cardiomyopathy. This occurs when rapid ventricular rates result in elevated left ventricular filling pressures, decreased contractility and reduced cardiac output, eventually leading to left ventricular dilatation and heart failure[73, 74]. The mechanisms underlying this are not fully defined but are believed to be related to abnormal calcium handling, abnormalities in energy metabolism and subclinical ischaemia[75, 76].

1.3.5 Valvular heart disease

Valvular heart disease has been associated with a 1.8-fold and 3.4-fold increased risk of AF in males and females respectively[63]. Although any form of valvular heart disease can be related to AF, stenotic left-sided valvular lesions, and particularly those related to rheumatic fever, have the highest prevalence rates[77]. In a similar way to heart failure, the prevalence of AF correlates with the severity of the valvular

obstruction. AF prevalence is 9.1% in patients with mild or moderate aortic stenosis[78], rising to 33.7% in those with severe aortic stenosis[79].

Valvular heart disease promotes AF via structural remodelling. Increased atrial pressure or volume loading as a consequence of a stenotic or regurgitant valve causes atrial enlargement and interstitial fibrosis, providing substrate for the development of AF[80].

1.3.6 Obesity

Obesity is an independent risk factor for AF[81] and it is currently the second highest population-attributable risk for the arrhythmia behind hypertension[82]. In the Framingham study, for every one unit increase in body mass index (BMI), the risk of AF increased by 4%[81]. Dynamic changes in weight can also influence AF risk. The Women's Health Study showed that moving from one weight category to the next (normal weight [BMI <25kg/m^2], overweight [BMI 25-29.99kg/m^2], obese [≥30kg/m^2]) increased or decreased the risk of AF in line with the direction of movement[83]. Furthermore, the risk of progression from paroxysmal to persistent AF has been shown to increase as the severity of obesity increases (HR 1.54 for BMI 30-34kg/m^2 and 1.87 for BMI ≥35kg/m^2)[84].

Obesity promotes left ventricular diastolic dysfunction and end-diastolic pressure as a consequence of myocardial fatty infiltration[85]. These alterations in cardiac function in turn, increase left ventricular mass, left atrial pressure and left atrial volume resulting in AF susceptibility[86]. Additionally, obesity causes inflammatory infiltrates and atrial interstitial fibrosis with the effect of slowing atrial conduction and increasing conduction heterogeneity[86].

1.3.7 Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is closely related to obesity with more than 40% of obese individuals having the condition[87]. Despite this, the relationship between OSA and AF has been shown to be independent of obesity[88]. One study has found that the risk of AF in patients with severe OSA is up to four times higher than those without OSA[89]. The presence of OSA also increases the risk of AF recurrence following catheter ablation by 25%[90] and cardioversion by 29%[91].

It remains a matter of debate as to whether OSA is a direct cause of AF or whether it simply reflects a shared risk factor profile, particularly in relation to obesity. However, an animal model has shown that the strongly negative intrathoracic pressures which occur during OSA increase venous return and enhance left atrial volume loading, leading to acute left atrial stretch and increased AF inducibility[92]. Interestingly, in this study, AF inducibility was not enhanced in obese or lean rats in the absence of OSA[92].

1.3.8 Thyroid dysfunction

Hyperthyroidism is an established risk factor for AF and those with the condition have a 3- to 6-fold increased incidence of AF compared with those with normal thyroid function[77]. Several mechanisms have been proposed to explain this. Hyperthyroidism causes autonomic imbalance with an increase in sympathetic tone[93]. This increases heart rate and cardiac inotropy which can cause subclinical ischaemia and over time lead to diastolic dysfunction, increased left ventricular mass and elevated left atrial pressure[94-96]. Additionally, higher sympathetic tone can enhance AF vulnerability by reducing atrial refractoriness and increasing automaticity and triggered activity[51, 97-99].

1.3.9 Anthropometry

Lean body mass, the difference between total body weight and body fat weight, has recently been shown to be the predominant anthropometric risk factor associated with the occurrence of AF[100]. A population-based study of 55,273 individuals found that lean body mass was associated with 37% increased risk of AF whilst other anthropometric measures such as fat mass, BMI and waist-to-hip ratio did not remain significant after adjustment for lean body mass. Lean body mass, which includes organ cell mass and non-fatty tissues such as muscles, bones and connective tissue, is responsible for almost all metabolic activity within the body and governs total oxygen demand; this in turn determines the required cardiac output and stroke volume[101]. Increased stroke volume as a result of lean body mass can lead to the development of LVH[101] and elevated left ventricular end-diastolic pressure which in turn, increases left atrial pressure and volume load, causing left atrial enlargement and wall stress[101], conditions which provide favourable substrate for AF development.

Height is closely related to left atrial volume[102] and so it is perhaps not surprising that height has been shown to be independently associated with the development of AF in multiple studies[103, 104]. Indeed the risk of AF increases by 35-65% for every 10cm difference in height[104]. However, one study has also found that the impact of height on the risk of AF is independent of atrial size[103]. The reason for this is uncertain but it has been speculated that the height-mediated increased AF risk may relate the genetic variations; recent genome-wide association studies have identified two genes, PITX2 and SFHX3, which are associated with growth pathways and an increased risk of AF[105, 106].

1.3.10 Alcohol

Excessive alcohol consumption (≥36g/day or approximately >3 drinks/day) is an established cause of AF with an adjusted hazard ratio ranging between 1.34 and 1.46[107, 108]. There is emerging evidence that even moderate levels of alcohol consumption (1-3 drinks/day) can increase the risk of AF by up to 14%[109].

A number of mechanisms have been postulated to explain the effects of alcohol on AF risk. Alcohol causes autonomic imbalance with an initial increase in sympathetic activity, followed by a compensatory rise in vagal tone. Sympathetic activity stimulates automaticity and triggered activity whilst vagal stimulation reduces atrial ERP and APD non-uniformly, facilitating re-entry[51, 110, 111]. Alcohol can also affect traditional risk factors for AF. For instance, chronic alcohol abuse is associated with hypertension[112], obesity[113], OSA[114] and cardiomyopathy[115]. Overall, it is likely that alcohol increases the risk of AF through a combination of direct effects on the atrial substrate and by contributing to other AF-related risk factors.

1.3.11 Physical activity

The association between exercise and the risk of AF follows a J-shaped curve with increasing physical activity modestly reducing the risk of AF but extreme exercise, such as that performed by endurance athletes, increasing the risk of AF significantly. The Cardiovascular Health Study found that those with the highest self-reported physical activity had a 46% reduction in AF risk[116] and these findings were reinforced by large population-based studies of Swedish men and women which showed that daily exercise lowered the risk of AF by 13% in men and 19% in women[117, 118]. In contrast, a meta-analysis examining the arrhythmia in athletes found that intense physical exercise was associated with a five-fold increase in the risk of AF[119].

Exercise generally has a positive influence on risk factors such as hypertension, glycaemic control and body weight and has been shown to slow the age-related decline in arterial elasticity and associated cardiovascular disease. However, at high levels, exercise can lead to morphological changes such as left atrial enlargement and LVH, the development of atrial fibrosis and increased vagal tone, all of which favour AF[120].

1.3.12 Genetics

In recent years, studies have suggested a probable link between genetics and the development of AF. Those examining familial AF have found that mutations within genes encoding potassium and sodium ion channels play an important role in the development of the condition (Table 1)[121]. The first gene that was linked to familial AF was KCNQ1 which is required for the expression of the slowly activating delayed rectifier potassium channel (I_{Ks})[122]. A gain-of-function mutation in this gene was shown to increase I_{Ks} and reduce atrial APD and ERP, creating a substrate for AF[122, 123]. Since then gain-of-function mutations in KCNH2, KCND3 and KCNJ2 which are responsible for the expression of the rapidly activating delayed rectifier potassium channel (I_{Kr}), I_{to}, and I_{K1} respectively, have been linked to the development of AF[124-126]. Mutations in genes responsible for voltage-gated sodium channels have also been seen. A combination of gain-of function and loss-of-function mutations in the SCN5A and SCN10A genes (responsible for the expression of $Na_v1.5$ and Na_v 1.8 sodium channels respectively) have been shown to prolong atrial APD and promote early after-depolarisations, increasing AF vulnerability[127-129].

Mutations which have been linked to AF can also occur in genes unrelated to ion channels. GJA5 encodes connexin-40, a gap junction protein which is responsible for the rapid conduction of action potentials between cardiomyocytes.

Mutations of this GJA5 may predispose to AF by prolonging atrial APD and promoting re-entry circuits[130]. Another gene, NPPA, encodes a precursor for atrial natriuretic peptide (ANP). Mutations within this gene produce a variant of ANP which is resistant to degradation[131]. Increased ANP levels subsequently shorten atrial ERP and APD[132] and over time may promote atrial remodelling and dilatation[133], changes which provide substrate for the development of AF.

Table 1. Potassium and sodium channel mutations linked to atrial fibrillation

Potassium channel mutations

Gene	Locus	Product	Ion channel	Type	Mechanism
KCNQ1	11P15.5-P15.4	α-subunit of voltage-gated potassium channel Kv7.1	I_{Ks}	Gain-of-function	↓ atrial ERP and APD
KCNH2	7q36.1	α-subunit of voltage-gated potassium channel Kv11.1	I_{Kr}	Gain-of-function	↓ atrial APD
KCND3	1p13.2	α-subunit of voltage-gated potassium channel Kv4.3	I_{to}	Gain-of-function	Unknown
KCNJ2	17q24.3	α-subunit of voltage-gated potassium channel Kir2.1	I_{K1}	Gain-of-function	↓ atrial APD

Sodium channel mutations

Gene	Locus	Product	Function	Type	Mechanism
SCN5A	3p22.2	α-subunit of Nav1.5	I_{Na}	Gain-of-function Loss-of-function	↑ atrial APD ↑ EADs
SCN10A	3p22.2	α-subunit of Nav1.8	I_{Na-L}	Gain-of-function Loss-of-function	↑ atrial APD ↑ EADs

Abbreviations: *ERP, effective refractory period; APD, action potential duration; EADs, Early afterdepolarisations*

A genome-wide association study (GWAS) is a novel approach whereby complete sets of DNA are examined in individuals with the same condition in an attempt to find genetic similarities. Over the last decade, these studies have

identified 27 genetic loci containing 29 single-nucleotide polymorphisms (SNPs) which have a modest association with AF[121, 123].

The first of these studies was performed on an Icelandic population in 2006 and the SNP which was associated most strongly with the development of AF was rs2200733T at the chromosome 4q25 locus[105]. Within the same study, this same SNP was closely related to cases of AF within a Han-Chinese population from Hong Kong. Studies have since shown a similar relationship in African-Americans[134], Japanese[135] and other European cohorts[136].

1.4 Epidemiology

The burden of AF varies with age, gender, geographical region and ethnicity but overall estimates suggest that it currently affects around 33.5 million individuals worldwide[12].

1.4.1 Age

The risk of developing AF is associated with increasing age. It is rare in children or healthy, young adults in the absence of structural heart disease. The prevalence of AF ranges from 0.1% in individuals below 55 years, 3.8% in individuals aged more than 60 and 10% in individuals above the age of 80[4]. A literature review which is summarised in table 2 highlights the effect of age on the prevalence of AF.

In the coming years, as a consequence of population ageing, the prevalence of AF is expected to increase further. In Europe, AF is projected to increase from a current estimated prevalence of 8.8 million to around 18 million by 2060[137] whilst in the USA, the prevalence of AF is expected to more than double from 5.2 million to around 12.1 million by 2030[138].

The incidence of AF also increases with advancing age. An observational study which followed up 3,983 healthy subjects over a 40 year period demonstrated an AF incidence of 0.5 per 1,000 person-years before the age of 50, rising to 9.7 per 1,000 person-years after the age of 70[61]. Estimates for the lifetime risk of AF are predominantly derived from developed countries in the Western world[139, 140]. Since the incidence of AF increases rapidly with each decade, the lifetime risk does not change significantly with increasing index age. Hence, individuals aged 40 have a lifetime risk of AF of around 25% whilst those aged 80 have a risk of around 22%.

Age increases the risk of AF through a combination of structural, electrophysiological and molecular changes as a result of aging itself and as a consequence of age-related comorbidities such as hypertension, diabetes mellitus, coronary artery disease and heart failure[141]. Left atrial size, a structural change which favours the perpetuation of AF, and atrial fibrosis both increase with age[142, 143]. These structural changes lead to inhomogeneity in atrial conduction, promoting re-entry and increasing AF vulnerability. Aging is associated with atrial APD prolongation and with an increase in spontaneous diastolic calcium release from the sarcoplasmic reticulum, changes that favour the development of afterdepolarisations and ectopic activity[141, 144]. There is also evidence indicating that atrial conduction disturbances may relate to alterations in membrane protein expression. Animal studies have found an association between increasing age and a downregulation of connexin-43[145]. A reduction in connexin-43 has, in turn, been shown to promote re-entry and AF in aging human hearts[146].

1.4.2 Gender

The prevalence of AF is significantly higher in men, regardless of age. Table 2 summarises previous epidemiological studies examining the effects of gender on the prevalence of AF. In a large observational study of North American adults aged

20 years and above, the prevalence of AF was 1.1% in men and 0.8% in women ($p<0.001$)[4] whilst in a study of European adults aged 20 years and above, the prevalence of AF was even higher, affecting 3.3% of men and 2.5% of women ($p<0.001$)[147].

The incidence of AF is also higher in men at all age groups[12, 139, 140]. After adjustment for age and other risk factors, AF in men has been shown to develop at a rate 1.5 times that of women[63]. In 2010, the worldwide estimated incidence rate of AF was 77.5 per 100,000 person-years in men and 59.5 per 100,000 person-years in women. Applying these estimated incidence rates to a world population would therefore suggest that the annual number of new AF cases is 2.7 million for men and 2.0 million for women.

Table 2. Literature review of AF prevalence and incidence based on gender and age

Author (year)	Study location	Study design	Participants	Age range (years)	Prevalence			Incidence		Prevalence (age range)
					Men (%)	Women (%)	Total (%)	Men (/1000 person-years)	Women (/1000 person-years)	
Go et al.[4] (2001)	USA		1,890,000	≥20	1.1	0.8	0.95	-	-	<55 years: 0.1% >80 years: 9.0%
Kannel et al.[62] (1998)	USA		4,731	65-84	9.1	4.7	6.9	-	-	<59 years: 0.5% >80 years: 9.0%
Furberg et al.[148] (1994)	USA		5,201	≥65	6.2	4.8	5.5	-	-	-
Wolf et al.[149] (1991)	USA		5,070	>50	-	-	4.0	-	-	-
Murphy et al.[150] (2007)	UK	Retrospective cohort study	362,155	≥18	0.9	0.8	0.9	0.9	0.8	<65 years: 0.3% >75 years: 7.5%
DeWilde et al.[151] (2006)	UK	Retrospective cohort study	1,000,000	All ages	1.3	1.1	-	-	-	-
Majeed et al.[152] (2001)	UK	Retrospective cohort study	1,400,000	≥20	1.2	1.3	1.2	-	-	<65 years: 0.3% >85 years: 10.8%
Stewart et al.[68] (2001)	UK		15,406	45-64	0.8	0.5	0.65	0.9	0.25	-
Sudlow et al.[153] (1998)	UK	Prospective cohort study	4,843	≥65	6.7	4.0	4.7	-	-	-
Friberg et al.[147] (2013)	Sweden	Retrospective cohort study	7,200,000	20	3.3	2.5	2.9	-	-	<60 years: 0.6% >80 years:11.2%

Table 2. Literature review of AF prevalence and incidence based on gender and age (*continued*)

Author (year)	Study location	Study design	Participants	Age range (years)	Prevalence			Incidence		Prevalence (age range)
					Men (%)	Women (%)	Total (%)	Men (/1000 person-years)	Women (/1000 person-years)	
Wilke et al.[154] (2013)	Germany	Retrospective cohort study	8,298,000	0-90	2.4	1.9	2.1	4.4	3.9	<60 years: 0.3% >80 years: 13.8%
Guize et al.[155] (2007)	France	Retrospective cohort study	154,070	≥30	0.23	0.11	0.19	-	-	-
Heeringa et al.[140] (2006)	Netherlands	Prospective cohort study	6,808	≥55	6.0	5.1	5.5	11.5	8.9	<60 years:0.7% >80 years: 15.4%
Lake et al.[156] (1989)	Australia		1,765	>60	5.6	4.2	4.9	-	-	-
Friberg et al.[157] (2003)	Denmark	Prospective cohort study	8,606	50-89	3.3	1.1	-	-	-	-
Chien et al.[158] (2010)	China	Prospective cohort study	3,560	≥35	1.4	0.7	1.1	1.68	0.76	-
Inoue et al.[159] (2009)	Japan	Retrospective cohort study	630,138	≥40	1.35	0.43	0.56	-	-	-
Zhou et al.[160] (2008)	China		29,079	≥30	0.91	0.65	0.77	-	-	-
Ohsawa et al.[161] (2007)	Japan	Prospective cohort study	9,483	≥30	0.65	0.62	0.64	-	-	-
Jeong et al.[162] (2005)	Korea	Retrospective cohort study	14,450	≥40	1.2	0.4	0.7	-	-	-
Saggu et al.[163] (2016)	India	Prospective cohort study	4,077	≥18	0.13	0.27	0.2	-	-	-

1.4.3 Geographical area

The vast majority of studies examining the prevalence of AF come from Western Europe and North America (table 2). A systematic review of 184 epidemiological studies showed that the highest prevalence rates of AF were estimated in North America, affecting 925.7/100,000 population in men and 520.8/100,000 population in women[12]. In Sub-Saharan Africa, the prevalence of AF was 659.8/100,000 population in men and 438.1/100,000 population in women whilst the Asia-Pacific region had the lowest prevalence rates, affecting 340.2/100,000 population in men and 196.0/100,000 population in women.

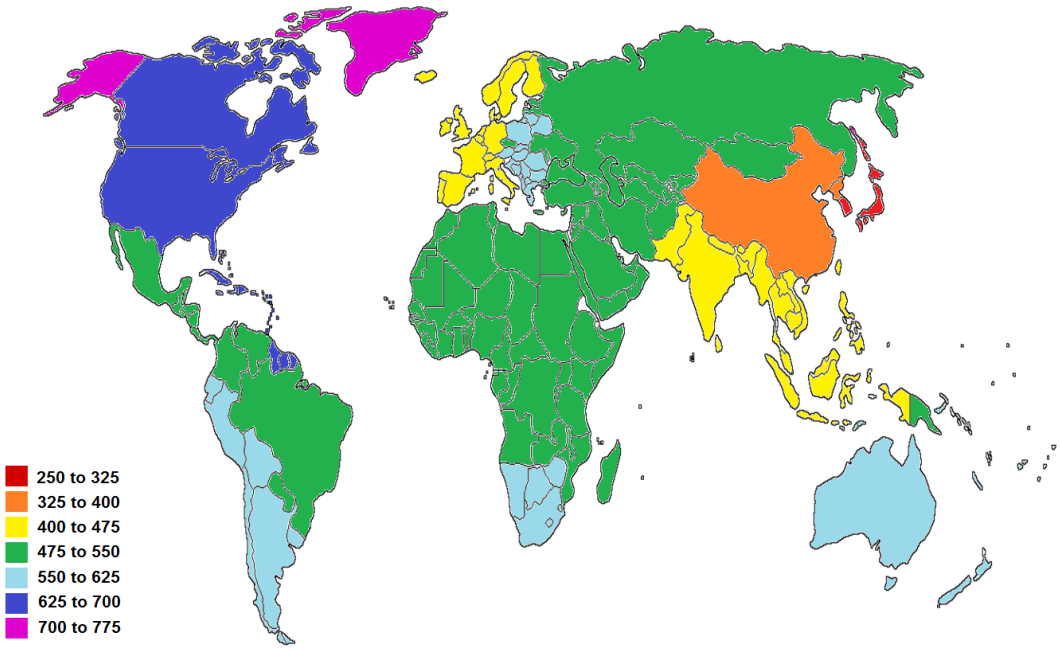

Figure 3. *Worldwide age-adjusted prevalence rates of atrial fibrillation (per 100,000 population)[12]*

The incidence of AF followed a similar geographical pattern. North America had the highest estimated incidence with rates of 264.5/100,000 person-years in men and 196.3/100,000 person-years in women. Sub-Saharan Africa was estimated to have an incidence rate of 58.4/100,000 person-years in men and 42.7/100,000 person-

years in women whilst the Asia-Pacific region were estimated to have the lowest incidence of AF with rates of 33.8/100,000 person-years in men and 19.8/100,000 person-years in women. Overall, there was a two-fold higher incidence rate in developed countries compared with developing countries and incidence significantly increased with age in all geographical areas.

1.4.4 Ethnicity

Epidemiological studies have shown that the prevalence of AF within different ethnic populations varies significantly. A summary of these studies is found in table 3.

1.4.4.1 African-American/Black population

The majority of trials examining the influence of ethnicity on AF originate from North America and primarily look at the burden of AF in Caucasians and African-Americans. Despite African-Americans having a higher prevalence of conventional risk factors for AF[164-166] as well as a higher incidence of stroke[164], they have a signficantly lower prevalence of AF compared with Caucasians. For instance, a cross-sectional study of 1.89 million adults over the aged of 20 demonstrated an AF prevalence of 2.2% in Whites and 1.5% in Blacks ($p<0.001$)[4] whilst in another study with 430,317 adults over the age of 60, the prevalence of AF was 8.0% in Whites and 3.8% in Blacks[167]. A lower rate of AF has also been noted in black patients with heart failure (38.3% in Whites vs. 19.7% in Blacks, $p<0.001$)[168] and following cardiac surgery (35% in Whites vs. 22% in Blacks, $p<0.001$)[169].

The reason for this is uncertain although some theories have been proposed. It was previously thought that the reduced prevalence of AF in African-Americans was in fact caused by under-detection of the arrhythmia due to African-Americans having less access to healthcare[170] and being more likely to suffer from paroxysmal AF[171]. However, a recent study which involved the interrogation of pacemakers in African-Americans and white-Americans found that during 3.7 (±1.8) years of follow-up,

rates of AF were consistently lower in African-Americans[172]. This would seem to indicate that potential underreporting of AF does not account for the disparity between the two ethnic groups.

The black population appears to have smaller atria in comparison to Caucasians[173, 174] with one study showing that in multivariate analyses, left atrial (LA) dimension in black males was 1.9mm less than in white males[173]. Genetics may also play a role. A study by Marcus et al[175] showed that the African-American risk of developing AF increased with increasing levels of European ancestry whilst Roberts et al[176] identified an SNP, rs10824026 on chromosome 10q22, which was significantly more common among African-Americans than Caucasians and is known to be protective against AF. It is therefore possible that the variation in AF prevalence between African-Americans and Caucasians is a consequence of both environmental and genetic factors.

