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LEFT ATRIAL SIZE AND FUNCTION IN A SOUTH ASIAN POPULATION AND THEIR POTENTIAL INFLUENCE ON THE RISK OF ATRIAL FIBRILLATION

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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).

Hypothesis South Asians