Table 3. Literature review of AF prevalence based on ethnicity

Author (year)	Study location	Study design	Participants	Age range (years)	Prevalence based on ethnicity					
					White (%)	Black (%)	South Asian (%)	East Asian (%)	Asian (%)	Hispanic (%)
Rader et al.[169] (2011)	USA	Retrospective cohort study of cardiac surgery patients	23,524	62.5 (mean)	35	22	-	-	-	-
Shen et al.[167] (2010)	USA	Cross-sectional study	430,317	≥60	8.0	3.8	-	-	3.6	3.9
Marcus et al.[174] (2010)	USA	Meta-analysis of 3 cohorts	6,611	74.0 (mean)	5	1	-	-	-	-
Haywood et al.[177] (2009)	USA	Prospective cohort study	39,056	-	1.34	0.59	-	-	-	-
Borzecki et al.[178] (2008)	USA	Health survey	664,754	-	5.7	3.4	-	-	3.6	3.0
Khairallah et al.[179] (2004)	USA	Retrospective study of AF-related hospital admissions	2,018,578	71.1 (mean)	71.5	5.6	-	-	-	-
Ruo et al.[168] (2004)	USA	Retrospective study of heart failure admissions	1,373	73.0 (mean)	38.3	19.7	-	-	-	-
Upshaw et al.[180] (2002)	USA	Retrospective cohort study	2,123	20-99	7.8	2.5	-	-	-	-
Go et al.[4] (2001)	USA	Cross-sectional study	1,890,000	>20	2.2	1.5	-	-	-	-
Sacco et al.[181] (2001)	USA	Prospective study of stroke patients	1,844	70.0 (mean)	8	5	-	-	-	4
Gillott et al[13] (2017)	UK	Cross-sectional study	417,575	≥18	2.43	-	0.46	-	-	-
Mathur et al.[182] (2013)	UK	Cross-sectional study	6,292	≥18	1.2	0.4	0.2	-	-	-
Gunarathne et al.[183] (2008)	UK	Retrospective study of stroke admission	3,083	74.7 (mean)	34.8	9.0	11.8	-	-	-
Markus et al.[184] (2007)	UK	Prospective study of stroke admissions	1,200	69.2 (mean)	32.4	11.2	-	-	-	-
Newton et al.[10] (2005)	UK	Retrospective study of heart failure admissions	528	69.0 (mean)	31	-	15	-	-	-
Conway et al.[9] (2003)	UK	Retrospective study of stroke admissions	832	74.0 (mean)	13	3	1	-	-	-

Table 3. Literature review of AF prevalence based on ethnicity (*continued*)

Author (year)	Study location	Study design	Participants	Age range (years)	Prevalence based on ethnicity					
					White (%)	Black (%)	South Asian (%)	East Asian (%)	Asian (%)	Hispanic (%)
Saggu et al.[163] (2016)	India	Prospective cohort study	4,077	≥18	-	-	0.2	-	-	-
Hingorani et al.[185] (2012)	India	Retrospective cohort study	3,978	18-76	-	-	0.03	-	-	-
Kaushal et al.[186] (1995)	Nepal	Prospective cohort study	984	≥18	-	-	0.1	-	-	-
Chen et al.[187] (2011)	China	Cross-sectional study	9,309	>20	-	-	-	0.9	-	-
Long et al.[188] (2011)	China	Cross-sectional study	20,430	≥50	-	-	-	0.8	-	-
Chien et al.[158] (2010)	China	Prospective cohort study	3,560	≥35	-	-	-	1.1	-	-
Zhou et al.[160] (2008)	China	Cross-sectional study	29,079	30-85	-	-	-	0.77	-	-
Yap et al.[189] (2007)	Singapore	Population-based study of Chinese residents	1,839	≥55	-	-	-	1.5	-	-
Inoue et al.[159] (2009)	Japan	Retrospective cohort study	630,138	≥40	-	-	-	0.56	-	-
Iguchi et al.[190] (2008)	Japan	Retrospective cohort study	41,436	72.1 (mean)	-	-	-	1.6	-	-
Ohsawa et al.[161] (2007)	Japan	Prospective cohort study	9,483	≥30	-	-	-	0.64	-	-
Lee et al.[191] (2008)	Korea	Retrospective cohort study	10,012	40-69	-	-	-	0.4	-	-
Jeong et al.[162] (2005)	Korea	Retrospective cohort study	14,450	≥40	-	-	-	0.7	-	-
Lim et al.[192] (2016)	Malaysia	Cross-sectional study	10,805	52.6 (mean)	-	-	-	0.54	-	-
Kiatchoosakun et al.[193] (1999)	Thailand	Health survey	8,791	-	-	-	-	0.36	-	-
Dewhurst et al.[194] (2012)	Tanzania	Cross-sectional study	2,232	≥70	-	0.67	-	-	-	-
Connor et al.[195] (2005)	South Africa	Multicentre observational study	9,731	50.7 (mean)	5	2	-	-	2	-

1.4.4.2 Other ethnicities

Outside of the Western World, the majority of data originate from East Asia. There are a number of population-based studies from China which demonstrate an AF prevalence of between 0.77% and 1.1%[158, 160, 187, 188]. In Japan, the AF prevalence rate ranges between 0.56% and 1.6%[159, 161, 190] whilst in Korea AF rates have been shown to be between 0.4 and 0.7%[162, 191]. Single cross-sectional studies in Malaysia and Thailand have revealed an AF prevalence of 0.54 and 0.36%[192, 193].

Elsewhere, an observational study of elderly Tanzanians (above 70 years of age) found an AF prevalence of just 0.67%[194]. And a multicentre study in South Africa demonstrated a 2% prevalence of AF in Black-Africans and Asians compared with a 5% AF prevalence in White-Africans[195].

Compared with an AF prevalence of around 3% that is seen in Caucasian populations living in North America and Europe[3], these findings indicate a significantly lower prevalence of AF in East Asian and Black populations.

1.5 South Asian population and atrial fibrillation

The South Asian population is a diverse ethnic group which comprises more than a fifth of the world's population and originates from the Indian sub-continent, incorporating the countries of India, Pakistan, Bangladesh, Sri Lanka, Nepal and Bhutan. This ethnic group is consistently shown to have a high prevalence of established risk factors for the development of AF but despite this risk profile, they too have been shown to have lower rates of AF[9-11, 13].

1.5.1 Risk factors for atrial fibrillation in South Asians

The most notable risk factor disparity in South Asians is found in the occurrence of diabetes mellitus and impaired glucose tolerance. A study assessing the national

burden of cardiovascular disease in the UK found a two-fold higher prevalence of diabetes mellitus in South Asian men (8.5% vs. 4.3%) and women (6.6 vs 3.4%) compared with the general population[196]. Similar results were noted in a Canadian population with a prevalence of 8.1% in South Asians versus 4.2% in Whites (P<0.001)[197]. Related conditions of metabolic syndrome (a combination of impaired glucose homeostasis, insulin resistance, abdominal obesity, hypertension, reduced HDL-cholesterol and elevated triglycerides) and obesity are also significantly higher in South Asians. A large multi-ethnic population-based study found that the prevalence of the metabolic syndrome was 46.3% in South Asian men (vs. 18.8% in European men, p<0.0001) and 30.8% in South Asian women (vs. 9.1% in European women, p<0.0001)[198]. The definition of obesity varies depending upon the anthropometric measure used (BMI, waist:hip ratio, body fat percentage). Most studies show that in comparison to Caucasians, South Asians have a similar or lower BMI and yet interestingly, the same studies demonstrate higher levels of visceral fat and higher body fat percentage[199, 200]. For instance, in a cross-sectional analysis of two multi-ethnic studies, BMI was 25.8 in South Asians and 27.8 in Caucasians (P<0.001) and yet South Asians had higher levels of hepatic and intermuscular fat and lower lean body mass[199]. South Asians are also more susceptible to OSA. In a study of patients attending a weight loss service in the UK, the prevalence of OSA was 85% in South Asians versus 66% in White Europeans (p= 0.017) and South Asians were more likely to have severe OSA (42.5% vs. 21.6%, p= 0.015).

Hypertension appears to be more prevalent in South Asians. A Canadian population-based study comparing South Asians with Caucasians demonstrated a prevalence of 17.0% and 13.7% respectively (p<0.001)[197]. More specifically, there is evidence that South Asians have higher resting systolic (124±17 vs. 122±16mmHg, p<0.001), diastolic (80±10 vs. 77±11mmHg, p<0.001) and mean arterial pressures

(95±12 vs. 92±12mmHg, p<0.001)[201]. However, the picture may be more complex and hypertension rates may vary within South Asian groups. A systematic review of 12 studies found that in comparison with Caucasians, blood pressure was higher in Indians, marginally lower in Pakistanis and significantly lower in Bangladeshis[202].

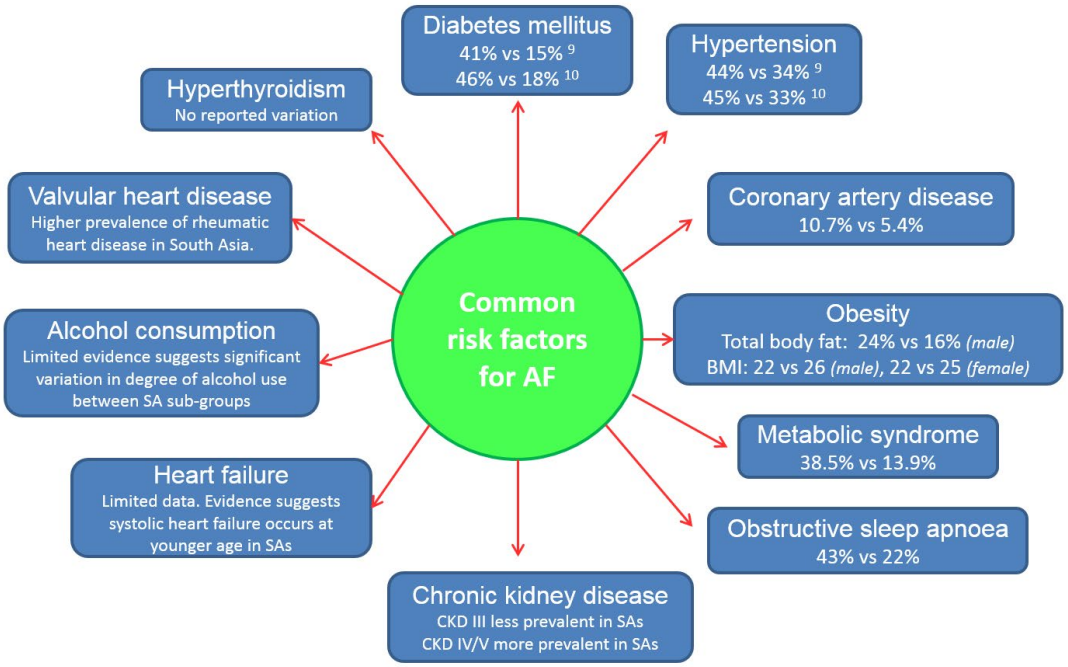

Figure 4. *Common risk factors for AF and their prevalence in South Asians vs. Caucasians (where applicable)*[9, 10, 136, 198, 203-206]

It is well known that South Asians have a heightened risk of coronary artery disease with prevalence rates more than double that of Caucasians. In one population-based study the prevalence of coronary disease was 10.7% in South Asians versus 4.6% in Europeans (p=0.001)[203]. South Asians also have a higher burden of premature coronary disease[207], more severe coronary artery disease[208], twice the hospitalisation rate from coronary disease[209] and a significantly higher mortality rate from the condition compared with Caucasians[210].

The prevalence of heart failure appears comparable between South Asians and other ethnicities (1.2% in South Asians[211] compared with UK national average of 1.6%[212]) although is perhaps less than anticipated given the high rates of cardiovascular disease. However, there is evidence to suggest that South Asians are significantly younger at the time of first hospitalisation for heart failure and it has been postulated that this may be a reflection of the higher prevalence of premature coronary artery disease[207, 213].

Studies have consistently shown that South Asians have a lower alcohol consumption (alcohol consumption ≥once/week: South Asian countries 10.7% vs. other countries 26.9%)[214, 215]. This was believed to relate to religious and cultural differences between South Asians and other ethnicities. However, this may be an incorrect assumption and drinking habits are likely to vary widely between different South Asian groups. For example, alcohol-related deaths are higher amongst Indian men compared with the general population and alcohol intake in Indian women has consistently increased in recent years. Conversely, individuals from Bangladesh and Pakistan are less likely to drink alcohol although Pakistani men who drink tend to consume more alcohol than other minority ethnic groups[216]. This reflects the diverse nature of the South Asian population.

Physical activity levels are significantly lower in South Asians compared with Caucasians (973 vs. 1465 metabolic equivalents of task [MET] /minute, $p<0.001$)[217, 218]. A UK population-based study found that exercise levels were significantly lower in South Asians across gender, age groups, South Asian sub-groups and were independent of socioeconomic and geographical factors[217].

1.5.2 Prevalence of atrial fibrillation in South Asians

Despite a high burden of cardiovascular risk factors, South Asians have a significantly lower prevalence of AF. The West Birmingham Stroke Project[9], a registry data review of 832 consecutive patients admitted with non-haemorrhagic stroke over a 2 year period demonstrated that patients of Indo-Asian origin had significantly higher rates of hypertension (44% vs 34%, $p<0.001$) and diabetes mellitus (41% vs. 15%, $p<0.001$) but an AF rate of only 1% (compared with 13% in the Caucasian group). A study in 2005 by Newton et al compared South Asian- and white- cohorts who were admitted acutely to hospital with a first presentation of heart failure[10]. Again, this study demonstrated higher rates of hypertension (45% vs. 33%) and diabetes (46% vs. 18%) in South Asians but with a significantly lower rate of AF (15% vs. 31%). A recent population-based study of 417,575 primary care records showed that AF prevalence was 2.43% in Caucasians and 0.46% in South Asians ($p<0.001$) despite a higher frequency of hypertension, diabetes mellitus and coronary artery disease[13]. These findings were further supported by a review of 98,982 clinical records of patients within the Heart of Birmingham Primary Care Trust in 2009/2010[11]; despite higher rates of diabetes mellitus, hypertension and coronary heart disease, patients of South Asian origin had a significantly lower prevalence of AF compared to those of white ethnicity.

1.5.3 Reasons for the low prevalence of atrial fibrillation in South Asians

The reason for the lower AF prevalence in South Asians is uncertain. Could it simply be due to an under-detection of the arrhythmia in the South Asian population, as was thought with African-Americans? In the UK, there is certainly evidence to show that South Asians are less likely to engage with medical services. For example, colorectal, breast and cervical cancer screening programmes all show a significantly

lower uptake within this ethnic group[219, 220], they are less likely to access or regularly attend antenatal care[221] and dementia services are not accessed until the condition is very advanced[222]. Although this might explain the variation in AF prevalence in epidemiological studies involving GP records, it would not account for the lower prevalence of AF seen in South Asian patients admitted acutely with non-haemorrhagic stroke or heart failure[9, 10]. Therefore other factors must be involved and there is limited evidence to suggest that South Asians have physiological variations in atrial morphology, electrophysiology and autonomic tone which in turn, may influence their risk of developing AF.

1.5.3.1 Cardiovascular morphology

South Asians appear to have smaller atria. A study by *Chahal et al* examined 458 patients of either Indo-Asian or European-White origin and assessed for differences in cardiac structure using echocardiography[223]. They found that those of Indo-Asian origin had smaller left atrial volumes (25.0±7.7 ml vs. 30.8±10.4 ml), even after indexing for body surface area (14.2±4.0 ml/m^2 vs. 16.3±4.8 ml/m^2) and lean body mass (5.3±1.6 g/kg vs. 5.8±1.7 g/kg). More recently, the EchoNoRMAL study was designed to provide reference values for standard echocardiographic measurements from geographically diverse population studies and included data from 22,404 adult volunteers, 1,751 of whom were South Asian[224]. The authors found that the upper reference values for left atrial diameter were lowest in the South Asian and African-Black populations and highest in the European and American-Black populations, even when indexed to body surface area.

South Asians not only have smaller atria but there is also evidence to suggest that they are of a smaller stature in general. They are shorter in comparison to the general UK population[225], have lower body surface area[206], smaller left ventricular (LV) size and volume[224] and smaller coronary[226, 227] and radial arteries[228]. However,

even when indexed for body size, the cardiac chamber size remains smaller in the SA population, suggesting that their overall heart size is relatively smaller.

The reason for this remains poorly understood but it is likely that genetic differences play a major role. Hur et al examined variations in height, weight and BMI between Caucasian and East Asian adolescent twins[229]. They found that Caucasian twins were taller, heavier and had higher BMIs compared to their East Asian counterparts and concluded that these differences were predominantly related to genetic rather than environmental factors. A more recent study by *Wilde et al* assessed the height of South Asian children living in the Netherlands and compared these results with the heights of Dutch children and South Asian children living in affluent parts of India[230]. They found that South Asian children living in the Netherlands were marginally taller than those in India but that Dutch children were consistently taller than their South Asian contemporaries at every age. They, too, concluded that the disparity in height between the ethnic groups was more likely to be related to genetic factors given that the environmental factors were similar between South Asian and Dutch children living in the Netherlands.

1.5.3.2 Atrial electrophysiology

Limited evidence currently exists with regard to variations in cardiac electrophysiology in South Asians. Two studies have examined South Asian electrocardiographic measurements non-invasively[231, 232] using standard 12-lead electrocardiograms (ECGs). Overall they found that in comparison with Caucasians, South Asian QRS duration (males: 87.08 vs 93.75ms, $p<0.001$; females: 82.07 vs. 86.07ms, $p= 0.002$) and corrected QT intervals (males: 390.07 vs. 403.88ms, $p<0.001$; females: 405.68 vs. 410.80, p,0.001) were shorter. There have been no studies which have invasively assessed intracardiac electrogram or conduction intervals.

In addition to a lower rate of AF, there is some evidence that South Asian ethnicity influences the prevalence of other arrhythmias. A recent observational study found that pacemaker implantation rates were significantly lower in South Asians with a crude incidence of 1.07/1,000 population compared with 6.15/1,000 population in Caucasians, suggesting a reduced susceptibility to bradycardias[233]. There is also a single study demonstrating a higher incidence of ventricular arrhythmias in South Asian patients with heart failure[213]. These findings would support the hypothesis that South Asians have variations in cardiac electrophysiology in comparison with Caucasians.

1.5.3.3 Autonomic nervous system

There is limited evidence to suggest that South Asians may also have variations in autonomic tone. *Bathula et al* measured heart rate variability (HRV) and baroreflex sensitivity in a sample of Indian-Asians and Europeans[234]. They found that Indian-Asians had lower mean R-R intervals (969 vs. 1,022ms, p= 0.002), less HRV (total RR interval power 925 vs. 1,224ms^2, p= 0.008) and reduced baroreflex sensitivity (5.7 vs. 6.6mmHg, p=0.01) compared with Europeans. They concluded that Indian-Asians may have variations in autonomic function with less vagal tone and increased sympathetic activity. This would explain the higher resting heart rate that is consistently seen in both South Asian children and adults compared with Caucasian counterparts[235-237]. However, as South Asian autonomic function has only been assessed in a single study, further research is required to confirm these findings.

1.5.4 Assessment of potential physiological variations in South Asians

A range of non-invasive investigations can be used to evaluate for differences in South Asian atrial morphology, atrial electrophysiology and autonomic tone. These techniques are summarised in the following sections.

1.5.4.1 Assessment of atrial morphology

Left atrial volume can be assessed with a range of imaging techniques. These include echocardiography, as demonstrated above, and multi-slice computed tomography. However, cardiovascular magnetic resonance imaging (MRI) is considered the most accurate technique for the non-invasive assessment of atrial volumes due to the high spatial resolution and excellent myocardial border definition[238].

Although South Asian atrial size has previously been assessed with echocardiography[223, 224], no data currently exist with regards to South Asian atrial size using the reference technique of cardiovascular MRI. Additionally, it is not known whether atrial function differs between South Asians and Caucasians.

1.5.4.2 Assessment of atrial electrophysiology

Although it is possible to assess atrial electrophysiology invasively with the use of diagnostic catheters at the time of a cardiac electrophysiology study, this approach carries procedural risks such as vascular injury, haemorrhage, cardiac perforation and thromboembolism[239]. As a consequence, it is not commonly used as a research tool to assess cardiac electrophysiology in healthy subjects.

Atrial electrophysiology can alternatively be assessed non-invasively. P wave indices are measurements derived from standard 12-lead ECGs which can quantify atrial electrophysiological function. They can reflect atrial remodelling and

differences in a range of P wave indices have been shown to be associated with the development of AF[240].

- ***P wave duration***

P wave duration (figure 5) is defined as the time between the P wave onset (intersection point of the upward deflection of the P wave in relation to the isoelectric line) and offset (intersection point of the downward deflection of the P wave in relation to the isoelectric line). It is a marker of intra- and inter-atrial conduction time[241]. Maximum P wave duration has been shown to be significantly higher in patients with idiopathic paroxysmal AF compared with control subjects[242] and has been shown to be a risk factor for AF, independent of hypertension and BMI[243]. Interestingly, significantly lower minimum P wave duration has also been found in idiopathic paroxysmal AF patients[241] and hypertensive patients with paroxysmal AF[244] in comparison with controls, suggesting that extremes of P wave duration are important in predicting AF risk. This is supported by a population-based ECG study of 285,933 individuals which found that very short (≤89ms, HR 1.60), intermediate (112-119ms, HR 1.22), long (120-129ms, HR 1.50) and very long (≥130ms, HR 2.06) median P wave duration was associated with an increased risk of incident AF[245].

- ***P wave dispersion***

P wave dispersion is defined as the difference between the maximum and minimum P wave duration measured on a 12-lead ECG. It reflects inhomogeneous and discontinuous propagation of sinus impulses. P wave dispersion has been shown to be significantly higher in patients with paroxysmal of AF compared with control subjects[242, 246]. In one study, a P wave dispersion of 40ms separated patients from controls with a sensitivity of 83%, a specificity of 85% and a positive predictive accuracy of 89%[242]. P wave dispersion is able to predict recurrence of AF following

cardioversion[247, 248] and can determine which patients with hypertension are at risk of developing AF[244].

- **P wave amplitude**

P wave amplitude (figure 5) is defined as the measurement between the wave's peak, or nadir, to the isoelectric line. It is indicative of the direction of atrial depolarisation and atrial myocardial mass and is believed to reflect the degree of atrial electro-anatomical remodelling[249]. Increased P wave amplitude has been shown to be independently associated with the development of new-onset AF[250] whilst reduced P wave amplitude of <0.1mV has been found to independently predict clinical recurrence of AF following radiofrequency catheter ablation[249].

- **P wave terminal force**

P wave terminal force in lead V_1 (PWTF-V_1, figure 5) of a standard 12-lead ECG is defined as the product of the duration and the amplitude of the negative terminal portion of the P wave in lead V_1[251]. It is a specific indicator of left atrial size[252] and correlates with left heart filling pressures[253, 254]. Increased PWTF-V1 is associated with a 1.9-fold increase in the risk of AF[255, 256].

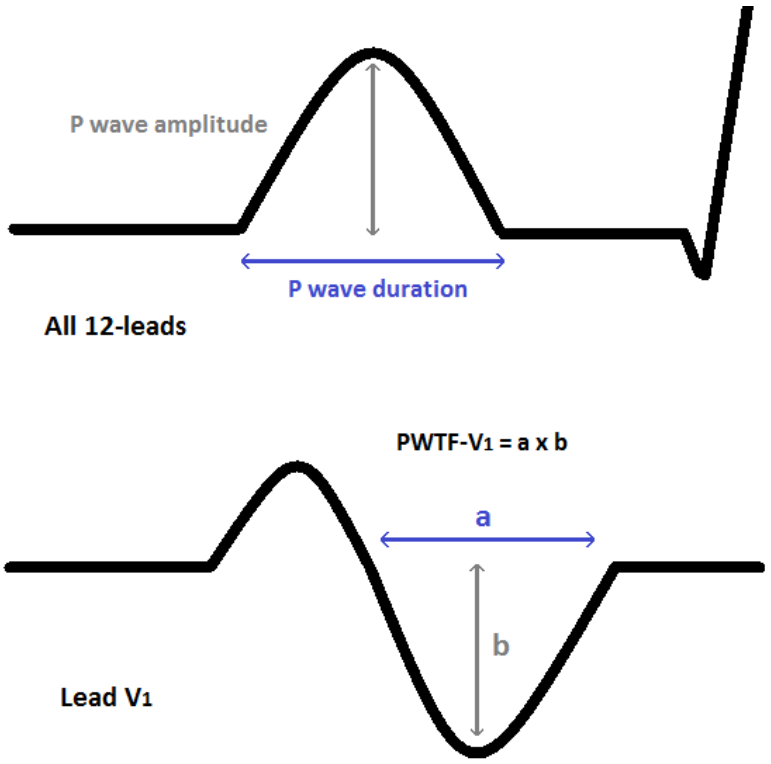

Figure 5. *P wave duration, P wave amplitude and P wave terminal force in lead V_1 ($PWTF\text{-}V_1$)*

1.5.4.3 Assessment of the autonomic nervous system

Due to the complex nature of the autonomic nervous system, there is currently no single test which can precisely evaluate its function. Instead, multiple different methods are needed to assess parasympathetic and sympathetic activity. The majority of investigations which are used to assess autonomic function evaluate cardiovascular reflexes which are triggered by performing specific, provocative manoeuvres. In the past, Ewing's battery of tests was performed, including heart rate responses to deep breathing, to standing and to the Valsalva manoeuvre and blood pressure responses to active standing and to sustained hand grip[257]. However, in recent years, HRV has evolved to become the most widely used non-invasive tool to assess autonomic tone.

HRV is a measure of heart rate fluctuations between consecutive normal-to-normal (NN) heartbeats (figure 6). Since heart rate is modulated by the autonomic nervous system, HRV is believed to reflect activity within the sympathetic and parasympathetic branches. Variations in heart rate can be evaluated using time-domain indices, which quantify the amount of variability in an unordered set of NN intervals, or frequency-domain indices, which distributes ordered NN intervals into different frequency bands. The commonly used variables are shown in table 4.

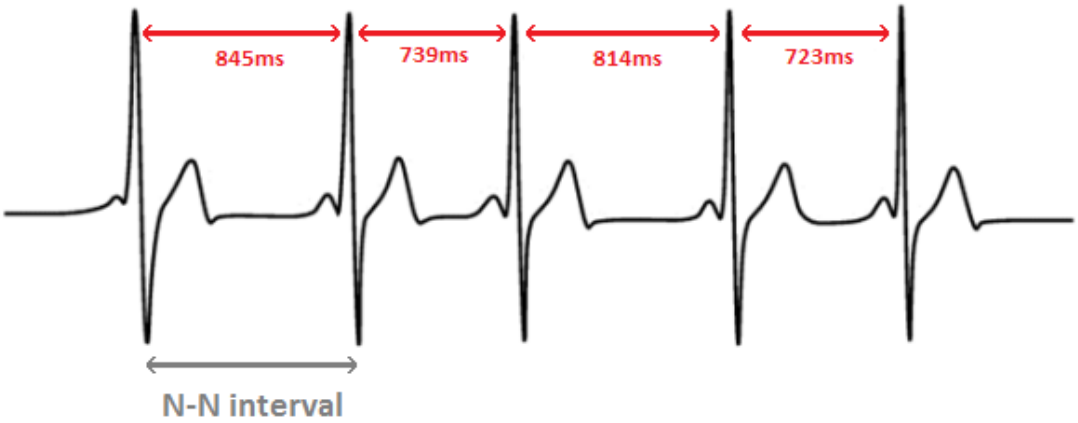

Figure 6. *Variation in sinus rate*

Time-domain indices are the simplest way of calculating heart rate variability. The commonest of these indices is the standard deviation of all N-N intervals (SDNN) which is a reflection of all cyclic components responsible for variability during the recording period. Both sympathetic and parasympathetic activity contribute to SDNN and it is a representation of total HRV[258]. Other commonly used indices include the standard deviation of the average N-N interval for each 5-minute segment of a 24-hour recording (SDANN) which provides information about external influences on HRV such as circadian variation and physical activity; and the square root of the mean of the sum of the squares of differences between adjacent N-N intervals (RMSSD) which is a marker of beat-to-beat variation mediated by vagal activity[258].

The calculation of frequency-domain indices is more complex and involves spectral techniques to convert each N-N interval into its corresponding frequency and quantify its relative intensity (power). This is commonly achieved using the fast Fourier transform method and four main spectral components are typically calculated: ultra-low frequency (ULF), very-low-frequency (VLF), low-frequency (LF), and high-frequency (HF). Signal within the VLF band reflects sympatho-vagal balance and is influenced by the renin-angiotensin system[259]; signal within the LF band can be produced by both parasympathetic and sympathetic activity[260]; and signal within the HF band reflects parasympathetic activity[260]. The ratio of LF to HF power has previously been used to measure sympatho-vagal balance with a low LF:HF reflecting parasympathetic predominance and a high LF:HF reflecting sympathetic predominance[261]. There is currently no consensus regarding the specific physiological process which generates the ULF band although very slow-acting biological processes such as circadian variation, thermoregulation, metabolism and the renin-angiotensin system are implicated[260].

Changes in heart rate variability have been shown to be associated with AF. A study of 57 patients with paroxysmal AF found that immediately prior to the onset of AF, most patients with structurally normal hearts had increased vagal tone (increased HF and reduced LF:HF ratio) whilst those with structural heart disease typically had increased sympathetic activity (decreased HF and increased LF:HF ratio)[49]. A study which assessed 93 patients who had recently undergone DC cardioversion for AF found that those with increased sympathetic and reduced vagal modulation (increased LF:HF ratio) were at significantly higher risk of early AF recurrence[262].

Table 4. Heart rate variability indices[263]

Variable	Definition	Physiological correlation
Time-domain indices		
SDNN	Standard deviation of all NN intervals	Represents total HRV
SDANN	Standard deviation of averages of NN intervals for each 5-minute segment of a 24-hour recording	Reflects sympathetic activity
SDNN index	Mean of standard deviations of all NN intervals for each 5-minute segment of a 24-hour recording	Reflects autonomic influence on HRV
RMSSD	Square root of the mean of the sum of the squares of differences between adjacent NN intervals	Reflects parasympathetic activity
Triangular index	Intergral of the density distribution divided by the maximum of the density distribution	Represents total HRV
Frequency domain indices		
Very low frequency (VLF)	Power in the very low frequency (0.003-0.04 Hz) range	Reflects sympatho-vagal balance
Low frequency (LF)	Power in the low frequency (0.04-0.15 Hz) range	Reflects sympathetic and parasympathetic activity
High frequency (HF)	Power in the high frequency (0.15-0.4 Hz) range	Reflects parasympathetic activity
LF/HF ratio	Ratio of LF to HF	Reflects sympatho-vagal balance

1.6 Aims of the thesis

There is evidence to suggest that South Asians have a lower burden of AF in comparison to Caucasians despite a suffering from a higher prevalence of established risk factors. The reason for this disparity remains uncertain however. It is possible that the lower prevalence of AF is simply due to an under-detection of the arrhythmia caused by South Asians engaging less with medical services. Alternatively, South Asians may have differences in atrial morphology, atrial electrophysiology, autonomic function or anthropometry compared with Caucasians and these variations may confer protection against the development of AF.

The subsequent chapters of the thesis each have a specific aim with individual introduction, methods, results and discussion:

Chapter 2: To investigate the incidence of subclinical AF in a retrospectively selected cohort of South Asian and Caucasian patients receiving an implanted cardiac device.

Chapter 3: To compare atrial morphology and function in South Asians and Caucasians using the reference technique of cardiovascular magnetic resonance imaging.

Chapter 4: To evaluate baseline electrocardiographic and intracardiac conduction intervals in a retrospectively selected cohort of South Asian and Caucasian patients undergoing invasive electrophysiology studies.

Chapter 5: To assess P-wave indices, left atrial size, supraventricular ectopy, heart rate variability, exercise capacity and anthropometry in a prospectively selected cohort of South Asian and Caucasian healthy volunteers.

Chapter 2. Incidence of subclinical atrial fibrillation in a South Asian population

2.1 Abstract

Background: South Asians have a lower prevalence of atrial fibrillation (AF) compared with Caucasians despite higher rates of conventional risk factors and a higher incidence of stroke. It is not clear whether South Asians truly experience less AF or whether this is due to under-detection of the arrhythmia. Therefore, the researcher aimed to determine whether South Asian patients with pacemakers have a lower incidence of device-detected subclinical episodes of AF compared with Caucasian controls.

Methods: A retrospective cohort study of South Asian and Caucasian patients who underwent pacemaker implantation between 2006 and 2016 was performed. Subclinical AF episodes detected during subsequent device clinic follow-up visits were identified and the occurrence of clinical AF, cerebrovascular events and all-cause mortality was recorded.

Results: A total of 5,648 patients underwent pacemaker implantation at the Yorkshire Heart Centre, UK, during the study period. Of these 169 were South Asian and 72 met the eligibility criteria. The cumulative incidence of subclinical AF was significantly lower in South Asians compared with Caucasians (log rank p=0.002) with an annual event rate of 6.9% versus 13.9%, and South Asian ethnicity was an independent predictor of a lower incidence of subclinical AF (OR 0.43; 95% CI 1.01-5.38).

Conclusions: South Asians with an implanted pacemaker have a lower rate of subclinical AF compared with Caucasians.

2.2 Introduction

The reduced prevalence of AF that is seen in South Asians may simply be a consequence of an under-detection of the arrhythmia within this ethnic group rather than a lower susceptibility to the condition. There is evidence to suggest that South Asians have less engagement with medical services[219-221]. As a consequence, episodes of AF may not be identified and recorded and the true occurrence of AF within South Asians may not be known.

Improvements in pacemaker technology now enable these devices to detect and record atrial arrhythmias and act as long-term cardiac rhythm monitors. Subclinical AF, defined as an asymptomatic atrial high rate episode (AHRE) at a rate of more than 190 beats per minute for more than six minutes [264], has been associated with the development of clinical AF, stroke and death[265, 266].

The city of Leeds, England, has a population of 751,485, 5.98% of whom are of South Asian descent[267]. It is therefore an ideal setting to compare South Asians and Caucasians whilst minimising potential bias from confounding environmental factors.

The aim of this study was to investigate the incidence of subclinical AF in a retrospectively selected cohort of South Asian and Caucasian patients receiving a cardiac implantable electronic device (CIED). The hypothesis was that South Asians would be less susceptible to asymptomatic AHREs and have a lower incidence of subclinical AF.

2.3 Methods

2.3.1 Study population

A single centre retrospective cohort study was performed examining de novo dual-chamber pacemaker and cardiac resynchronisation therapy pacemaker implantations at the Yorkshire Heart Centre, Leeds Teaching Hospitals NHS Trust, between 1st January 2006 and 31st December 2016. Patients were identified retrospectively from the local cardiac device database and every South Asian patient was considered for enrolment in the study. Caucasian controls were defined as the subsequent Caucasian patient located in the database that followed the South Asian subject and who was a match for age, gender and type of device. Patients were excluded if they had a history of atrial arrhythmia, if CIED follow-up was performed at a different centre, if no atrial lead was present or if they had congenital heart disease.

Ethnicity was identified using information from the NHS Patient Administration System. Patients are routinely asked to define their ethnicity during clinic visits and this is categorised using 18 national Ethnic Category codes, as used in the 2001 and 2011 census[267]. Based upon the definition of South Asia rendered by the United Nations[268], patients who had self-reported their ethnicity as Indian, Pakistani, Bangladeshi, Sri Lankan, Nepalese, Maldivian or Bhutanese were classified as South Asian. Patients who had self-reported their ethnicity as White British were defined as Caucasian.

The records of every CIED clinic visit were analysed for each subject and the date and occurrence of every subclinical AF episode (defined as an AHRE of >190 beats per minute, lasting for more than six minutes[264]) was recorded. The interrogation report for each visit documented the date, time and duration of every AHRE

recorded and every device had a preset AHRE detection rate of more than 190 beats per minute. Electronic patient records were screened to obtain information on patients' co-morbidity and medication history and for the occurrence of clinical AF, stroke or transient ischaemic attack (TIA) or death.

The study was reviewed by the Research and Innovation Department at Leeds Teaching Hospitals NHS Trust and approved as a Service Evaluation Project.

2.3.2 Study outcomes

The primary outcome of this study was the incidence of subclinical AF identified on CIED interrogation. Secondary outcomes included the incidence of clinical AF, cerebrovascular events and all-cause mortality in South Asian subjects. Clinical AF was defined as a cardiology clinic or hospital discharge diagnosis of AF. Cerebrovascular events were defined as a neurology clinic or hospital discharge diagnosis of stroke or TIA.

2.3.3 Statistical analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics Version 22.0, IBM Corporation, Armonk, New York). Normality of data was tested using a Shapiro-Wilk test. Continuous variables were expressed as mean ± SD if normally distributed or median (interquartile range [IQR]) if non-normally distributed. Student t test or Mann Whitney U test were used to compare continuous variables depending on normality. Categorical variables were expressed as percentages and compared using Pearson's chi-square test.

Kaplan-Meier survival statistics were used to assess the cumulative incidence of sub-clinical AF in South Asians and Caucasians and were compared with the use of

a log-rank test. Subjects entered observation at the time of their CIED implantation and were censored at the time of an outcome or their last follow-up attendance.

Predictors of subclinical AF were assessed using logistic regression analysis. In the multivariable analysis for assessing the presence of subclinical AF, the model was adjusted for age, gender, ethnicity, hypertension, diabetes mellitus and ischaemic heart disease. Hazard ratios with corresponding 95% confidence intervals were calculated using binomial logisitic regression. *P*-values of less than 0.05 were considered statistically significant. For the long-term clinical outcomes analysis, annual event rates (%/year) were calculated as the number of events per patient-years of follow-up and compared using Pearson's chi-square test.

2.4 Results

2.4.1 Study cohort

A total of 5,648 pacemaker and cardiac resynchronisation therapy device implantations were performed at the Yorkshire Heart Centre during the study period and 169 patients were of South Asian ethnicity. Of these, 97 patients were excluded as shown in figure 7, leaving a final South Asian cohort of 72 patients which were matched with Caucasian controls.

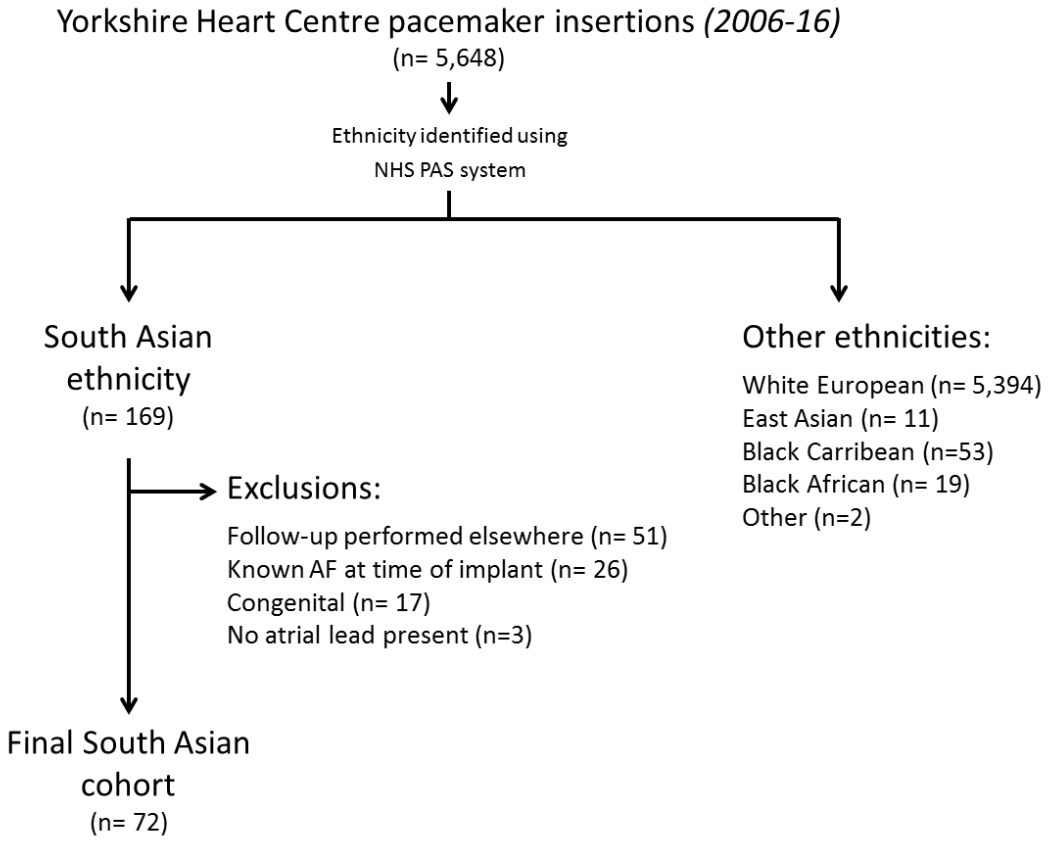

Figure 7. *Flow chart of ethnic distribution of pacemaker insertions at the Yorkshire Heart Centre between 2006 - 2016*

2.4.2 Baseline characteristics

Baseline characteristics of study participants are summarised in table 5. South Asian patients had a higher prevalence of hypertension, diabetes mellitus and ischaemic heart disease. The prevalence of structural heart disease and previous thromboembolic events were similar amongst the two ethnic groups and there was no significant difference in the length of CIED clinic follow-up. In association with the higher prevalence of hypertension, the use of angiotensin converting enzyme (ACE) inhibitors, diuretics and aldosterone antagonists were also higher in South Asians. There was no significant difference in the use of these medications in South Asian and Caucasian patients with heart failure ($p=0.251$ for ACE inhibitors, $p=0.216$ for diuretics and $p=0.09$ for aldosterone antagonists).

Table 5. Baseline characteristics

	South Asian	Caucasian	P-value
N	72	72	*
Age	74.4±10.9	74.5 ± 11.0	0.951
Female gender, n [%]	38 [52.7]	38 [52.7]	1.000
Dual-chamber pacemaker, n [%]	52 [72.2]	52 [72.2]	1.000
Biventricular pacemaker, n [%]	20 [27.8]	20 [27.8]	1.000
Length of follow-up, days	1196 (1506)	1169 (1233)	0.999
Left atrial size, mm	39.5±6.8	40.1±5.9	0.611
Mild LVSD, n [%]	12 [16.7]	10 [13.9]	0.643
Moderate LVSD, n [%]	14 [19.4]	15 [20.8]	0.835
Severe LVSD, n [%]	14 [19.4]	13 [18.1]	0.831
Aortic valve disease, n [%]	11 [15.2]	5 [6.9]	0.113
Mitral valve disease, n [%]	10 [13.9]	10 [13.9]	1.000
Hypertension, n [%]	50 [69.4]	33 [45.8]	**0.004**
Diabetes mellitus, n [%]	44 [61.1]	13 [18.1]	**<0.001**
Previous stroke/TIA, n [%]	9 [12.5]	9 [12.5]	1.000
Venous thromboembolism, n [%]	2 [2.8]	2 [2.8]	1.000
Ischaemic heart disease, n [%]	35 [48.6]	23 [31.9]	**0.042**
Peripheral arterial disease, n [%]	2 [2.8]	2 [2.8]	1.000
Chronic kidney disease stage III-V, n[%]	25 [34.7]	32 [44.4]	0.233
Average CHA_2DS_2VASc score	4.9±1.9	3.7±1.4	**<0.001**
Medication			
ACE-i/ARB, n [%]	48 [66.7]	30 [41.7]	**0.003**
Beta-blocker, n [%]	30 [41.7]	28 [38.9]	0.735
Calcium-channel blocker, n [%]	17 [23.6]	12 [16.7]	0.301
Diuretic, n [%]	34 [47.2]	21 [29.2]	**0.026**
Aldosterone antagonist, n [%]	12 [16.7]	3 [4.2]	**0.014**
Digoxin, n [%]	2 [2.8]	0 [0]	0.156
Statin, n [%]	48 [66.7]	38 [52.8]	0.090
Antiplatelet, n [%]	49 [68.1]	43 [59.7]	0.300
Anticoagulation, n [%]	2 [2.8]	2 [2.8]	1.000
Pacemaker implant indication			
Sinus node dysfunction	16 [22.2]	13 [18.1]	0.533
Atrioventricular block	36 [50.0]	39 [54.1]	0.615
Atrioventricular block + LVSD	2 [2.8]	2 [2.8]	1.000
LVSD and LBBB	18 [25.0]	18 [25.0]	1.000

Abbreviations: LVSD, left ventricular systolic dysfunction; TIA, transient ischaemic attack; ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LBBB, left bundle branch block.

2.4.3 Subclinical atrial fibrillation

During the study period, subclinical AF was detected in 18 South Asian and 36 Caucasian subjects. The cumulative incidence of subclinical AF was significantly lower in South Asians (log rank p=0.002, figure 8) with an annual event rate of 6.9% compared with 13.9% in Caucasians. Table 6 summarises the multivariable regression analysis. Diabetes mellitus was an independent predictor of subclinical AF (odds ratio [OR] 2.64; 95% confidence interval [CI] 1.10-6.36) whilst South Asian ethnicity was independently associated with a lower rate of the arrhythmia (OR 0.39; 95% CI 0.17-0.87). Age, gender, hypertension and ischaemic heart disease did not predict subclinical AF in this study population.

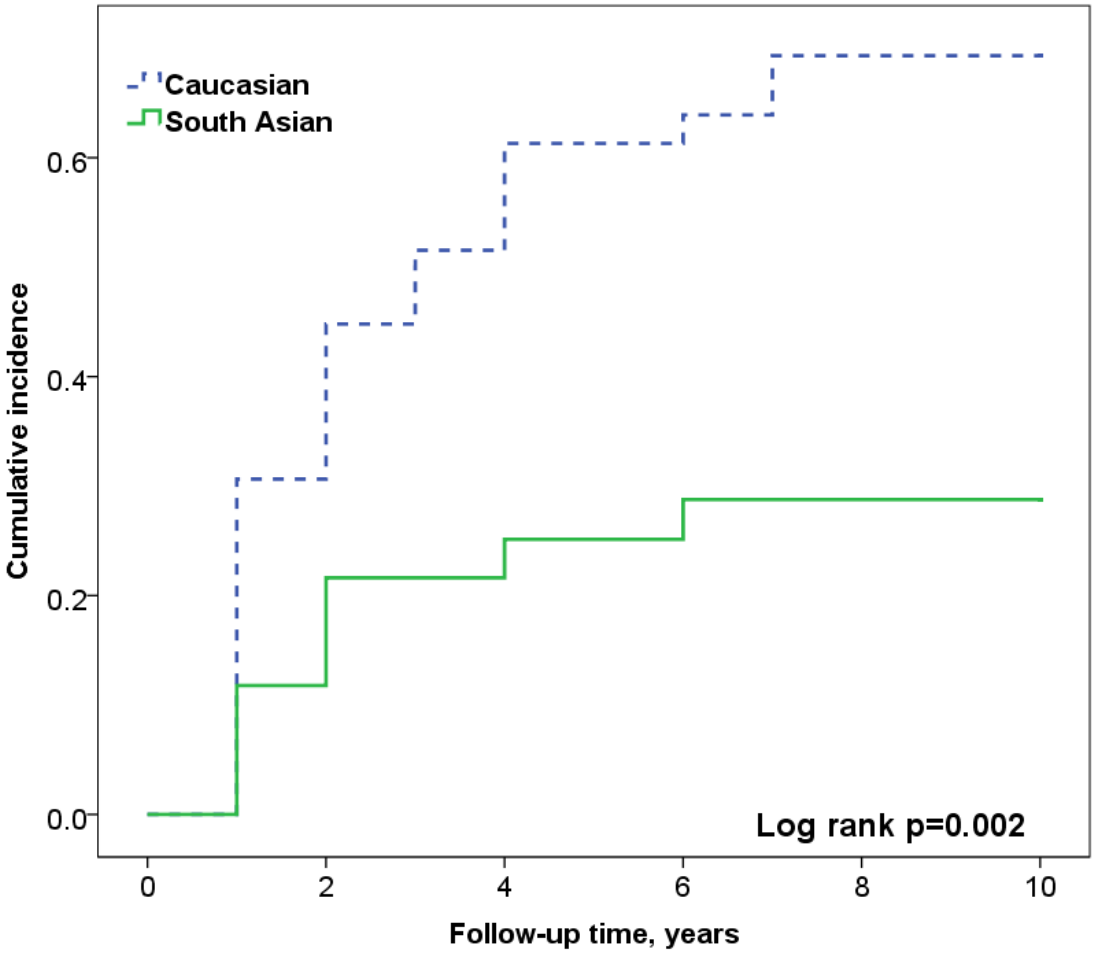

Figure 8. *Cumulative incidence of subclinical atrial fibrillation in South Asian and Caucasian patients with pacemakers*

Table 6. Multivariable regression analysis for the presence of subclinical atrial fibrillation

Variable	OR (95% CI)	*p*-value
Age	0.990 (0.957-1.024)	0.564
Female gender	1.048 (0.491-2.237)	0.904
South Asian	0.386 (0.171-0.869)	**0.022**
Hypertension	0.930 (0.425-2.039)	0.857
Diabetes mellitus	2.639 (1.096-6.355)	**0.030**
Ischaemic heart disease	2.146 (0.935-4.927)	0.072

2.4.4 Long-term clinical outcomes

Table 7 demonstrates clinical outcomes in the presence and absence of AHREs. Clinical AF was only diagnosed in subjects who had evidence of AHREs. This occurred at an annual incidence of 10.2% in South Asians, a rate which was similar to that seen within Caucasian subjects (10.3%, p=0.840). The presence of AHREs did not significantly affect the incidence of cerebrovascular events or all-cause mortality in South Asians or Caucasians.

Table 7. Long-term clinical outcomes of South Asian and Caucasian patients in the presence and absence of atrial high rate episodes

South Asian ethnicity					
	AHREs present (n=18)		AHREs absent (n=54)		p-value
Outcome	Events	% /year	Events	% /year	
Clinical AF	6	10.21	0	0	**<0.001**
Stroke/TIA	2	3.40	8	4.00	0.694
Death	11	18.72	22	10.99	0.133
Caucasian ethnicity					
	AHREs present (n=36)		AHREs absent (n=36)		p-value
Outcome	Events	% /year	Events	% /year	
Clinical AF	13	10.32	0	0	**<0.001**
Stroke/TIA	3	2.26	2	1.59	0.643
Death	8	6.35	7	5.27	0.772

Abbreviations: AHREs, atrial high rate episodes; AF, atrial fibrillation; TIA, transient ischaemic attack.

2.5 Discussion

To the best of the researcher's knowledge, this is the first study to demonstrate a significantly lower incidence of device-detected subclinical AF in South Asians compared with Caucasians. This is despite South Asians having a higher prevalence of risk factors for the condition such as hypertension, ischaemic heart disease and diabetes mellitus, a condition which was also shown to be an independent predictor of subclinical AF. Furthermore, these results indicate that South Asian ethnicity is independently predictive of a lower incidence of subclinical AF.

The findings of this study are consistent with previous studies which have shown a lower prevalence of clinical AF in South Asians[9, 10, 13]. However, these studies involved the screening of hospital or general practice records either to identify a clinical diagnosis of AF or to analyse electrocardiograms demonstrating AF; they did not involve long-term cardiac rhythm monitoring. As a consequence, it had previously been postulated that the lower prevalence of AF seen within South Asians was due to under-detection of the arrhythmia either because of a lower engagement of the population with medical services or because they experienced higher rates of paroxysmal AF which, by its nature, is more challenging to detect[269]. The results indicate that both of these scenarios are unlikely and support the observation that South Asians have a lower prevalence of AF.

It is currently unclear why the incidence of AF is lower in South Asians. Echocardiographic studies have indicated that this ethnic group have smaller left atrial volumes when compared with Caucasians[223, 224]. Therefore, it is possible that South Asians have variations in left atrial structure which reduce the risk of developing atrial arrhythmia. Interestingly, no difference in left atrial size was seen in this study. The reason for this is uncertain but may relate to the fact that the

population in this study had a mean age of 74 years and so any previous difference in atrial size had slowly diminished over time due to the higher prevalence of risk factors known to increase atrial size such as hypertension, diabetes mellitus and coronary artery disease. Alternatively, the echocardiograms that were performed assessed left atrial diameter only and so did not necessarily accurately reflect differences in left atrial volumes.

There is limited evidence that South Asians have differences in autonomic function with less vagal contribution compared with Caucasians[234] and it is well recognised that the autonomic nervous system plays a crucial role in the development and maintenance of AF. Consequently, an alternative hypothesis is that the reduced incidence of AF in South Asians is related to variations in autonomic function. Finally it is possible that South Asians have differences in atrial electrophysiology which protect against the development of AF. Further research is required to explore these areas further.

Within the study population, clinical AF exclusively occurred in patients with AHREs at an annual rate of around 10%. This is consistent with the findings of previous cardiac device studies[265, 266]. Although a logical finding, it highlights the importance of recognising AHREs as potential precursors to the development of clinical AF and as an indication to assess a patient's potential stroke risk.

There was no significant difference in the risk of stroke or all-cause mortality in patients who have evidence of AHREs although there was a trend towards a higher mortality rate in South Asians with AHREs. The findings of this study are in contrast to previous studies which found an association between the detection of AHREs and a significantly increased risk of thromboembolic events and cardiovascular mortality[265, 266]. It is likely therefore that the sample size and number of endpoints were not large enough to detect any underlying differences in these outcomes.

Finally, CIED implantation rates appeared to be lower in South Asians. South Asians constitute around 6% of the local population and yet only 3% of CIEDs were implanted in this ethnic group. A similar finding was recently demonstrated in an observational study of South Asians living in Leicestershire, England[233]. This raises the possibility that as well as a lower prevalence of AF, South Asians may also be less susceptible to bradyarrhythmias. The mechanisms underlying the differences in arrhythmia burden remain to be determined but may relate to variations in South Asian cardiac electrophysiology or the South Asian genome, areas which should be the focus of future research.

2.5.1 Limitations

Firstly, this is a retrospective cohort study and so exposes it to selection and recall bias. Although selection bias was possible, it was minimised through the recruitment of consecutive South Asian patients who met the eligibility criteria and the selection of the Caucasian controls was performed prior to screening of their medical records or any assessment of the incidence of atrial arrhythmia. Recall bias was minimised through the comprehensive assessment of the subjects' medical records. Secondly, only patients with CIEDs were included in the analysis and so the results may not be generalizable to the whole South Asian population. However, the results are supported by and consistent with the findings of previous population-based studies. Thirdly, the researcher was not able to view every atrial electrogram demonstrating an AHRE due to the limitations of device storage capacity. As a consequence, the researcher only recorded AHREs that had been measured using device diagnostics and algorithms. The accuracy of these algorithms has previously been validated[270] and therefore, the researcher do not believe that false positive or false negative detections will have significantly influenced the results. Finally, due to the settings on some CIEDs, although the researcher was able to record whether an AHRE

lasted six minutes or not, the researcher was not able to accurately record the total length of subclinical AF in every patient. This prevented analysis on whether there was a difference in the overall burden of subclinical AF between ethnic groups.

2.6 Conclusion

In patients with a CIED, the incidence of subclinical AF is significantly lower in South Asians compared with Caucasians despite South Asians having a higher prevalence of hypertension, diabetes mellitus and ischaemic heart disease. Moreover, it is South Asian ethnicity itself which is an independent predictor of a lower incidence of subclinical AF.

Chapter 3. Left atrial size and function in a South Asian population and their potential influence on the risk of atrial fibrillation

3.1 Abstract

Background South Asians have a low prevalence of atrial fibrillation (AF) compared with Caucasians despite having a higher prevalence of conventional risk factors for the arrhythmia. The reason for this disparity is uncertain but may be due to ethnic differences in atrial morphology. This study examines the association between ethnicity and left atrial (LA) size and function in South Asian and Caucasian subjects using the reference technique of cardiovascular magnetic resonance imaging (MRI).

Methods Retrospective case-control study of 60 South Asian and 60 Caucasian patients who had undergone a clinically-indicated MRI between April 2010 and October 2017 and had been found to have a structurally normal heart. LA and left ventricular (LV) volume and function were assessed and compared between the ethnicities.

Results In comparison with Caucasians, South Asians had significantly lower minimum (27.7±11.1 ml vs 34.9±12.3 ml, $p=0.002$) and maximum LA volumes (64.7±21.1 ml vs 80.9±22.5 ml, $p<0.001$), lower LV end-diastolic volume ($p<0.001$), lower LV stroke volume ($p<0.001$) and lower LV mass ($p=0.022$) and these values remained significant after correcting for body surface area. Further analysis revealed that LA volume was independently associated with South Asian ethnicity. There was no difference in LA function between the ethnic groups.

Conclusions South Asians have reduced LA volumes and a proportionally smaller heart size in comparison to Caucasians. Smaller LA size may protect against the development of AF by reducing the risk of re-entrant circuit formation and atrial fibrosis development.

3.2 Introduction

Structural remodelling of the atria plays a significant role in the development and maintenance of AF. It is therefore possible that the atrial structure in South Asians is morphologically different to Caucasian atria and that these variations confer protection against the development of AF.

Studies have previously demonstrated that the risk of developing AF increases with increasing left atrial (LA) size[38-40, 271]. There is also evidence that lower passive and total LA emptying fractions (LAEFs) measured by cardiovascular magnetic resonance imaging (MRI) are independently associated with the development of AF[271, 272].

Although echocardiographic studies have previously suggested that South Asian atria may be proportionally smaller to Caucasian atria[223, 224], the atrial size and function of South Asians has not been formally assessed using the reference technique of cardiovascular MRI.

Therefore, the aim of this study was to use MRI to investigate atrial morphology and function in a retrospectively selected cohort of South Asian and Caucasian patients. The hypothesis was that South Asians have smaller LA size and therefore increased LA function. Any variations in LA size in South Asian patients may help improve our understanding of the low prevalence of AF in this ethnic group.

3.3 Methods

3.3.1 Study population

This was a single centre case-control study involving 60 patients of South Asian origin and 60 Caucasian controls matched for age and sex (figure 9). Patients were identified retrospectively from the local MRI database at Leeds Teaching Hospitals NHS Trust. All patients who had undergone a clinically indicated MRI scan for suspected cardiomyopathy between April 2010 and October 2017 were eligible for inclusion if their MRI scan had shown a structurally normal heart (based upon previously published normal values[273]) with no evidence of cardiomyopathy and patients had been discharged from further cardiology follow-up.

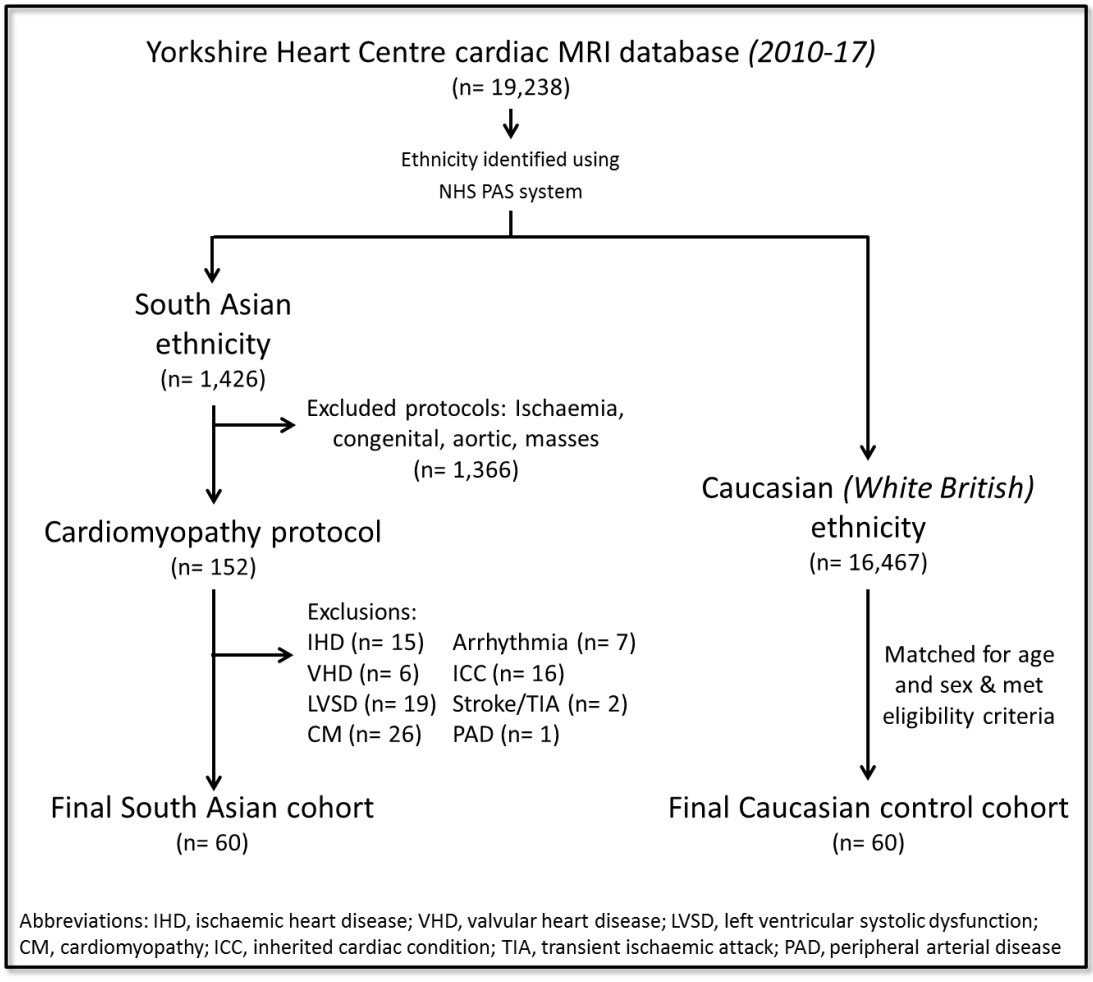

Figure 9. *Flow chart of ethnic distribution of cardiac MRI scans at the Yorkshire Heart Centre between 2010 - 2017*

Prior to recruiting patients to the study, electronic hospital and GP patient records were screened for information regarding underlying co-morbidities. Subjects were excluded if they had evidence of ischaemic, valvular or structural heart disease, cerebrovascular disease, peripheral arterial disease, a history of cardiac arrhythmia or a confirmed inherited cardiac condition.

The ethnicity of patients was populated using information from the NHS Patient Administration System. Patients were defined as South Asian if they had self-reported their ethnicity as Indian, Pakistani, Bangladeshi, Sri Lankan, Nepalese or Bhutanese. Patients were defined as Caucasian if they had self-reported their ethnicity as White British.

All participants had given written consent for their MRI images to be used for research purposes and the study was approved by the East Midlands - Derby Research Ethics Committee (REC reference 16/EM/0340).

3.3.2 Image acquisition

All MRI studies were performed using a 1.5 Tesla MR scanner (Intera or Ingenia CV, Philips Healthcare, Best, The Netherlands) and a vector ECG. Following acquisition of low resolution scout images, the main cardiac axes were planned using steady state free procession (SSFP) cine imaging. Long-axis steady SSFP cine images were obtained in 2-chamber and 4-chamber views. From these, a short axis stack covering the entire LV (thickness 10mm, gap 0mm) was planned and acquired. An axial stack of SSFP cine images was acquired covering the heart from the inferior cardiac aspect to the pulmonary artery bifurcation (slice thickness 6mm, no gap). Typical parameters for SSFP cine acquisitions were as follows: prospective gating, breath holding in end expiration, TR 2.6 ms, TE 1.3 ms, flip angle 40°, field of view 320 × 340 mm × 100 mm, voxel size 2 × 1.62 × 10 mm, 30 cardiac phases.

Ten minutes after administration of 0.2 mmol/kg Gadolinium DTPA contrast (Gadovist, Bayer AG, Zurich, Switzerland), late gadolinium enhancement (LGE) imaging was then performed. A stack covering the LV in 10-12 short axis slices (10mm thickness, 0mm gap) as well as 2-chamber view and 4-chamber views were obtained using an inversion recovery-prepared T1 weighted echo pulse sequence. The optimal inversion time (TI) to null normal myocardial signal was ascertained by the Look Locker approach.

3.3.3 Image analysis

Using the same software (CVI 42, Circle Cardiovascular Imaging, Calgary, Canada), post-processing analysis was performed by myself (1 years' cardiac MRI experience) and reviewed by a consultant cardiologist with 7 years' experience. LV volume and mass were manually calculated by contouring the endocardial and epicardial borders at end-diastole and end-systole of the LV short axis SSFP cine stack. LV papillary muscles were considered part of the LV cavity.

Maximum, minimum and pre-atrial contraction LA volumes were assessed by manually tracing the LA endocardial border in the axial SSFP cine stack (figure 10). The atrial appendage was included in the analysis but the pulmonary veins were excluded. LA volume was calculated using the disk summation method[273].

Maximum LA Volume (LAV_{max}) was defined as the volume at end-systole before mitral valve opening. Minimum LA volume (LAV_{min}) was defined as the volume at end-diastole, immediately after mitral valve closure. Pre-atrial contraction LA volume (LAV_{PreA}) was defined as the volume immediately before atrial contraction.

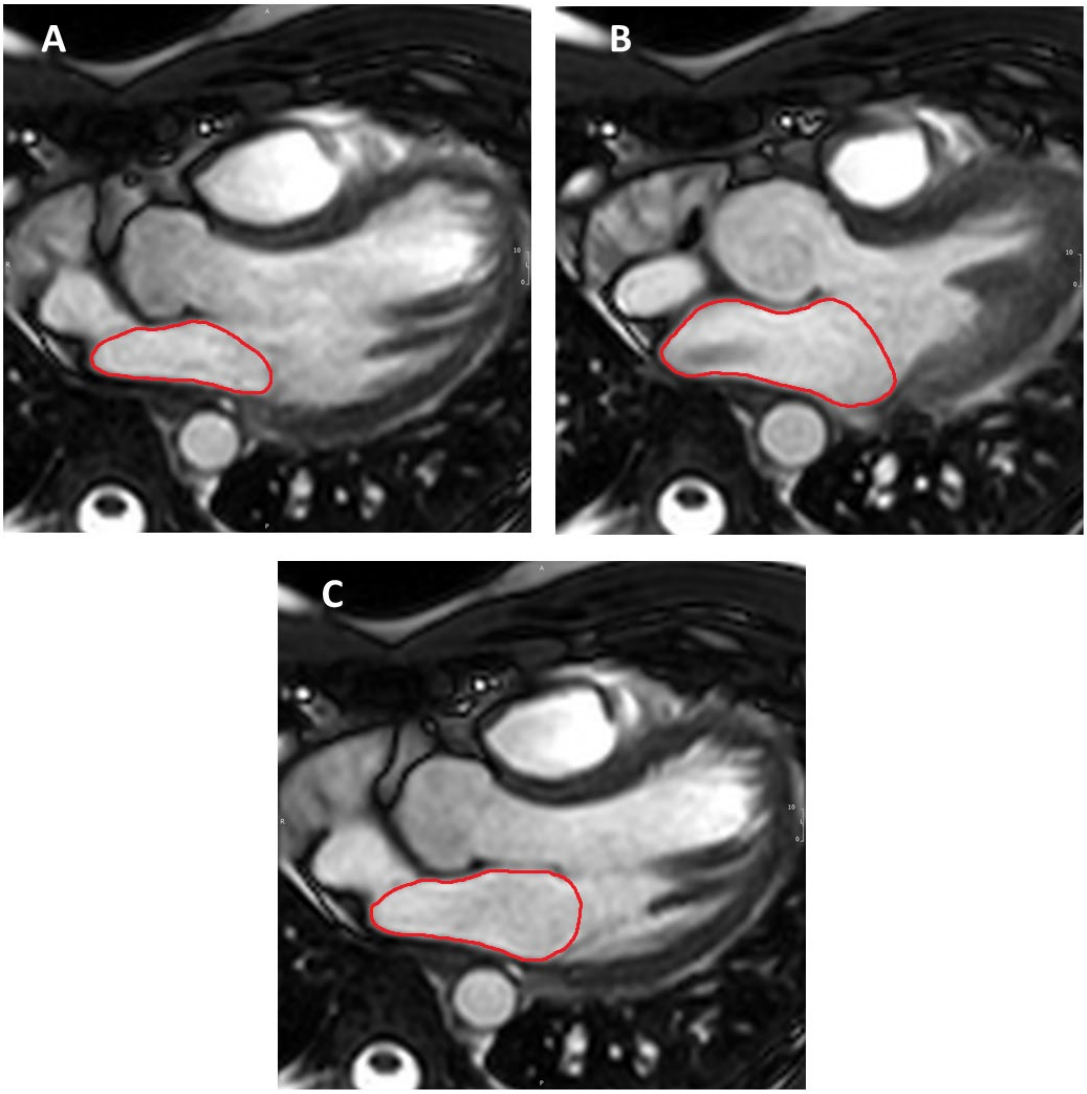

Figure 10. *Manual tracing of LA endocardial border in axial stack.*
A. Minimum LA volume; B. Maximum LA volume; C. Pre-atrial contraction LA volume.

Using these LA volume measurements, LA function was calculated as follows:

- Total LA emptying fraction (LAEF): $(LAV_{max}–LAV_{min})/LAV_{max}$
- Passive LAEF: $(LAV_{max} – LAV_{pre\text{-}a})/LAV_{max}$
- Active LAEF:$(LAV_{pre\text{-}a} – LAV_{min})/LAV_{pre\text{-}a}$

All values were then indexed for body surface area (BSA) using the Mosteller method[274] :

- $\text{BSA } (m^2) = \sqrt{\frac{\text{Height (cm) x Weight (kg)}}{3600}}$

3.3.4 Statistical analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics Version 22.0, IBM Corporation, Armonk, New York). Normality of data was tested using a Shapiro-Wilk test. Continuous variables were expressed as mean ± SD if normally distributed or median (interquartile range [IQR]) if non-normally distributed. Depending upon normality, a Student *t* test or Mann Whitney *U* test was used to compare continuous variables. Categorical variables were expressed as percentages and compared using Pearson's chi-square test.

For the regression model, the following independent variables were used. Age[224, 275, 276], male gender[224, 276], BMI[267] and the presence of hypertension[277-279] or diabetes[280, 281] were chosen due to their relationship with LA volume. Ethnicity was included to determine its relationship with LA size and function. LV function, which is closely associated with LA volume[282-287], was represented by LV ejection fraction (LVEF) and LV mass as measures of LV systolic and diastolic function respectively. Multivariable linear regression was used for variables with a statistical significance of <0.1 on univariable linear regression. *P* Values of less than 0.05 were considered statistically significant.

3.4 Results

3.4.1 Baseline characteristics

A total of 60 South Asian subjects and 60 Caucasian controls were studied. The baseline characteristics of the South Asian and Caucasian cohorts are presented in table 8. The age range of participants was 18 to 70. Of the 60 South Asian subjects, 41 were Pakistani, 17 were Indian and 2 were Bangladeshi. South Asians were significantly smaller (p=0.001) with a lower body surface area (BSA, p=0.016). The two cohorts were otherwise well matched.

3.4.2 Variations in cardiac structure and function

A comparison of LA and LV morphology and function in South Asians and Caucasians is shown in table 9. LAV_{min} and LAV_{max} were 20.6% and 20.0% smaller in South Asians compared with Caucasians and this trend remained significant after correcting for BSA. Passive, active and total LA function were not significantly different between South Asians and Caucasians. There was no significant difference in LV function between the two cohorts. However, South Asians had lower absolute LV mass and LV end-diastolic volume (LV EDV) and these differences remained significant after correcting for BSA. LGE was absent in all subjects.

3.4.3 Univariable and multivariable regression analysis

Univariable and multivariable relationships of LAV_{min}, LAV_{max} and LA function are shown in table 10 and table 11. LAV_{min} and LAV_{max} corrected for BSA were positively associated with age, body mass index (BMI), BSA-corrected LV mass and a history of hypertension. South Asian ethnicity was also a univariable predictor of smaller LA volumes. However, on multivariable linear regression, only age, South Asian ethnicity and BSA-corrected LV mass were independent predictors of LAV_{min} and LAV_{max}.

Total LA function was negatively associated with age, BMI and LV mass corrected for BSA on univariable regression. Of these variables, age and LV mass/BSA had a significant association with reduced LA function on multivariable analysis. Passive and active LA function demonstrated similar results.

Table 8. Baseline characteristics

	South Asian	Caucasian	P-value
N	60	60	
Age	35.0 (22)	34.0 (22)	0.902
Male gender, n [%]	30 [50]	30 [50]	1.000
Height, cm	165.3 ± 11.5	171.6 ± 9.3	**0.001**
Weight, kg	72.5 ± 16.6	78.6 ± 17.3	0.052
Body surface area, m^2	1.82	1.93	**0.016**
Body mass index, kg/m^2	26.1 (6.0)	26.1 (6.5)	0.865
BP- systolic, mmHg	123 (7)	121 (16)	0.117
BP- diastolic, mmHg	74 (6)	73 (12)	0.123
Heart rate, bpm	75.5 ± 16.9	71.6 ±15.6	0.068
Diabetes, n [%]	5 [8.3]	1 [1.7]	0.094
HbA1c, mmol/mol	60 ± 18.1	77	0.101
HbA1c, %	7.6 ± 1.6	9.2	0.101
Treated hypertension, n [%]	5 [8.3]	6 [10.0]	0.752
Aspirin, n [%]	3 [5.0]	2 [3.3]	0.648
Statin, n [%]	5 [8.3]	3 [5.0]	0.464
ACE-inhibitor, n [%]	6 [10.0]	7 [11.7]	0.769
Beta blocker, n [%]	2 [3.3]	4 [6.7]	0.402
Calcium channel blocker, n [%]	4 [6.7]	4 [6.7]	1.000
Diuretic, n [%]	1 [1.7]	2 [3.3]	0.559

Abbreviations: *BP, blood pressure; HbA1c, haemoglobin A1c; ACE, angiotensin-converting enzyme.*

Table 9. Left atrial volume and function and left ventricular mass, volume and function

	South Asian	Caucasian	P-value
LAV_{min} , ml	27.7 ± 11.1	34.9 ± 12.3	**0.002**
LAV_{min}/BSA, ml/m²	*14.9 ± 5.1*	*18.1 ± 5.8*	***0.004***
LAV_{max} , ml	64.7 ± 21.1	80.9 ± 22.5	**<0.001**
LAV_{max}/BSA, ml/m²	*35.2 ± 9.1*	*41.9 ± 10.5*	***0.001***
Passive LAEF, %	34.1 ± 11.2	33.2 ± 10.4	0.567
Active LAEF, %	35.4 ± 10.0	34.8 ± 10.2	0.720
Total LAEF, %	57.8 ± 7.4	56.8 ± 7.9	0.603
LV ejection fraction, %	60.0 (7.7)	62.0 (7.5)	0.147
LV mass, g	83.9 ± 28.8	94.8 ± 24.6	**0.022**
LV mass/BSA, g/m²	*44.8 ± 10.4*	*49.0 ± 10.2*	***0.028***
LVEDV, ml	130.9 ± 33.4	159.7 ± 33.0	**<0.001**
LVEDV/BSA, ml/m²	*71.9 ± 14.4*	*82.8 ± 13.5*	***<0.001***
LVESV, ml	54.8 ± 24.3	60.4 ± 17.0	0.148
LVESV/BSA, ml/m²	*30.0 ± 12.0*	*31.3 ± 7.8*	*0.150*
LV SV, ml	76.9 ± 19.0	99.3 ± 20.3	**<0.001**
LV SV/BSA, ml/m²	*42.3 ± 8.0*	*51.5 ± 8.4*	***<0.001***

Abbreviations: *LAV_{min}, minimum left atrial volume; BSA, body surface area; LAV_{max}, maximum left atrial volume; LAEF, left atrial ejection fraction; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVSDV, left ventricular end-systolic volume; LV SV, left ventricular stroke volume.*

Table 10. Univariable and multivariable linear regression analysis for LAV_{min}/BSA, LAV_{max}/BSA

	Univariable model			Multivariable model		
	Beta coefficient	Standard error	p value	Beta coefficient	Standard error	p value
LAV_{min}/BSA						
Age	0.457	1.327	**<0.001**	0.383	0.034	**<0.001**
Male gender	0.153	1.029	0.094	-0.012	0.987	0.894
South Asian	-0.274	1.001	**0.001**	-0.201	0.837	**0.008**
Body mass index	0.259	0.098	**0.004**	0.104	0.086	0.183
LV ejection fraction	0.108	0.043	0.239			
LV mass/BSA	0.403	0.046	**<0.001**	0.357	0.048	**<0.001**
Hypertension	0.229	1.756	**0.012**	0.083	1.518	0.286
Diabetes mellitus	0.014	2.388	0.882			
LAV_{max}/BSA						
Age	0.356	0.064	**<0.001**	0.291	0.066	**0.001**
Male gender	0.112	1.882	0.221			
South Asian	-0.325	1.792	**<0.001**	-0.267	1.625	**0.001**
Body mass index	0.206	0.181	**0.024**	0.083	0.166	0.317
LV ejection fraction	0.093	0.079	0.312			
LV mass/BSA	0.339	0.085	**<0.001**	0.277	0.078	0.001
Hypertension	0.203	3.214	**0.026**	0.089	2.970	0.288
Diabetes mellitus	0.000	4.346	0.999			

Abbreviations: *LAV_{min}, minimum left atrial volume; LAV_{max}, maximum left atrial volume; LV, left ventricular; BSA, body surface area.*

Table 11. Univariable and multivariable linear regression analysis for passive, active and total LA EF

	Univariable model			Multivariable model		
Passive LA EF	Beta coefficient	Standard error	p value	Beta coefficient	Standard error	p value
Age	-0.529	0.001	**<0.001**	-0.491	0.001	**<0.001**
Male gender	-0.021	0.020	0.819			
South Asian	0.040	0.020	0.665			
Body mass index	-0.260	0.002	**0.004**	-0.081	0.002	0.330
LV ejection fraction	-0.113	0.001	0.221			
LV mass/BSA	-0.081	0.001	0.382			
Hypertension	-0.175	0.034	0.056	0.034	0.032	0.286
Diabetes mellitus	-0.219	0.044	**0.016**	-0.133	0.039	0.098
Active LA EF						
Age	0.218	0.001	**0.017**	0.193	0.001	**0.031**
Male gender	-0.097	0.018	0.290			
South Asian	0.033	0.018	0.720			
Body mass index	0.059	0.002	0.520			
LV ejection fraction	0.028	0.001	0.761			
LV mass/BSA	-0.202	0.001	**0.027**	-0.191	0.001	**0.031**
Hypertension	0.039	0.032	0.676			
Diabetes mellitus	0.220	0.041	**0.016**	0.168	0.041	0.062
Total LA EF						
Age	-0.304	0.000	**0.001**	-0.272	0.000	**0.003**
Male gender	-0.125	0.014	0.174			
South Asian	0.068	0.014	0.458			
Body mass index	-0.180	0.001	**0.049**	-0.077	0.001	0.397
LV ejection fraction	-0.084	0.001	0.360			
LV mass/BSA	-0.258	0.001	**0.004**	-0.248	0.001	**0.004**
Hypertension	-0.119	0.024	0.196			
Diabetes mellitus	-0.012	0.032	0.893			

Abbreviations: *LA EF, left atrial ejection fraction; LV, left ventricular; BSA, body surface area.*

3.5 Discussion

To the best of the researcher's knowledge, this is first study to compare LA volume and function between South Asians and Caucasians using the reference technique of cardiovascular MRI. The researcher has demonstrated that South Asians have significantly reduced minimum and maximum LA volumes compared with Caucasians, even after correction for BSA. This is despite the fact that South Asians have a higher prevalence of risk factors for LA enlargement such as hypertension[9, 10], diabetes mellitus[9, 10] and obesity[206]. This study also shows that South Asians have lower LV mass, smaller LV EDV and lower LV stroke volume compared with Caucasians. In combination with the reduced LA volume, this would indicate that the South Asian heart is proportionally smaller than the Caucasian heart.

On multivariable linear regression, South Asian ethnicity remains an independent predictor of reduced LA size, even when measures of body size are included, and indicates that South Asian ethnicity plays a significant role in the morphology of the left atrium. Age and LV mass/BSA (a measure of diastolic function) are also independently associated with LA volume. These results support the findings of previous echocardiographic studies which demonstrated higher LA volume indexed for BSA (LAVi) in healthy subjects ≥50 years as compared with those <50 years of age (33.4±12.5 vs. 29.1±13.5, $p< 0.001$) and in normal LV geometry compared with LVH (23±5.1 vs. 26.2±7.3, $p<0.001$)[276, 285].

No difference in LA function was seen between South Asians and Caucasians although this is not entirely unexpected. Whilst LA dysfunction has been shown to be independently associated with the development of AF, in the absence of any known cardiac pathology, a reduction in LA function would be unusual, particularly in cohorts who are well matched in terms of baseline characteristics. Age was shown to be an independent predictor of a change in LA function, an expected

finding which is consistent with other studies[276, 288]. LV mass/BSA was also identified as being independently associated with LA function. This is likely to reflect the changes in diastolic function which occur with increasing LV mass[289] and lead to a reduction in LA function[290].

3.5.1 Comparison with other imaging studies

Echocardiographic studies have previously been performed to compare cardiac chamber sizes in different ethnic groups. Chahal *et al* found that South Asians had smaller LA volumes compared with Caucasians (25.0±7.7 ml vs. 30.8±10.4 ml), even after indexing for BSA (14.2±4.0 ml/m^2 vs. 16.3±4.8 ml/m^2)[223] whilst the EchoNoRMAL study showed that LA diameter, LV size and LV volume were lowest in the South Asian ethnic group[224]. The results of this study, using MRI, support these findings. However, volumetric analysis by MRI is superior to echocardiography[291, 292] and it is likely that these results will have greater reproducibility in future studies.

3.5.2 South Asian ethnicity and its relationship with body size

This study indicates that South Asians have a smaller heart size, shorter height and lower body surface area compared with Caucasian counterparts. These findings are consistent with those of other studies which show that South Asians are consistently of a smaller body size[206, 225, 230]. The study population was derived from the same geographical area where they are likely to be subjected to similar socioeconomic conditions and exposed to the same environmental factors known to influence growth, namely disease, nutrition and access to healthcare[293]. Therefore, although the reason for this disparity in body size is not certain, it is more likely to be related to a genetic rather than environmental cause. There is evidence to support this from a study by Wilde *et al* comparing South Asian children living in the Netherlands with South Asian children living in India[230]. They found similar growth trajectories in both

groups, suggesting that genetic influences play a more important role than environmental factors.

3.5.3 South Asian atrial size and the risk of atrial fibrillation

South Asians have a lower prevalence of AF compared with Caucasians and this may be related to their smaller LA size. It is well established that increasing LA size is an important independent predictor of AF[40]. This observation is likely to be related to the fact that increasing atrial size can provide favourable substrate for the development of AF through increased local intra-atrial conduction block and the creation of multiple re-entrant circuits[42, 294]. There is also an increased risk of developing atrial fibrosis with atrial enlargement due to inflammation, oxidative stress and the expression of pro-fibrotic factors (transforming growth factor beta-1 and angiotensin-II) which can subsequently alter atrial conduction and atrial ERPs[36]. The combination of these changes favours the development of re-entry and therefore the occurrence of AF.

It seems reasonable to conclude therefore that since South Asians have smaller atria compared to Caucasians, their LA volume is required to increase to a much larger size proportionally before AF can develop and become sustained. As a result of this, the rate of AF amongst South Asians is significantly lower.

3.5.4 Limitations

Firstly, the study population was taken from individuals attending for clinical cardiac MRI scans. Although there was no evidence of cardiovascular disease, it is possible that they may have had occult conditions that were not apparent. However, the researcher rigorously screened patient records and excluded anyone who was subsequently found to have cardiac pathology. Secondly, the retrospective design of this study is associated with selection bias, which was minimised by recruiting consecutive patients who met the eligibility criteria, and recall bias which was

minimised through the assessment of subjects' hospital records and the contacting of their general practitioners for any missing information.

3.6 Conclusion

This is the first study which demonstrates that South Asians have smaller LA volumes compared with Caucasians, even when matching for BSA, using the reference technique of MRI to measure cardiac dimensions. South Asians also have reduced LV EDV and smaller LV mass indicating that the South Asian heart is proportionally smaller to the Caucasian heart and this is likely to be due to genetic factors. Reduced LA volume may confer a degree of protection against the development of re-entrant circuits and fibrosis within the atria and may explain why South Asians have a reduced prevalence of AF.

Chapter 4. Electrophysiological properties of the South Asian heart

4.1 Abstract

Objective: The South Asian population has a lower burden of arrhythmia compared with Caucasians despite a higher prevalence of traditional cardiovascular risk factors. The researcher aimed to determine whether this was due to differences in the electrophysiological properties of the South Asian heart.

Methods: A retrospective cohort study of South Asian and Caucasian patients who underwent an electrophysiology study for supraventricular tachycardia (SVT) between 2005 and 2017 was performed. Surface electrocardiogram, intracardiac electrogram and intracardiac conduction intervals were measured and a comparison between the two ethnic cohorts was performed.

Results: A total of 5,908 patients underwent an electrophysiology study at the Yorkshire Heart Centre, UK, during the study period. Of these 262 were South Asian and 113 met the eligibility criteria. South Asians had a significantly higher resting heart rate (p= 0.024), shorter QRS duration (p= 0.012) and a shorter atrioventricular (AV; p= 0.001)) and ventriculoatrial (VA; p= 0.013) effective refractory period (ERP). There was no difference in atrial or ventricular ERP. On linear regression analysis, South Asian ethnicity was independently predictive of a higher resting heart rate, narrower QRS and shorter AV-ERP and VA-ERP.

Conclusions: South Asians have significant differences in their resting heart rate, QRS duration and AV nodal function compared with Caucasians. These differences may reflect variations in autonomic function and may also be influenced by genetic

factors. Electrophysiological differences such as these may help to explain why South Asians have a lower burden of arrhythmia.

4.2 Introduction

South Asians appears to have a significantly different burden of arrhythmia in comparison with Caucasians. The prevalence of AF is lower but there is also evidence to suggest that South Asians are at less risk of bradyarrhythmia[233] whilst being at more risk of ventricular arrhythmia[213].

The mechanisms underlying this altered susceptibility to arrhythmia remains unclear but it raises the possibility of a difference in the cardiac electrophysiology of South Asian hearts, an area which has not previously been investigated.

Therefore to improve our understanding of South Asian cardiac electrophysiology, the aim of this study was to investigate baseline electrocardiographic and intracardiac conduction intervals in a retrospectively selected cohort of South Asian and Caucasian patients undergoing invasive electrophysiology studies. The researcher hypothesized that South Asians would have differences in cardiac conduction compared with Caucasians.

4.3 Methods

4.3.1 Study population

A single centre retrospective cohort study was performed on patients undergoing electrophysiology studies for supraventricular tachycardia (SVT) at the Yorkshire Heart Centre, Leeds Teaching Hospitals NHS Trust, between 1st January 2005 and 31st December 2017. Patients were identified from the local cardiac electrophysiology database and all South Asian patients were considered for enrolment into the study. Patients were excluded if they were under the age of 16 years, underwent ablation for atrial fibrillation, atrial flutter or ventricular tachycardia or had a history of congenital or structural heart disease. Caucasian controls matched for age and sex, who also had a diagnosis of SVT, were identified from the same local cardiac electrophysiology database.

Ethnicity was identified using data from the NHS Patient Administration System. Patients were defined as South Asian if they had self-reported their ethnicity as Indian, Pakistani, Bangladeshi, Sri Lankan or Nepalese. Patients were defined as Caucasian if they had self-reported their ethnicity as White British.

4.3.2 Electrophysiology study

All patients underwent electrophysiology study in a fasted state. Antiarrhythmic or rate-limiting medications were discontinued for at least five half-lives prior to the procedure. Procedures were either performed under general anaesthetic or under local anaesthetic with the option of sedation. Three or four diagnostic electrophysiology catheters were introduced into the right and/or left femoral veins. Quadripolar or octapolar catheters were positioned at the His bundle and right ventricular apex. A decapolar catheter was positioned in the coronary sinus. At the operator’s discretion, a quadripolar catheter was also positioned in the high right atrium. Surface and intracardiac electrocardiograms were continuously recorded

and stored using the CardioLab Electrophysiology recording system (General Electric Medical Systems, Milwaukee, Wisconsin, USA). Programmed right ventricular stimulation was performed with a single extrastimulus at a cycle length of 600 milliseconds (ms) until either ventricular or ventriculoatrial (VA) ERP was reached. Programmed atrial stimulation was performed with a single extrastimulus at a cycle length of 600ms until either atrial ERP or atrioventricular (AV) ERP was reached. Incremental atrial pacing was performed until atrioventricular block occurred in order to record atrioventricular Wenkebach (AVW) cycle length. In patients with atrioventricular nodal re-entrant tachycardia or a concealed accessory pathway, measurements were taken at the start of the study, prior to the administration of isoprenaline. In patients with a manifest accessory pathway, measurements were taken following ablation, after the administration of isoprenaline, and once the heart rate had returned to baseline.

4.3.3 Data collection

The conduction intervals of each electrophysiology study were measured using CardioLab analysis software (General Electric Medical Systems, Milwaukee, Wisconsin, USA). Heart rate, P-wave duration, and the RR, PR, QRS, QT and QTC intervals were all measured on the surface electrocardiogram (Figure 11). The AA interval (sinus cycle length), PA interval, AH interval (AV node conduction time) and HV interval (His-purkinje conduction) and the atrial ERP, atrioventricular ERP, atrioventricular Wenkebach cycle length, ventriculoatrial ERP and ventricular ERP were all measured using the intracardiac electrogram (Figure 11, Figure 12, Figure 13, Figure 14). The intervals were measured using electronic calipers at a sweep speed of 200 millimetres/second. All surface electrocardiogram intervals were measured in lead II. The definition of each conduction interval is found in table 12.

Table 12. Definitions of conduction intervals measured on the surface and intracardiac electrocardiograms

Surface electrocardiogram	
P wave duration	Time interval between the onset and offset of the P wave
RR	The time interval between two successive R-waves of the QRS complex
PR	Time interval between the onset of the P wave and the onset of the QRS complex
QRS	Time interval between the onset of the Q wave and the offset of the S wave
QT	Time interval between the onset of the QRS complex and the offset of the T wave
QTc	QT interval corrected for heart rate
Intracardiac electrogram	
AA	The time interval between two successive A waves
PA	The time interval between the onset of the P wave on the surface ECG and the rapid deflection of the A wave on the HIS channel.
AH	Time interval between the rapid deflection of the A wave to the onset of the H deflection using the HIS channel.
HV	Time interval between the onset of the H deflection to the earliest onset of ventricular activation in either the intracardiac or surface ECG.
Atrial ERP	Maximum S1-S2 coupling interval which fails to produce an A wave
Atrioventricular ERP	Maximum S1-S2 coupling interval which fails to produce a HIS potential
Ventricular ERP	Maximum S1-S2 coupling interval which fails to produce a V wave
Venriculoatrial ERP	Maximum S1-S2 coupling interval which fails to produce a HIS potential
AVW	Maximum S1-S1 interval which fails to produce a V wave during incremental atrial pacing

Abbreviations: ERP, effective refractory period; AVW, atrioventricular wenckebach.

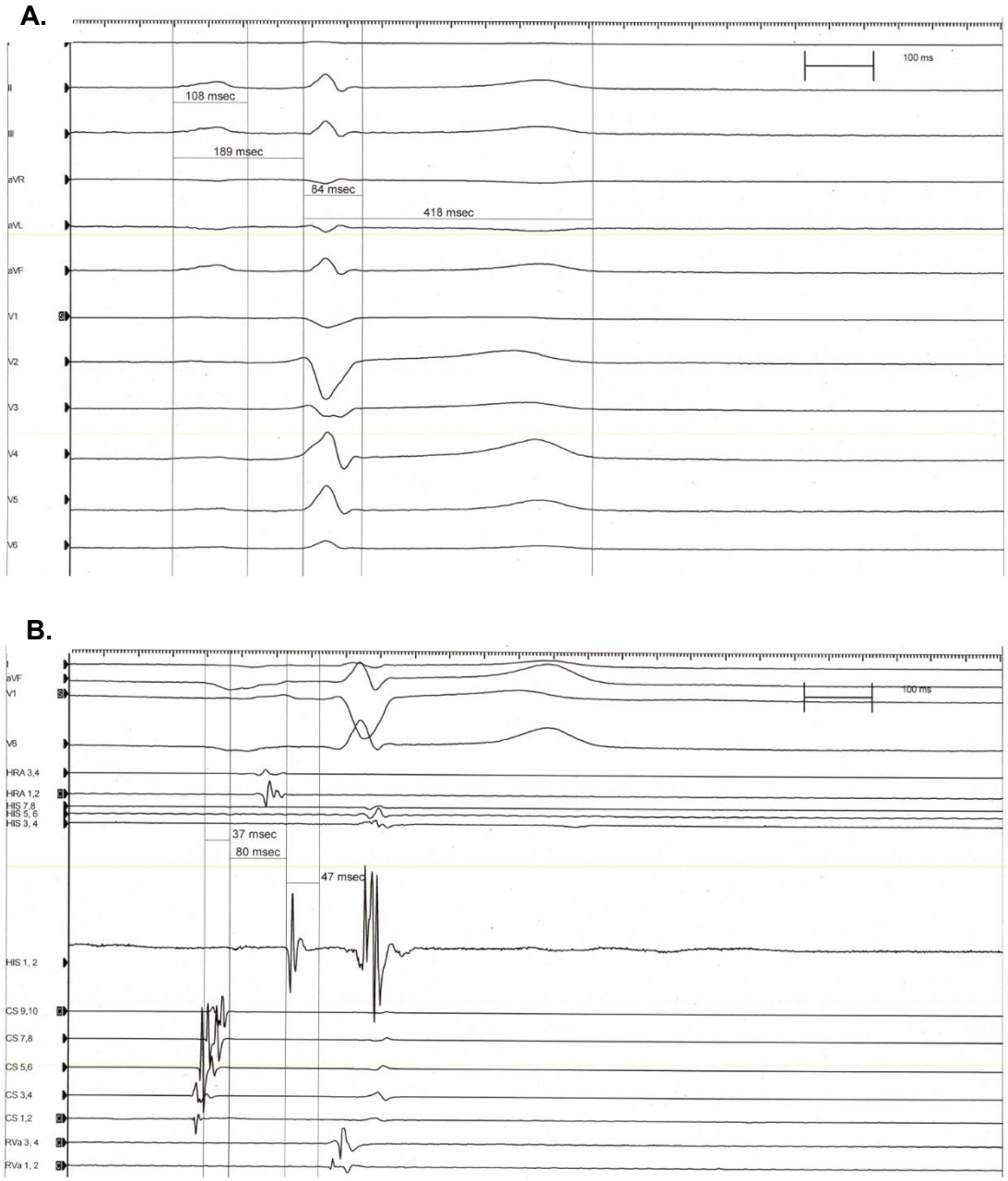

Figure 11. Surface and intracardiac electrocardiogram measurements

A. *P wave duration (108ms), PR (189ms), QRS (84ms) and QT (418ms) intervals.*

B. *PA (37ms), AH (80ms) and HV (47ms) intervals.*

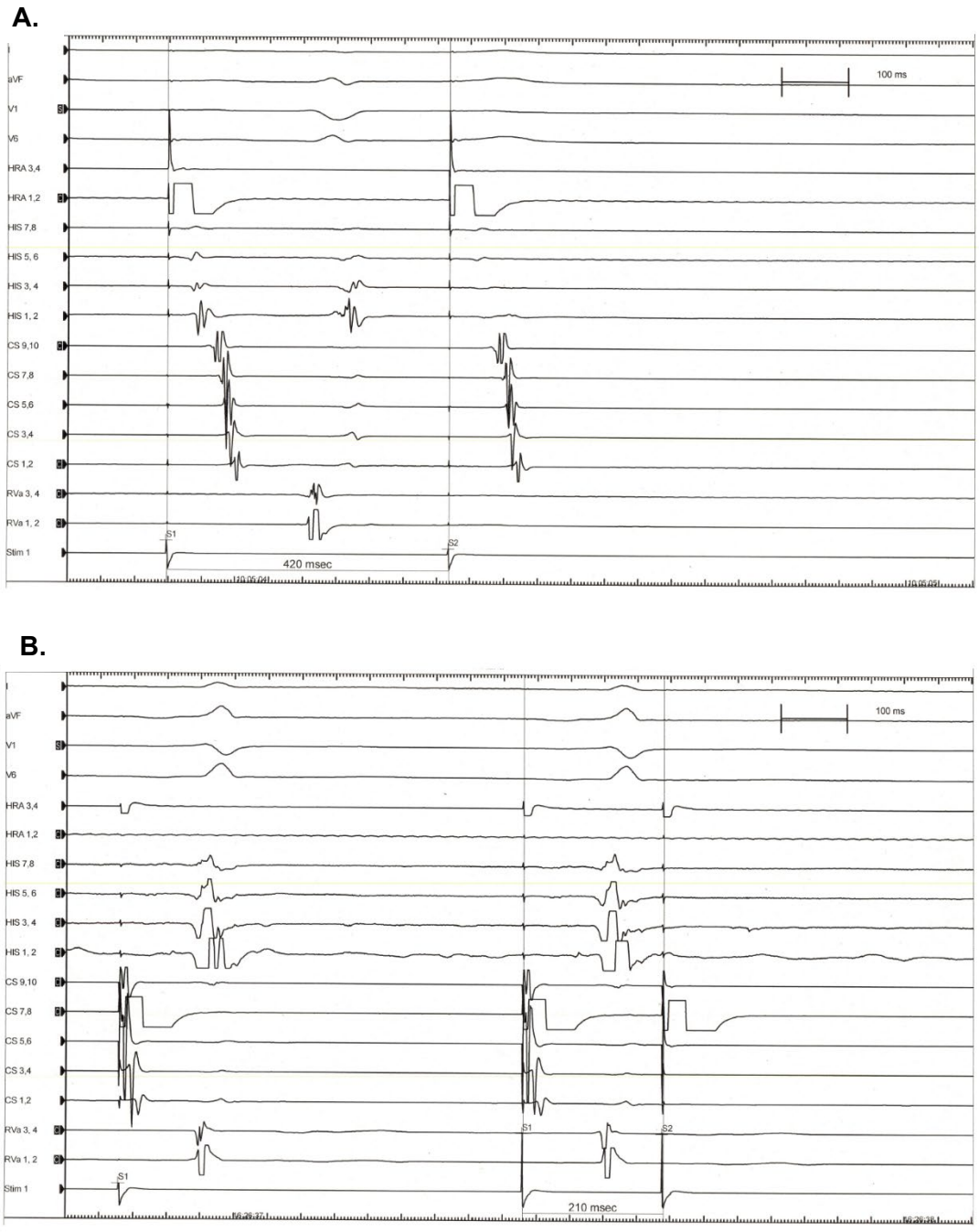

Figure 12. Measurement of effective refractory period (ERP).

A. *Measurement of atrioventricular ERP.*

B. *Measurement of atrial ERP.*

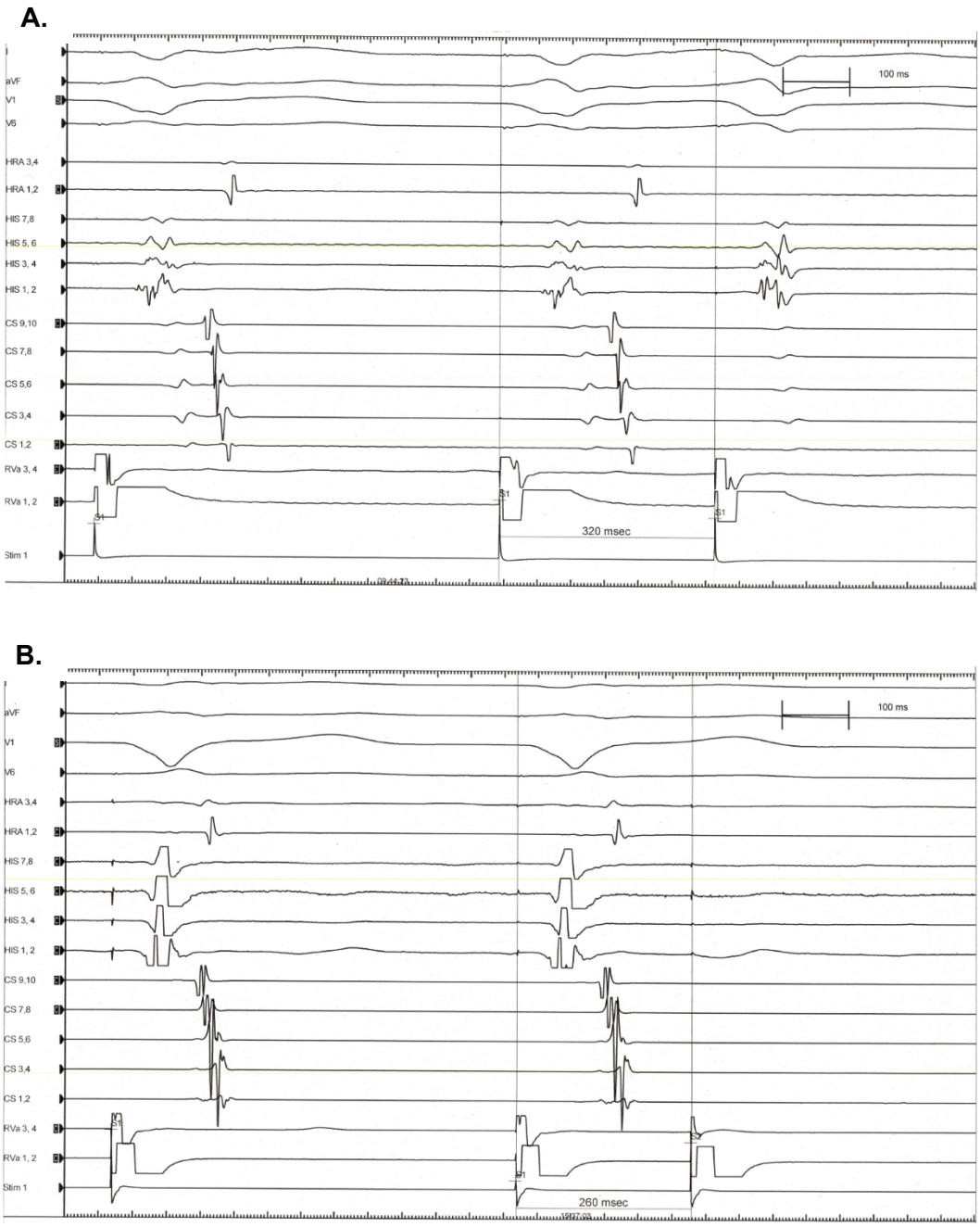

Figure 13. Measurement of effective refractory period (ERP).

A. *Measurement of ventriculoatrial ERP.*

B. *Measurement of ventricular ERP.*

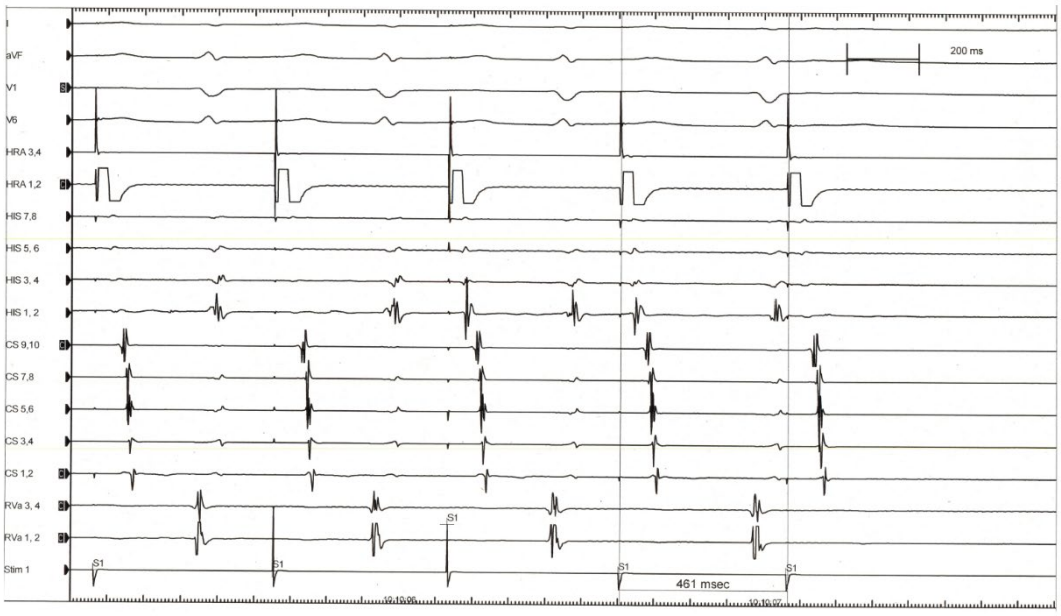

Figure 14. *Measurement of atrioventricular Wenckebach.*

Electronic patient records were examined and information on patients' co-morbidities, medication history, length of cardiology follow-up following the electrophysiology study and evidence of SVT recurrence was recorded. The study was reviewed by the Research and Innovation Department at Leeds Teaching Hospitals NHS Trust and approved as a Service Evaluation Project.

4.3.4 Statistical analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics Version 22.0, IBM Corporation, Armonk, New York). Normality of data was tested using a Shapiro-Wilk test. Continuous variables were expressed as mean ± SD if normally distributed or median (interquartile range [IQR]) if non-normally distributed. Student t test or Mann Whitney U test were used to compare continuous variables depending on normality. Categorical variables were expressed as percentages and compared using Pearson's chi-square test. *P* values of less than 0.05 were considered statistically significant.

Linear regression analysis was used to further evaluate the relationship between ethnicity and any statistically significant electrophysiological intervals with adjustment for age, gender, left atrial diameter, hypertension and diabetes mellitus. Univariable linear regression was initially performed and any variable with a statistical significance of <0.1 was included in the multivariable regression model.

4.4 Results

4.4.1 Study cohort

During the study period, a total of 5,908 electrophysiology studies were performed at the Yorkshire Heart Centre with 5,583 procedures performed in Caucasians and 262 procedures performed in South Asians. The total referral population includes 1,814,206 Caucasians and 264,438 South Asians. Therefore, electrophysiological studies were performed in 0.31% of the Caucasian population and 0.09% of the South Asian population. A summary of the indications for the electrophysiology studies in each cohort is found in table 13.

Table 13. Summary of the indications for electrophysiology studies in all Caucasians and South Asians

	Caucasian *(n= 5,583)*	South Asian *(n= 262)*
Atrial fibrillation	1713 (30.7%)	20 (7.6%)
Atrial flutter	1052 (18.8%)	21 (8.1%)
Atrial tachycardia	202 (3.6%)	6 (2.3%)
SVT	1413 (25.3%)	135 (51.5%)
WPW	563 (10.1%)	49 (18.7%)
Ventricular arrhythmia	640 (11.5%)	31 (11.8%)

Abbreviations: SVT, supraventricular tachycardia; WPW, Wolff-Parkinson-White syndrome

A final South Asian cohort of 113 subjects was identified and matched with Caucasian controls after 149 patients failed to meet the eligibility criteria (figure 15).

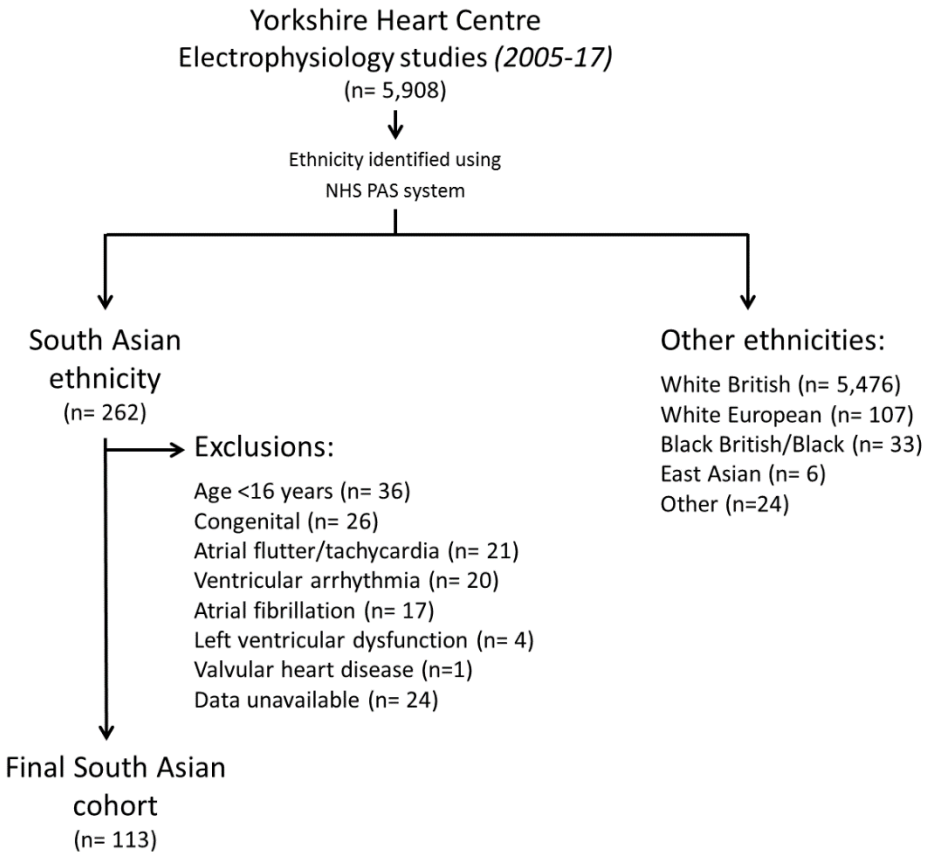

Figure 15. *Flow chart of ethnic distribution of electrophysiology studies at the Yorkshire Heart Centre between 2005 – 2017.*

4.4.2 Baseline characteristics

The characteristics of the study participants are summarised in table 14. The two cohorts were well matched with no significant difference in co-morbidities, medication, length of follow up or the recurrence of arrhythmia. There was a non-significant trend towards a higher prevalence of diabetes mellitus and ischaemic heart disease amongst South Asians.

4.4.3 Surface electrocardiogram intervals

Resting heart rate was significantly higher (p= 0.024) and QRS duration was significantly shorter (p= 0.012) in South Asians as shown in table 15. There was no significant difference in the P wave duration or PR interval between the ethnicities and once corrected for heart rate, there was no difference in the QT interval.

Table 14. Baseline characteristics

	South Asian	Caucasian	P-value
N	113	113	*
Age	41.3±13.6	41.3±13.6	0.981
Male gender, n [%]	39 [34.5]	39 [34.5]	1.000
Height, centimetres	163.8±7.9	169.8±10.4	**0.023**
Weight, kilograms	76.5±18.1	76.1±20.4	0.592
Left atrial diameter, millimetres	34.0±5.9	33.7±3.9	0.840
Hypertension, n [%]	13 [11.5]	10 [8.8]	0.509
Diabetes mellitus, n [%]	12 [10.6]	6 [5.3]	0.140
Previous stroke/TIA, n [%]	1 [0.9]	2 [1.8]	0.561
Venous thromboembolism, n [%]	0 [0.0]	1 [0.9]	0.316
Ischaemic heart disease, n [%]	6 [5.3]	2 [1.8]	0.150
Peripheral arterial disease, n [%]	0 [0.0]	0 [0.0]	*
CKD stage III-V, n[%]	2 [1.8]	1 [0.9]	0.561
Diagnosis			
AVNRT, n[%]	78 [69.0]	81 [71.6]	0.662
Accessory pathway, n[%]	15 [13.3]	9 [8.0]	0.195
No inducible arrhythmia, n[%]	20 [17.7]	23 [20.4]	0.611
Medication			
ACE-i/ARB, n [%]	15 [13.3]	9 [8.0]	0.195
Beta-blocker, n [%]	52 [46.0]	39 [34.5]	0.078
Calcium-channel blocker, n [%]	17 [15.0]	9 [8.0]	0.095
Diuretic, n [%]	1 [0.9]	2 [1.8]	0.561
Aldosterone antagonist, n [%]	0 [0.0]	0 [0.0]	*
Statin, n [%]	10 [8.8]	10 [8.8]	1.000
Antiplatelet, n [%]	8 [7.1]	7 [6.2]	0.789
Anticoagulation, n [%]	0 [0.0]	1 [0.9]	0.316
Antiarrhythmic, n [%]	14 [12.4]	10 [8.8]	0.677
Procedural anaesthesia			
General anaesthetic, n [%]	6 [5.3]	6 [5.3]	1.000
Local anaesthetic + sedation, n [%]	73 [64.6]	71 [62.8]	0.771
Local anaesthetic only, n [%]	34 [30.1]	36 [31.9]	0.771
Follow-up			
Length of follow-up, days	107 (153)	103 (129)	0.929
Recurrence of arrhythmia, n [%]	4 [3.5]	5 [4.4]	0.734

Abbreviations: TIA, transient ischaemic attack; CKD, chronic kidney disease; AVNRT, atrioventricular nodal reentrant tachycardia; ACE-i, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

Table 15. Electrocardiographic and conduction intervals

	South Asian	Caucasian	p-value
Surface electrocardiogram intervals			
Heart rate, BPM	82.5 (18)	78.0 (18)	**0.024**
P-wave duration, ms	107.0 (19)	105.0 (22)	0.221
RR, ms	726.5 (171)	764.0 (177)	**0.025**
PR, ms	155.9±20.7	158.7±22.6	0.351
QRS, ms	92.0 (16)	96.0 (15)	**0.012**
QT, ms	372.5 (43)	387.0 (36)	**0.001**
QTc, ms	433.9 (53)	441.0 (42)	0.182
Intracardiac electrogram intervals			
AA, ms	720.0 (180)	763.0 (161)	0.070
PA, ms	44.0 (18)	41.0 (14)	0.169
AH, ms	66.0 (23)	71.0 (26)	0.093
HV, ms	37.0 (12)	37.5 (13)	0.841
Intracardiac conduction intervals			
Atrial ERP, ms Total number of measurements*	250 (60) 66	240 (40) 54	0.332
Atrioventricular ERP, ms Total number of measurements*	280 (50) 47	300 (60) 59	**0.001**
AVW cycle length, ms Total number of measurements	320 (58) 113	340 (68) 113	**0.045**
Ventriculoatrial ERP, ms Total number of measurements*	300 (60) 51	320 (93) 52	**0.013**
Ventricular ERP, ms Total number of measurements*	240 (30) 62	240 (35) 61	0.172

Abbreviations: BPM, beats per minute; ms, milliseconds; ERP, effective refractory period; AVW, atrioventricular wenckebach.

** Measurements recorded at a cycle length of 600 ms.*

4.4.4 Intracardiac electrogram and conduction intervals

South Asians had significantly shorter AV-ERP (p= 0.001) and VA-ERP (p= 0.013) intervals (table 15). The AVW cycle length (p= 0.045) was correspondingly shorter (table 15). There were no differences in atrial or ventricular ERP between the two

groups and no differences were seen in the intracardiac electrogram intervals (table 15).

4.4.5 Linear regression analysis

On univariable analysis, South Asian ethnicity was associated with a higher heart rate, narrower QRS and lower AV- and VA-ERP (table 16). Male gender was associated with a lower heart rate and wider QRS whilst diabetes mellitus was predictive of a higher heart rate (table 16). No variable was found to be associated with AVW cycle length. On multivariable analysis, South Asian ethnicity and male gender remained independently predictive of heart rate, QRS duration and AV-ERP (table 16).

Table 16. Univariable and multivariable linear regression analysis for predictors of heart rate, QRS, AV-ERP, VA-ERP and AVW

	Univariable model			Multivariable model		
	B	(95% CI)	p value	B	(95% CI)	p value
Heart rate						
Age	0.005	(-0.145 to 0.155)	0.950			
Male gender	-6.800	(-10.985 to -2.615)	**0.002**	-6.687	(-10.815 to -2.559)	**0.002**
SA ethnicity	4.354	(0.321 to 8.387)	**0.034**	4.049	(0.108 to 7.990)	**0.044**
LA diameter	-0.274	(1.353 to 0.805)	0.612			
Hypertension	5.312	(-1.375 to 11.999)	0.119			
Diabetes mellitus	8.254	(0.625 to 15.884)	**0.034**	7.220	(-0.240 to 14.680)	0.058
QRS						
Age	-0.075	(-0.200 to 0.050)	0.238			
Male gender	5.985	(2.498 to 9.472)	**0.001**	5.997	(2.539 to 9.456)	**0.001**
SA ethnicity	-3.597	(-6.967 to -0.227)	**0.037**	-3.616	(-6.908 to -0.324)	**0.032**
LA diameter	0.198	(-0.496 to 0.893)	0.568			
Hypertension	0.065	(-5.552 to 5.681)	0.982			
Diabetes mellitus	-3.033	(-9.459 to 3.393)	0.353			
AV-ERP						
Age	-0.230	(-1.078 to 0.618)	0.591			
Male gender	17.082	(-4.951 to 39.115)	0.127			
SA ethnicity	-36.158	(-56.976 to -15.340)	**0.001**	-96.721	(-169.363 to -24.079)	**0.012**
LA diameter	8.147	(-0.961 to 17.256)	0.076	9.121	(1.379 to 16.864)	**0.024**
Hypertension	0.407	(-35.559 to 36.373)	0.982			
Diabetes mellitus	-19.342	(-58.518 to 19.834)	0.330			
VA-ERP						
Age				-0.475	(-1.751 to 0.800)	0.461
Male gender				24.841	(-11.196 to 60.878)	0.174
SA ethnicity				-47.894	(-82.973 to -12.814)	**0.008**
LA diameter				-0.439	(-8.131 to 7.252)	0.905
Hypertension				-34.946	(-110.857 to 40.964)	0.363
Diabetes mellitus				-58.447	(-140.675 to 23.782)	0.162
AVW						
Age	-0.132	(-0.722 to 0.458)	0.660			
Male gender	13.971	(-2.845 to 30.787)	0.103			
SA ethnicity	-13.803	(-29.840 to 2.234)	0.091	-12.820	(-28.809 to 3.168)	0.115
LA diameter	2.629	(-1.166 to 6.424)	0.170			
Hypertension	-25.985	(-52.659 to 0.690)	0.056	-24.560	(-51.204 to 2.083)	0.071
Diabetes mellitus	-22.831	(-53.756 to 8.094)	0.147			

Abbreviations: SA, South Asian; LA, Left atrial; AV-ERP, atrioventricular effective refractory period; AVW, atrioventricular wenckebach cycle length; VA-ERP, ventriculoatrial effective refractory period.

4.5 Discussion

To the best of the researcher's knowledge, this is the first study to compare the electrophysiological properties of South Asian and Caucasian hearts using invasive techniques. Within a diverse multi-ethnic population over a 13 year period, this study has found that electrophysiology studies were performed three times more often in Caucasians than in South Asians. It has shown a significant difference in heart rate, AV nodal function and QRS duration between South Asians and Caucasians but no difference in atrial ERP or P wave duration.

4.5.1 Heart rate and AV nodal function

The findings of this study indicate that South Asians have a higher resting heart rate, lower AV-ERP and lower VA-ERP compared with Caucasians and that these differences are independently associated with ethnicity. A plausible explanation for this is that South Asians may have differences in autonomic function.

The autonomic nervous system (ANS) heavily influences cardiac conduction through a complex interaction between sympathetic and parasympathetic innervation and this effect is most apparent at the AV node and sinoatrial node. Sympathetic activity increases sinoatrial node automaticity and enhances AV nodal conduction with the overall effect of increasing heart rate whilst parasympathetic activity has the opposing effects[48]. There is limited evidence to suggest that South Asians have impaired autonomic function with less vagal contribution and increased sympathetic tone[234]. Higher sympathetic activity could explain the study's findings of an increased heart rate and reduced AV nodal refractoriness in South Asians.

Differences in autonomic function might also influence South Asians susceptibility to developing AF. It is now well recognised that the ANS plays an important role in the genesis of AF. The onset of paroxysmal AF is often preceded by an increase in parasympathetic activity, particularly in those without structural heart disease[44]. This

is likely to be due to the fact that vagal stimulation causes heterogeneous shortening of atrial APDs and ERPs creating an environment suitable for the development of atrial re-entrant circuits[45-47]. If South Asians do have increased sympathetic tone, this may play a role in preventing the development of AF. However, further research is required to confirm these findings.

4.5.2 QRS duration

My findings show that South Asians have a shorter QRS duration. Despite previous studies having demonstrated ethnic differences in QRS duration between black and white Americans[295] and in a multi-ethnic Asian population[296], the aetiology behind these differences has not been established.

QRS duration has been shown to correlate with body size[297] and South Asians are known to be of a smaller stature[225] with smaller hearts[224] compared with Caucasians. Therefore, in the South Asian cohort, it is possible that a shorter QRS duration simply relates to their smaller heart size.

More interestingly, the difference in QRS duration could be related to genetic variation. The QRS complex represents ventricular depolarisation and conduction time, processes which occur due to the fast activation of voltage dependent sodium channels. Genome-wide association studies have been performed to examine genes, such as SCN10A and SCN5A, which are responsible for the expression of voltage-gated sodium channels within cardiac tissue[298-300]. They have identified a number of single-nucleotide polymorphisms which can affect the length of the QRS complex. Genetic factors therefore appear to influence QRS duration and could explain the differences seen in this study. However, further research exploring the relationship between the South Asian genome and electrocardiographic parameters is required to clarify this.

4.5.3 Atrial ERP and P wave duration

No difference in atrial ERP or P wave duration was observed between the study cohorts. This would suggest that atrial refractoriness and intra-atrial conduction time are similar amongst the two ethnicities and that the lower prevalence of AF in South Asians is unrelated to these factors. However, it must be remembered that atrial ERP could only be measured in around half of subjects. It is therefore conceivable that there is a difference between the ethnic groups which was not possible to demonstrate.

4.5.4 Burden of arrhythmia in South Asians

During a study period of 13 years, 0.31% of Caucasians underwent electrophysiology studies compared with only 0.09% of South Asians. Potential reasons for this include ethnic variations in the use of healthcare resources although the evidence for this is mixed. South Asians have been found to have less engagement with cancer screening programmes[219, 220], antenatal services[221] and smoking cessation facilities[301]. However, they have also been shown to be more likely to access specialist chest pain clinics[302]. An alternative theory is that South Asians have biological variations which make them less susceptible to arrhythmia. Recent evidence suggests that South Asians are less likely to develop bradyarrhythmia[233] and the same may be true of tachyarrhythmias such as AF. The results of this study suggest ethnic differences in cardiac conduction which may have a genetic basis. If the mechanisms responsible for the reduced arrhythmia burden in South Asians can be fully determined, they may help in the development of novel treatment approaches in the future.

4.5.5 Limitations

Firstly, this is a retrospective cohort study raising the possibility of selection and recall bias. Selection bias was minimised through the recruitment of consecutive South Asian patients who met the eligibility criteria and through the selection of

Caucasian controls based only on age and gender, prior to any screening of their medical records or electrophysiology study. Recall bias was minimised through the comprehensive assessment of the subjects' medical records. Secondly, the data was taken from a single centre and so it may not be generalizable to the whole South Asian population. However, the Yorkshire Heart Centre covers a large geographical area which includes over 260,000 South Asians and so is likely to provide a broad overview of the ethnic group.

4.6 Conclusion

South Asians have differences in heart rate, QRS duration and AV nodal function compared with Caucasians and these effects are independently associated with South Asian ethnicity. These differences may reflect variations in autonomic function or even genetic variants and may help to explain why South Asians seemingly have a lower burden of arrhythmia.

Chapter 5. P wave indices, heart rate variability and anthropometry in a healthy South Asian population

5.1 Abstract

Background: South Asians have a low prevalence of atrial fibrillation (AF) in comparison with White Europeans despite a higher burden of hypertension, diabetes mellitus and coronary artery disease. The reason for this disparity is unclear but may relate to electrophysiological or structural differences within the atria or variations in autonomic function. The researcher aimed to assess these areas using a range of non-invasive cardiac investigations.

Methods: A prospective cohort study was performed on 200 South Asian and 200 Caucasian healthy volunteers aged 18-40 years. All subjects underwent electrocardiography (ECG), echocardiography and anthropometric measurements. Eighty subjects in each cohort underwent 24 hour ambulatory ECG and fifty subjects in each cohort underwent exercise testing.

Results: Compared with White Europeans, South Asians were of a smaller height with lower lean body mass and smaller left atrial size. They had reduced P wave dispersion and P wave terminal force in lead V_1. South Asians had a lower burden of supraventricular ectopy. They had a higher mean heart rate and South Asian males had lower heart rate variability, suggestive of sympathetic predominance. Exercise capacity was lower in South Asians.

Conclusions: South Asians have differences in left atrial size, P wave indices, burden of supraventricular ectopy, heart rate, heart rate variability and anthropometric measurements. These differences may relate to variations in atrial

morphology, atrial electrophysiology and autonomic function and might help to explain why South Asians are less susceptible to developing AF.

5.2 Introduction

The prevalence of AF in South Asians is significantly lower than Caucasians despite higher rates of conventional risk factors. It is feasible that South Asian ethnicity is associated with certain physiological variations with confer protection against the development of AF and that these differences are present in South Asians from birth.

The development of AF not only requires an ectopic focus to act as a trigger for the arrhythmia but also changes in atrial conduction, increases in atrial size and variations in autonomic function to provide an environment capable of maintaining it[37, 44]. Non-invasive cardiac investigations can indirectly assess many of these factors without the inherent risks of invasive testing. A 12-lead electrocardiogram (ECG) can measure P-wave indices, markers of atrial conduction; an ambulatory ECG can determine the burden of supraventricular ectopy (SVE) and measure heart rate variability (HRV), a marker of autonomic tone; echocardiography can be used to measure atrial size; and exercise testing can assess heart rate recovery, a marker of vagal activity, and exercise capacity.

West Yorkshire, England, has a population of over two million,11.9% of whom are of South Asian descent[267]. It is therefore an ideal setting to study why South Asians have less AF. The researcher hypothesized that South Asians would have differences in atrial electrophysiology and autonomic function compared with White Europeans and aimed to assess this by performing a range of non-invasive cardiac investigations. Healthy volunteers were studied to determine the effects of ethnicity on these measurements without potential bias from co-existent cardiovascular conditions.

5.3 Methods

5.3.1 Study population

A single centre prospective cohort study on healthy South Asian and Caucasian volunteers aged 18 to 40 years was performed between 14th February 2017 and 14th December 2017. Subjects were recruited from Leeds Teaching Hospitals NHS Trust, the University of Leeds and local community centres using poster and email advertisements (Figure 16). The study was further publicised at stalls during the University of Leeds Fresher's week and the annual Leeds Sikh festival, and through attendances at local Mosques, Mandirs, Gurdwaras and South Asian sports centres.

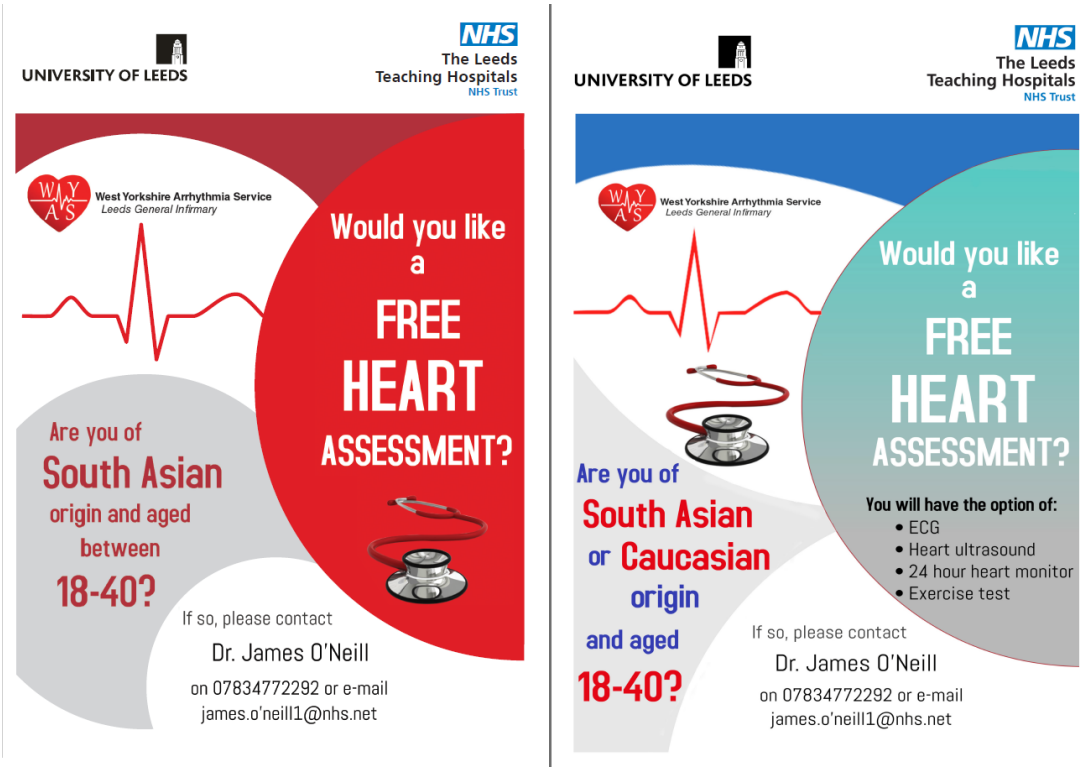

Figure 16. *Examples of poster advertisements*

Subjects were excluded if there was a history of cardiovascular disease, hypertension, diabetes mellitus or dyslipidaemia or if they had evidence of structural heart disease on initial

Figure 17. *Example of social media advertisement*

screening. Adults over the age of 40 were not recruited in order to minimise the risk of subjects having undiagnosed cardiovascular disease. Ethnicity was self-reported and fell into two categories: South Asian (defined as Indian, Pakistani, Bangladeshi, Sri Lankan or Nepalese) and Caucasian (defined as White British or White European). All subjects lived in West Yorkshire and all were born in the United Kingdom except for four South Asians who were born in the Indian sub-continent and two White Europeans who were born in Europe.

Leeds Teaching Hospitals NHS Trust
20 February 2017 ·

Here's a great story that shows how success in research can lead to direct improvements in patient care.

One of our most productive research teams has been able to use part of their research income to supply innovative new heart monitoring devices for clinical use.

The electrophysiology (EP) research team has donated £11,000 to the Cardiac Investigations team at LGI for devices that are smaller and able to record heart rhythms for longer than the current ones. As a result they will improve patient management and care.

In return the clinical unit will be helping the EP research team with a new study looking at why people of South Asian ethnicity are much less likely to develop a common heart rhythm disturbance, atrial fibrillation, despite having many risk factors for the condition.

The research team aim to recruit 200 volunteers of South Asian descent and 200 volunteers of European descent, all of whom are healthy and aged between 18 and 40 years of age.

Everybody who takes part in the trial will have a standard heart tracing (electrocardiogram or ECG). A proportion of participants will also have the opportunity to have a more comprehensive assessment of the heart's function including an ultrasound scan, heart monitor and exercise test. The Cardiac Investigations Unit will help to perform and analyse these tests.

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If you are interested in taking part in the study or would like further information, please contact: Dr James O'Neill, 07834 772292 or email: james.o'neill1@nhs.net.

After obtaining informed consent, all subjects underwent anthropometric and blood pressure measurements, transthoracic echocardiography and 12-lead ECG. Based on the researcher's power calculations, a cohort of 160 volunteers underwent a 24-hour ambulatory ECG and 100 volunteers underwent exercise testing.

The study was approved by the London - Surrey Borders Ethics Committee (REC reference 16/LO/2220).

5.3.2 Anthropometric measurements

All measurements were performed by a single investigator in order to reduce variability. Height was measured to the nearest millimetre using a stadiometer (SECA, model 799, Hamburg, Germany). Participants were asked to remove their shoes and stand with their feet together, heels against the back-board, knees straight and looking straight ahead (with their eyes at the same level as their ears). They were then asked to fully inhale and stand tall and whilst in this position, the measuring arm was moved down on to their head and the measurement recorded[303]. Weight was measured to the nearest 100 grams using a digital scale (SECA, model 799, Hamburg, Germany). Participants were asked to remove their shoes and wear light clothing. They were asked to stand still with one foot on each side of the scale, facing forward with their arms by their sides. Once the measurement was stable, it was recorded[303]. Body mass index (BMI) was calculated by dividing weight by the square of the height and body surface area (BSA) was calculated using the Mosteller method (see Section 3.3.3)[274].

Figure 18. *Height and weight measurement using a stadiometer*

Waist and hip circumference were calculated to the nearest centimetre with an anthropometric tape (Gulick II tape measure, Country Technology, Wisconsin, USA). Measurements were taken without clothing or over very light clothing if this was not possible. For waist circumference, measurements were taken at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest with the participants arms relaxed at their sides and their feet together and at the end of a normal expiration[303]. For hip circumference, measurements were taken at the maximal circumference over the buttocks with the participants arms relaxed at their sides and their feet together[303].

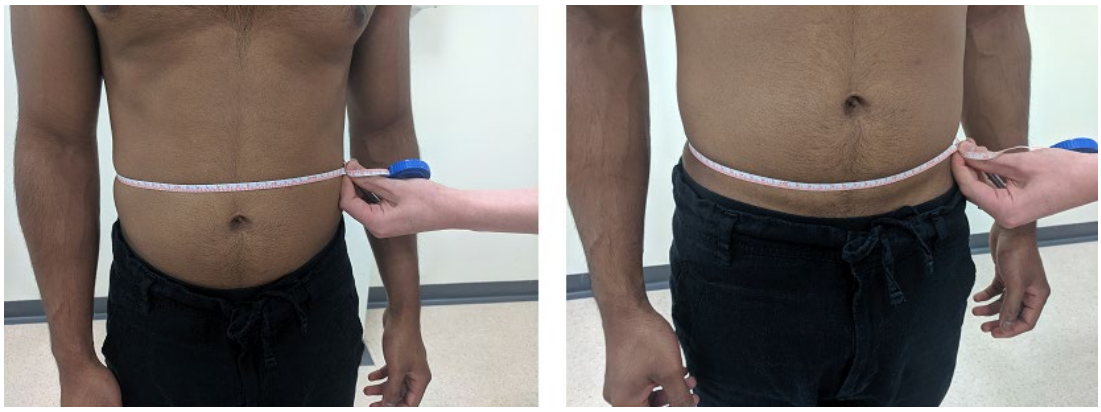

Figure 19. *Waist and hip circumference measurement*

Body fat content was assessed using the skinfold thickness technique[304]. Participants were asked to stand in an upright position and all measurements were taken on the left-side of the body using a Harpenden skinfold caliper (HSK-BI, Burgess Hill, United Kingdom) to the nearest 0.1mm. Measurements were taken at

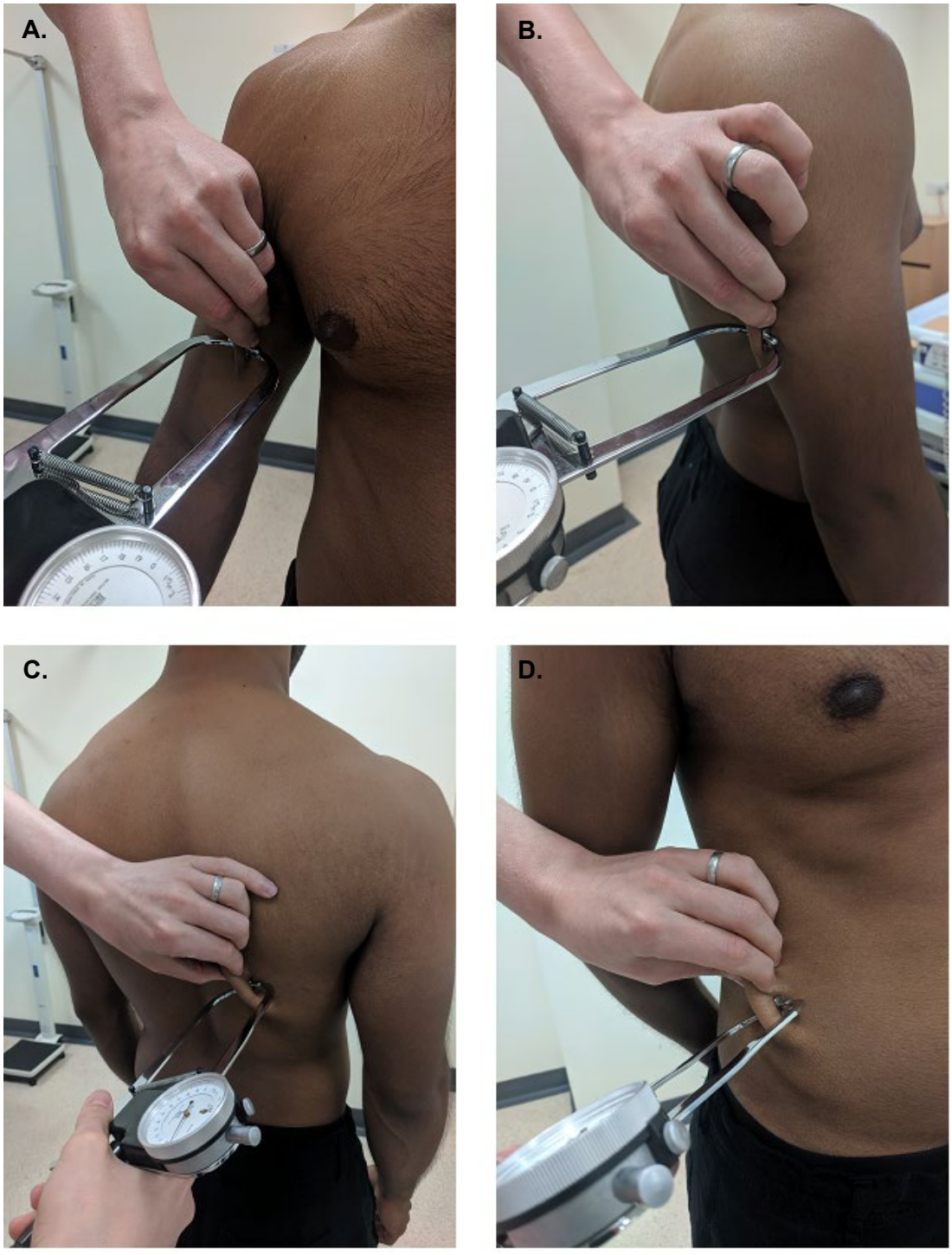

Figure 20. *Skinfold thickness measurements*

A. Bicep B. Tricep C. Subscapular D. Suprailiac

the following sites: tricep (halfway between the acromion process and the olecranon process), bicep (at the same level as the tricep skinfold), subscapular (20mm below the lower angle of the scapula, at an angle of 45° to the horizontal) and suprailiac (20mm above the iliac crest in the mid-axillary line at 45° to the horizontal). At each site, the skinfold was firmly grasped by the investigator's thumb and index finger and pulled away from the body. The caliper was placed onto the skinfold and the measurement was taken four seconds from release of the caliper. Skinfolds were measured in triplicate and the mean of the three values was used in analysis. Skinfold measurements were converted into body fat using the Durnin-Womersley method[305]:

Table 17. Durnin-Womersley method[305]

Age (years)	Body density (male)	Body density (female)	Body fat (%)
18-19	1.1533 - (0.0630*L)	1.1549 - (0.0678*L)	(495/Body Density) - 450
20-29	1.1631 - (0.0632*L)	1.1599 - (0.0717*L)	
30-39	1.1422 - (0.0544*L)	1.1423 - (0.0632*L)	
40	1.1620 - (0.0700*L)	1.1333 - (0.0612*L)	

Abbreviations: L, log of the sum of skinfolds

5.3.3 Blood pressure measurement

Blood pressure was measured in duplicate after subjects had rested for 10 minutes using a semiautomatic validated device (model HEM-59, Omron Healthcare, Netherlands). Measurements were taken using an appropriate sized cuff on the right arm with the subject in a seated position.

Figure 21. *Blood pressure measurement*

5.3.4 Transthoracic echocardiogram

A focussed transthoracic echocardiogram (Vivid S6 and Vscan, GE Healthcare, Milwaukee, USA) was performed on all volunteers to screen for evidence of significant (moderate or severe) valvular heart disease or left ventricular dysfunction. Left atrial diameter was measured in the parasternal long-axis view at ventricular end-systole.

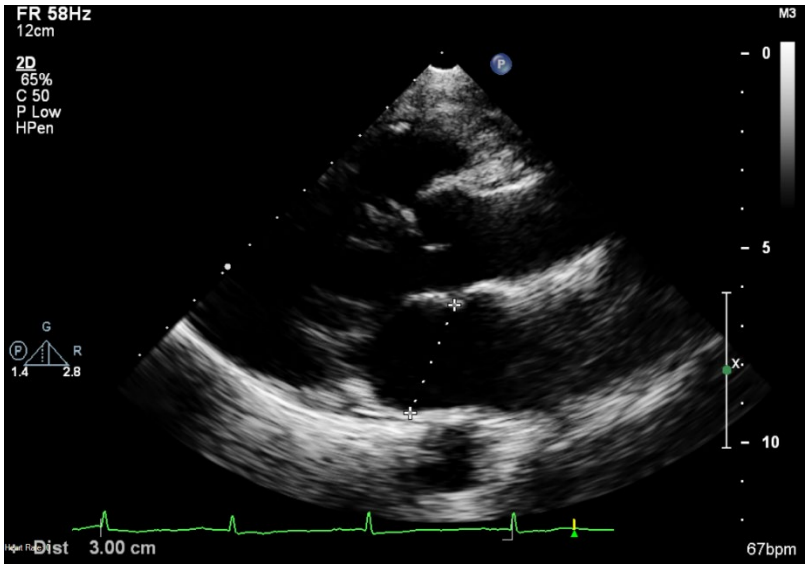

Figure 22. *Left atrial diameter measured by transthoracic echocardiography*

5.3.5 Electrocardiogram

Standard 12-lead ECGs were acquired digitally (Norav PC-ECG 1200, Norav Medical Ltd, Israel) at a calibration of 10mm/mV and a speed of 25mm/s. ECG data was analysed digitally (Resting PC-ECG Application version 5.514, Norav Medical Ltd, Israel) by a single operator who was blinded to the study population. Four electrodes were attached to the arms and legs, slightly proximal to the wrist/ankle. Six electrodes (V1-V6) were placed across the precordium in the conventional anatomical positions as demonstrated in figure 23.

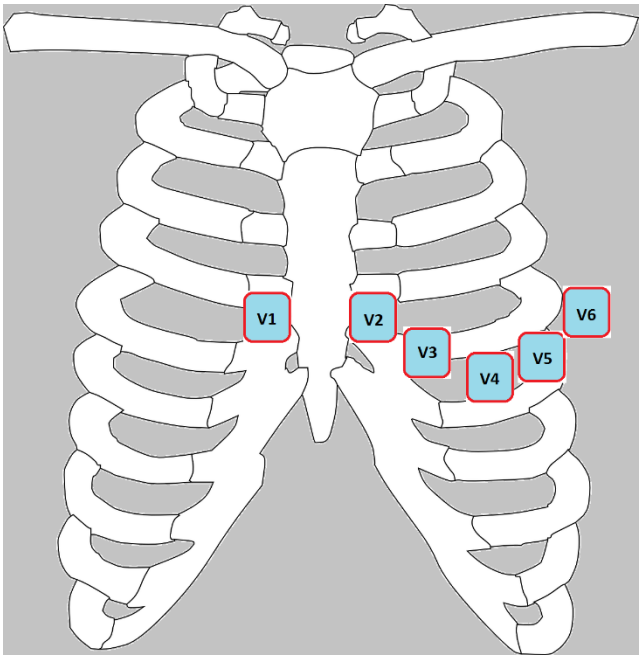

***Figure 23**. Standard precordial electrode placement*

Heart rate, baseline ECG intervals and P wave indices which have been shown to be associated with the development of AF[242, 245, 250, 256] were recorded. Maximum, minimum and mean P wave duration (the onset and offset points of the P wave were defined as the intersection point of upward or downward deflection in relation to the isoelectric line) and P wave amplitude were measured in all 12 leads. P wave dispersion (derived from the difference between maximum and minimum P wave

duration) and P wave terminal force in lead V_1 (PWTF-V_1, defined as the product of the duration and amplitude of the negative terminal portion of the P wave) were also calculated. Measurements were made manually using electronic calipers at a calibration of 40mm/mV and a sweep speed of 200mm/s.

5.3.6 24 hour electrocardiogram

Ambulatory ECG monitoring was performed over a 24 hour period using a 3-lead Holter monitoring device (Lifecard CF Holter, Spacelabs Healthcare, USA). Electrodes were attached under the right and left clavicles in the mid-clavicular line and on the lower edge of the left rib cage.

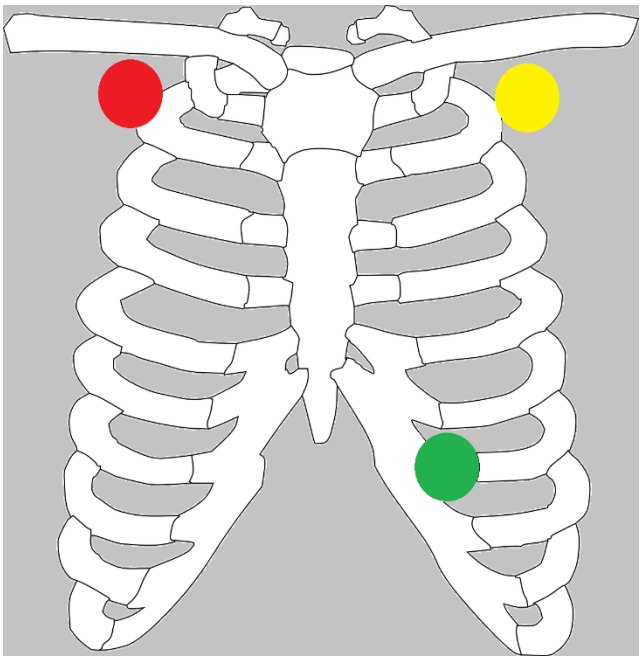

Figure 24. *Ambulatory 3-lead ECG placement*

Subjects were encouraged to continue their usual daily activities, including exercise. Recordings were digitally sampled and analysed (Pathfinder SL, Spacelabs Healthcare, USA) by two operators who were blinded to the study population. The burden of SVE or arrhythmia was recorded. HRV was measured after the manual

removal of artefact and ectopy. Ambulatory ECGs with less than 18 hours of recording or with less than 90% of the recording suitable for analysis were excluded to avoid confounding effects of circadian variations in HRV.

Time-domain and frequency-domain measures of HRV were analysed according to previously published guidelines (see section 1.5.4.3)[263]. Time-domain measurements included the standard deviation of all normal RR intervals (SDNN), the standard deviation of the average normal RR intervals in all 5 minute segments of the entire recording (SDANN), the mean of the standard deviations of all normal RR intervals for each 5 minute segment of the entire recording (SDNN index), the square root of the mean of the sum of the squares of differences between adjacent normal RR intervals (rMSSD) and the integral of the total number of all normal RR intervals divided by the height of the histogram of normal RR intervals (HRV triangular index). Spectral analysis was performed using the fast Fourier transform method. Three frequency bands were calculated: very low frequency power (VLF, 0.017-0.049 Hz), low frequency power (LF, 0.05-0.15 Hz) and high frequency power (HF, 0.15-0.35 Hz).

5.3.7 Exercise test

Treadmill stress testing was performed according to the standard Bruce protocol[306]. A 12-lead ECG was attached with precordial electrodes placed in the standard positions (Figure 23). Limb leads were attached to the right and left infraclavicular fossae (medial to the border of the deltoid muscle) and iliac fossae rather than the arms and legs in order to minimise excessive movement in the limb wires (Mason-Likar 12-lead position[307]). A resting ECG and blood pressure were performed prior to the test commencing at 1.7 miles-per-hour at a 10% gradient. The speed and gradient were then increased every 3-minutes (Table 18) until the subject reached maximal workload and requested termination of the test. At this point, subjects

entered an active recovery phase with the treadmill at a speed of 1.5 miles/hour and a gradient of 2% before a passive recovery phase of four minutes with subjects resting in a semi-recumbent position. Heart rate recovery, defined as the difference in heart rate between peak exercise and after one minute of active recovery was recorded.

Table 18. Standard Bruce protocol stages

Stage	Time (minutes)	Speed (miles/hour)	Gradient (%)
1	3	1.7	10
2	6	2.5	12
3	9	3.4	14
4	12	4.2	16
5	15	5.0	18
6	18	5.5	20
7	21	6.0	22

5.3.8 Statistical analysis

The researcher's power calculations were based upon the results of previous studies which had demonstrated a standard deviation (SD) of 12ms for P wave duration, 8ms for P wave dispersion, 33mV for P wave amplitude, 1.8mm•s for PWTF-V_1, 0.5ms for SDNN and 9 beats-per-minute for heart rate recovery[50, 308, 309]. The researcher calculated that a sample size of 400 subjects would have 80% power to detect a difference of 5ms for P wave duration, 2ms for P wave dispersion, 11mV for P wave amplitude and 0.6mm•s for PWTF-V_1 at a 5% significance level. The researcher calculated that a cohort of 160 subjects for ambulatory ECGs and 100 subjects for exercise tests would have 80%power to detect a difference of 0.1ms for SDNN and 6 beats-per-minute for heart rate recovery at a 5% significance level.

Statistical analysis was performed using SPSS (IBM SPSS Statistics Version 22.0, IBM Corporation, Armonk, New York). Normality of data was tested using a Shapiro-

Wilk test. Continuous variables were expressed as mean ± SD if normally distributed or median (interquartile range [IQR]) if non-normally distributed. Student t test or Mann Whitney U test were used to compare continuous variables depending on normality. Categorical variables were expressed as percentages and compared using Pearson's chi-square test. *P* values of less than 0.05 were considered statistically significant.

5.4 Results

5.4.1 Study cohort

A total of 200 South Asians and 200 White Europeans were recruited. All subjects underwent ECG, echocardiography and anthropometric measurements. Eighty individuals from each cohort underwent 24 hour ambulatory ECG and fifty individuals from each group underwent exercise testing (table 19).

5.4.2 Anthropometric measurements

South Asians were of a significantly smaller height, lower body weight, reduced BSA and lower lean body mass in comparison with White Europeans (table 19). Waist:hip ratio was higher in South Asians but there was no difference in BMI. Importantly, South Asians had evidence of a smaller left atrium, even after correction for BSA.

5.4.3 12-lead ECG and P wave indices

South Asians had a narrower QRS complex in comparison to White Europeans and South Asian females also had a shorter QTc interval (table 20). There was no difference in the PR interval or cardiac axis.

P wave dispersion and PWTF-V_1 were significantly lower in South Asians compared with White Europeans. South Asian females had increased P wave duration but no difference was seen in South Asian males. P wave amplitude was similar in both ethnic groups.

5.4.4 24 hour ECG and heart rate variability

South Asians had higher average heart rates and a significantly smaller burden of SVE (table 21). South Asian males had reduced HRV in all time-domain measures and LF with a trend towards a lower VLF and HF (table 21). No differences in HRV were seen in females.

Data from six South Asian females was invalid due to either artefact or prolonged removal of the ECG leads.

5.4.5 Exercise test

Total exercise time was lower in South Asians and they achieved a lower maximum metabolic equivalents (METs, table 22). There was no difference in heart rate recovery at one minute.

Table 19. Baseline characteristics

	Male			Female		
	Caucasian	South Asian	p-value	Caucasian	South Asian	p-value
Subjects	100	100	*	100	100	*
Age, years	28.0 (7)	28.0 (13)	0.757	23.5 (8)	22.0 (8)	0.687
Alcohol consumption, units/week	10.0 (16)	0.0 (2)	**<0.001**	5.0 (10)	0.0 (0)	**<0.001**
BP- systolic, mmHg	128.3±11.8	129.0±11.6	0.674	122.4±10.0	120.5±12.3	0.313
BP- diastolic, mmHg	77.7±8.5	78.1±9.8	0.781	78.8±8.8	79.2±9.7	0.720
Height, cm	180.5±6.3	173.8±6.8	**<0.001**	165.6±6.2	161.3±5.8	**<0.001**
Weight, kg	81.3 (19.4)	75.0 (16.8)	**<0.001**	62.6 (11.8)	59.5 (13.7)	**0.047**
Body mass index, kg/m^2	24.6 (4.6)	24.2 (4.4)	0.226	22.9 (4.5)	22.9 (4.7)	0.546
Body surface area, m^2	2.0 (0.3)	1.9 (0.3)	**<0.001**	1.7 (0.2)	1.6 (0.2)	**0.006**
Waist circumference, cm	82.0 (17)	83.0 (13)	0.658	71.0 (11)	74.0 (16)	0.059
Hip circumference, cm	99.0 (12)	96.0 (10)	**<0.001**	95.0 (10)	94.0 (12)	0.769
Waist:hip ratio	0.83 (0.1)	0.85 (0.1)	**0.023**	0.75 (0.1)	0.79 (0.1)	**<0.001**
Biceps SFT, mm	5.4 (3.3)	5.6 (4.1)	0.784	8.2 (4.1)	9.2 (4.8)	**0.048**
Triceps SFT, mm	11.9 (6.7)	10.6 (7.7)	0.282	18.7 (7.7)	17.7 (8.5)	0.476
Subscapular SFT, mm	13.1 (8.4)	15.9 (8.5)	**0.003**	14.1 (6.6)	18.8 (8.8)	**<0.001**
Suprailiac SFT, mm	23.6 (13.8)	27.0 (14.6)	**0.027**	20.1 (11.0)	26.3 (9.6)	**<0.001**
Body fat, %	21.9±5.4	22.6±5.4	0.356	29.2±4.7	31.4±5.0	**0.001**
Fat mass, kg	17.5 (8.9)	16.4 (7.9)	0.301	17.6 (6.3)	18.1 (8.2)	0.538
Lean body mass, kg	63.4 (12.1)	57.8 (10.2)	**<0.001**	45.4 (7.0)	41.5 (7.3)	**<0.001**
LA diameter, cm	3.3 (0.6)	3.0 (0.4)	**<0.001**	2.8 (0.4)	2.6 (0.5)	**0.001**
LA diameter/BSA, cm/m^2	1.64 (0.1)	1.58 (0.1)	**<0.001**	1.64 (0.0)	1.58 (0.1)	**0.008**

Values displayed are mean ± SD or median (interquartile range).

Abbreviations: BP, blood pressure; SFT, skinfold thickness; LA, left atrial, BSA, body surface area.

Table 20. Reference ranges for South Asian and Caucasian ECG and P-wave indices

	Male			Female		
	Caucasian	South Asian	p-value	Caucasian	South Asian	p-value
Heart rate, beats/minute	63.0 (16)	67.0 (17)	**0.004**	72.0 (17)	72.0 (15)	0.960
PR, ms	154.0 (28)	150.0 (29)	0.134	144.0 (22)	144.0 (32)	0.889
QRS, ms	84.0 (10)	78.0 (6)	**<0.001**	76.0 (8)	74.0 (6)	**0.002**
QTc, ms	387.0 (30)	382.0 (24)	0.173	400.0 (29)	395.0 (27)	**0.038**
P axis	44.5 (35)	46.5 (25)	0.886	41.5 (32)	44.0 (26)	0.347
QRS axis	48.0 (38)	49.0 (35)	0.845	51.0 (34)	49.0 (30)	0.545
T axis	29.5 (25)	28.0 (24)	0.572	30.0 (23)	28.0 (28)	0.691
Maximum P wave duration, ms	110.0 (12)	110.0 (12)	0.453	102.0 (12)	106.0 (12)	**0.002**
Minimum P wave duration, ms	82.0 (10)	84.0 (10)	0.073	76.0 (12)	84.0 (8)	**<0.001**
Mean P wave duration, ms	99.0 (8)	99.0 (9)	0.251	91.0 (10)	95.0 (7)	**<0.001**
P wave dispersion, ms	28.0 (12)	25.0 (12)	**0.039**	24.0 (12)	22.0 (12)	**0.004**
Maximum P wave amplitude, mV	0.12 (0.06)	0.12 (0.04)	0.883	0.12 (0.04)	0.12 (0.04)	0.783
Minimum P wave amplitude, mV	0.03 (0.01)	0.03 (0.02)	0.937	0.04 (0.02)	0.04 (0.01)	0.618
Mean P wave amplitude, mV	0.07 (0.02)	0.07 (0.02)	0.617	0.07 (0.03)	0.07 (0.02)	0.742
P wave amplitude-lead II, mV	0.11 (0.05)	0.11 (0.05)	0.407	0.11 (0.05)	0.11 (0.05)	0.998
P wave amplitude-lead V1, mV	0.08 (0.04)	0.07 (0.03)	0.370	0.07 (0.04)	0.07 (0.03)	0.883
P wave terminal force, mm•s	0.031 (0.04)	0.021 (0.03)	**0.023**	0.036 (0.04)	0.024 (0.04)	**0.030**

Values displayed are median (interquartile range).

Abbreviation: mm•s, product of millimetres and seconds.

Table 21. 24 hour electrocardiogram and heart rate variability data

	Male			Female		
	Caucasian	South Asian	p-value	Caucasian	South Asian	p-value
Subjects	40	40	*	40	34	*
Age, years	30.0 (6)	32.0 (11)	0.388	24.5 (11)	24.0 (9)	0.815
Length of recording, minutes	1332.8±88.5	1327.9±91.6	0.844	1350.7±78.9	1292.1±84.5	**0.015**
Heart rate (minimum)	49.0±6.1	53.8±6.7	**0.001**	53.6±7.7	56.2±4.8	**0.048**
Heart rate (maximum)	140.1±22.0	137.6±18.0	0.966	146.2±18.2	148.7±18.0	0.517
Heart rate (mean)	72.6±7.6	78.4±7.4	**0.001**	75.8±8.5	81.2±7.4	**0.003**
SVE total % of recording	0.0041 (0.004)	0.0015 (0.002)	**0.024**	0.0020 (0.004)	0.0000 (0.001)	**0.008**
HRV: Time-domain measures						
SDNN, ms	170.1 (59.6)	155.6 (36.6)	**0.011**	158.5 (61.4)	150.8 (44.3)	0.206
SDANN, ms	161.0 (54.9)	140.1 (46.2)	**0.036**	144.9 (47.6)	128.7 (36.4)	0.155
SDNN index, ms	68.8 (19.6)	57.0 (17.6)	**0.002**	63.5 (24.9)	57.8 (12.0)	0.326
RMSSD, ms	49.9 (26.3)	40.1 (16.8)	**0.013**	45.9 (29.9)	42.4 (20.9)	0.622
Triangular index	48.4 (18.2)	42.3 (11.0)	**0.010**	44.1 (23.4)	43.9 (12.2)	0.416
HRV: Frequency-domain measures						
VLF, ms^2	1485 (684)	1184 (948)	0.065	1127 (869)	1048 (635)	0.812
LF, ms^2	2004 (1212)	1274 (1423)	**0.005**	1341 (1091)	1285 (739)	0.803
HF, ms^2	873 (1189)	780 (591)	0.079	941 (1189)	870 (1061)	0.610
LF/HF, %	3.4 (2.7)	3.1 (2.2)	0.909	2.5 (1.7)	2.3 (1.5)	0.789

Values displayed are mean ± SD or median (interquartile range).

Abbreviation: SVE, supraventricular ectopic; HRV, heart rate variability.

Table 22. Exercise test results

	Male			Female		
	Caucasian	South Asian	p-value	Caucasian	South Asian	p-value
Subjects	25	25	*	25	25	*
Age, years	29.5±6.1	32.7±6.1	0.059	26.2±6.9	25.9±6.0	0.804
Resting heart rate, bpm	83.3±10.8	85.7±12.8	0.457	90.6±7.8	91.6±10.8	0.711
Resting systolic BP, mmHg	119.9±7.0	119.2±13.5	0.840	112.8±11.0	104.5±10.0	**0.005**
Resting diastolic BP, mmHg	71.5±6.2	77.4±8.2	**0.001**	72.2±10.3	66.1±8.0	**0.038**
Total exercise time, seconds	961.0±180.7	803.2±167.5	**0.002**	772.0±147.1	633.0±115.6	**<0.001**
Maximum heart rate, bpm	191.2±11.0	193.3±10.8	0.473	193.7±9.7	190.0±14.3	0.280
Maximum systolic BP, mmHg	159.2±14.6	157.8±15.0	0.722	137.7±13.9	138.3±16.1	0.883
Maximum diastolic BP, mmHg	70.0±7.6	70.7±6.7	0.794	69.9±8.9	70.5±16.4	0.209
% of target heart rate	100.0±5.3	103.3±5.1	**0.025**	100.1±4.6	97.7±6.5	0.140
Maximum METS achieved	18.7±3.3	15.7±3.1	**0.001**	15.2±2.9	12.5±2.1	**<0.001**
Heart rate at 1 minute recovery, bpm	160.7±13.4	166.2±12.1	0.122	163.3±11.1	160.7±19.3	0.565
Heart rate at 6 minutes recovery, bpm	108.3±12.4	117.6±9.9	**0.004**	108.3±9.5	111.0±16.8	0.479
Heart rate recovery- 1 minute, bpm	30.0±7.4	26.9±6.9	0.139	29.5±7.5	29.2±9.9	0.626

Values displayed are mean ± SD.

Abbreviations: bpm, beats per minute; BP, blood pressure; METS, metabolic equivalents.

5.5 Discussion

This study provides normal reference ranges for ECG intervals and HRV in a young South Asian population without evidence of cardiovascular disease or its risk factors. Additionally, it demonstrates differences in anthropometric measurements, P wave indices and HRV between South Asians and White Europeans.

5.5.1 Baseline characteristics and anthropometric measurements

Height, weight and BSA were all lower in South Asians, consistent with previous small observational studies[206, 225]. Body size correlates with heart chamber dimensions and increasing height is closely related to increasing left atrial volume[102]. It is not surprising therefore that South Asians had a smaller left atrium compared with White Europeans although interestingly, left atrial size remained significantly smaller even after matching for BSA, suggesting that South Asians have proportionally smaller atria. Atrial enlargement is associated with a higher risk of AF[40] due to its effects on atrial refractory periods and the development of re-entrant circuits[294]. One study has also found that the impact of height on the risk of AF is independent of atrial size and it has been suggested that since increasing body size is related to increased stroke volume and cardiac output[310], the increased risk of AF could be linked to a higher volume load. Consequently, the reduced prevalence of AF seen in South Asians could relate to their smaller stature and reduced left atrial size.

My findings show that South Asians have a significantly lower lean body mass, a measure which has recently been shown to be the predominant anthropometric risk factor associated with the occurrence of AF[100]. It has been speculated that high lean body mass increases stroke volume and cardiac output[101] which in turn can lead to the development of left ventricular hypertrophy[101] and atrial enlargement[101]. These structural changes provide favourable substrate for AF development. Whether lower

lean body mass influences the risk of developing AF in South Asians remains to be determined.

Alcohol consumption was significantly lower in South Asians. Alcohol intake is closely associated with the development of AF, even when consumed at moderate levels[109] and this is believed to be due to its effects on atrial conduction, morphological alteration and autonomic impairment. Therefore, the lower level of alcohol consumption in South Asians may be protective against the development of AF.

5.5.2 P wave indices

South Asians have significantly lower P wave dispersion and PWTF-V_1 in comparison to White Europeans. P wave dispersion is a marker of inhomogeneity in the propagation of sinus impulses across the atria and is influenced by increases in atrial pressure, atrial size and metabolic stress. It has been shown to predict paroxysmal lone AF[242] as well as AF recurrence[248]. PWTF-V_1 correlates with left heart filling pressures, is a specific indicator of left atrial enlargement and is associated with an increased risk of AF[256]. Reduced P wave dispersion and PWTF-V_1 is consistent with South Asians having smaller atrial size. Variations in these indices may also reflect differences in the atrial conduction homogeneity and left heart filling pressures, both of which would influence AF risk, although more invasive techniques are required to confirm this.

South Asian females unexpectedly had a longer P wave duration compared with Caucasian females, implying differences in atrial conduction time. Studies have shown that both a prolonged[245] and shortened[245] P wave duration are associated with the development of AF. Therefore, the relevance of this finding in relation to the risk of AF in South Asians is uncertain.

5.5.3 24 hour ECG and heart rate variability

South Asians had a lower SVE burden in comparison with White Europeans although as one might expect in healthy cohorts, the overall burden of SVE was low in both groups. SVE detected on ambulatory monitoring has been shown to independently predict AF[311].

South Asians had a significantly higher minimum and mean heart rate compared with White Europeans. Heart rate is heavily influenced by the autonomic nervous system and a lower heart rate relates to a relative predominance of parasympathetic activity which in turn has been linked with a higher AF risk[312, 313].

HRV was within normal range in all subjects. Interestingly, South Asian males had significantly lower SDNN, SDANN and triangular index in comparison with Caucasian males. These indices are all markers of overall HRV and mainly reflect increased sympathetic activity[314]. They also had lower RMSSD and a trend towards lower VLF and HF, all of which are markers of lower parasympathetic activity. Differences in HRV have previously been seen in South Asian children[315] but to the researcher's knowledge, this is the first time a difference has been demonstrated amongst South Asian adult males.

Overall, the differences seen in heart rate and HRV may reflect differences in autonomic function and would be most consistent with South Asians having sympathetic predominance. Whether this influences South Asians risk of developing AF is less clear.

5.5.4 Exercise test

Total exercise time and METs achieved were significantly lower in South Asians implying that they are generally less physically active than White Europeans. There was a trend towards lower heart rate recovery in South Asian males, suggestive of

higher sympathetic tone, but no difference was seen in females. The association between exercise and the risk of AF follows a J-shaped curve with increasing physical activity modestly reducing the risk of AF but extreme exercise, such as that performed by endurance athletes, increasing the risk of AF significantly. There are several different mechanisms to explain this. Exercise generally has a positive influence on risk factors such as hypertension, diabetes mellitus and obesity and has been shown to slow the age-related decline in arterial elasticity and associated cardiovascular disease. However, at high levels, exercise can lead to morphological changes such as left atrial enlargement and LVH and increases in vagal tone, all of which favour AF. Although lower exercise levels are likely to increase the risk of AF in South Asians, it is feasible that reduced activity might have the effect of minimising structural and autonomic changes within the heart.

5.5.5 Limitations

Firstly, this study's findings are derived from non-invasive investigations and are consequently indirect measurements of atrial conduction and autonomic function. Nevertheless, this study has identified significant differences between South Asians and White Europeans and the findings have highlighted areas of research for future clinical, genetic and experimental studies. Secondly, the reported reference ranges relate to healthy individuals aged 18 to 40 years of age and so may not be applicable to older subjects. Thirdly, these results are taken from a single-centre cohort and this may limit the generalisability of the findings.

5.6 Conclusion

In comparison with White Europeans, South Asians are of a smaller stature with reduced lean body mass and smaller left atrial size. They have reduced P wave dispersion, indicative of less inhomogeneity of atrial conduction, and lower PWTF-V_1, implying smaller atrial size and potentially lower left heart filling pressures. They also have a lower burden of SVE. Additionally, South Asians have increased mean heart rate and South Asian males have reduced heart rate variability, suggestive of sympathetic predominance. These morphological, electrophysiological and autonomic variations may help to explain why South Asians have a lower prevalence of arrhythmias such as AF.

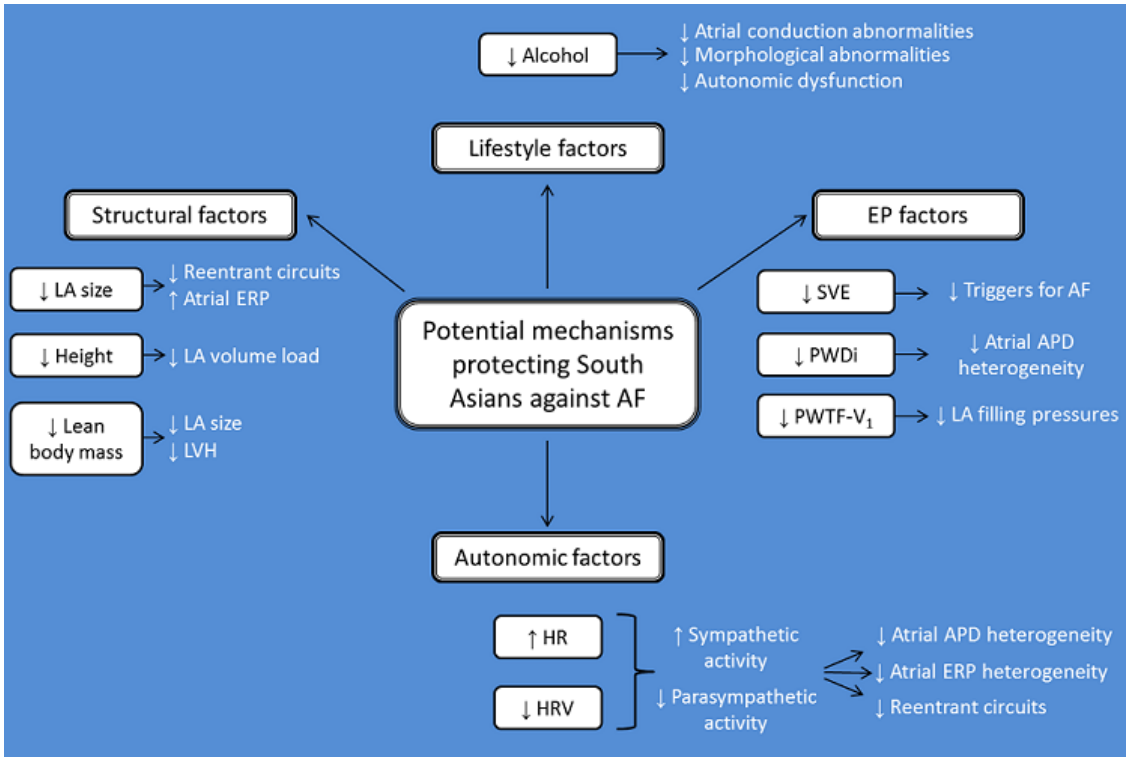

Figure 25. *Summary of findings and their association with risk of atrial fibrillation*

Abbreviations: *LA, left atrial; ERP, effective refractory period; LVH, left ventricular hypertrophy; EP, electrophysiological; SVE, supraventricular ectopy; AF, atrial fibrillation; PWDi, P wave dispersion; APD, action potential duration; PWTF-V1, P wave terminal force in lead V1; HR, heart rate; HRV, heart rate variability.*

Chapter 6. Conclusion

The overall aim of this body of work was to provide a detailed assessment of the morphology and electrophysiology of the South Asian heart and in doing so, determine why South Asians have a lower prevalence of AF in comparison to Caucasians despite an unfavourable cardiovascular risk profile.

The disparity in the prevalence of AF amongst South Asians originates from observational studies which have relied on standard 12-lead electrocardiogram results or primary care records of the arrhythmia. This has led to speculation that rather than having lower rates of AF, South Asians were either less likely to engage with medical services and therefore not have accurate health records or that they were more at risk of paroxysmal AF which would not necessarily be detected with short-term cardiac rhythm monitoring.

Therefore, the initial aim of this work was to clarify AF rates in South Asians with the use of more prolonged cardiac rhythm monitoring methods. In a review of South Asian and Caucasian pacemaker patients, the researcher found that the cumulative incidence of subclinical AF was significantly lower in South Asians with an annual event rate of 6.9% compared with 13.9% in Caucasians. It was also shown that the lower incidence of subclinical AF was independently associated with South Asian ethnicity.

The South Asian heart appears to have a number of important morphological differences in comparison to the Caucasian heart. Firstly, left atrial size is smaller in South Asians and the researcher has demonstrated this with the use of echocardiography and the reference standard of cardiovascular MRI. Additionally, South Asians have reduced left ventricular mass and end-diastolic volume and lower stroke volume. These findings would seem logical since the researcher has

also shown that South Asians are of a smaller height and lower lean body mass, factors which correlate with a lower circulatory volume load and cardiac chamber size. Interestingly however, the structural differences seen in the South Asian heart remained significant after matching for BSA. This would indicate that the South Asian heart is proportionally smaller to the Caucasian heart. Although the exact reason for this is uncertain, given that the study population was exposed to similar environmental factors, it is likely to reflect genetic variation.

South Asians seem to have notable differences in terms of atrial electrophysiology. In comparison with Caucasians, they have been shown to have a lower burden of supraventricular ectopy and differences in P wave indices. P wave dispersion, a non-invasive marker of the inhomogeneity of atrial conduction, was lower in South Asians and they had reduced PWTF-V_1, an indicator of left atrial size and filling pressures.

Additionally, South Asians appear to have differences in autonomic function. Heart rate was consistently higher in South Asians, both during invasive and non-invasive testing. South Asians had reduced atrioventricular nodal refractoriness during electrophysiology studies and South Asian males had lower HRV compared with their Caucasian counterparts. A unifying explanation for these findings would be that South Asians have sympathetic predominance.

The morphological, electrophysiological and autonomic differences identified in South Asians may help to explain why this ethnic group has a lower prevalence of AF. Left atrial size is closely related to the development of AF. As atrial size increases, its ability to accommodate and sustain multiple re-entrant circuits also increases. Therefore if South Asian atria are smaller, they may be less susceptible to re-entry thereby reducing the risk of developing AF. The differences seen in the left ventricle are likely to contribute to this effect. Lower left ventricular end-diastolic

volume and stroke volume equates to a reduced volume load whilst lower left ventricular mass results in reduced left-sided filling pressures. Studies have previously shown that left atrial size increases with left heart pressure and volume and so if these factors are lower, left atrial enlargement is less likely to develop.

To facilitate the initiation of AF, a trigger in the form of an ectopic beat is typically required. South Asians have been shown to have a lower burden of supraventricular ectopy. It would therefore follow that if they have a lower burden of the triggers of AF, it is likely that their risk of AF will also be lower. The maintenance of AF requires abnormalities within atrial tissue. Inhomogeneity in atrial conduction, usually as a consequence of interstitial fibrosis, facilitates the development of re-entrant circuits which in turn enable the perpetuation of AF. The researcher has demonstrated that a non-invasive marker of this, P wave dispersion, is significantly lower in South Asians. This may reflect less heterogeneity in atrial conduction which in turn may reduce their chance of developing re-entry, thus lowering their risk of AF.

The autonomic nervous system plays an important role in the genesis and maintenance of AF. The findings, though not conclusive, do imply a difference in autonomic function and are most in keeping with increased sympathetic activity. In structurally normal hearts, the onset of AF is generally preceded by increased parasympathetic activity which produces focal triggers and creates heterogeneity in conduction within the atria. If South Asians do have more sympathetic dominance with less parasympathetic contribution, this might play a role in reducing their risk of developing AF.

6.1 Future directions

Although the findings from this body of work have highlighted differences within the South Asian heart, the exact reason for the lower prevalence of AF in this ethnic group remains to be fully determined. Further research specifically looking at atrial conduction, autonomic function and the genetics of South Asians is therefore required.

With the use of non-invasive techniques, the researcher has provided evidence which suggests that South Asians may have less inhomogeneity in atrial conduction. It was not possible to directly assess atrial conduction during the examination of invasive electrophysiology studies as this is not a part of the standard protocol. Intra-atrial conduction can be measured with the use of multisite incremental pacing and future work examining this in South Asians would help to clarify whether they do have differences in atrial conduction.

My findings suggest differences in autonomic function in South Asians and support the results of previous studies which have implied that South Asians have higher sympathetic tone. Due to the complexity of the autonomic nervous system, it remains difficult to accurately measure or quantify. More studies examining autonomic tone in South Asians are needed in order to provide further evidence and help confirm whether this ethnic group does indeed have increased sympathetic activity.

Fundamentally, however, the most exciting area of future research will revolve around the genetic profile of South Asians. This population clearly has a lower burden of AF and left atrial size, increased heart rate and differences in atrioventricular nodal function have all been independently associated with South Asian ethnicity. Does this reflect some degree of genetic protection against the development of AF? Do South Asians lack common genetic variants which

predispose to AF? Alternatively, could the differences in South Asian cardiac structure and electrophysiology be related to genetic differences? Genome-wide association studies of AF have yet to be performed in South Asians and these will be essential if the cause for the lower prevalence of AF in South Asians is to be fully determined.

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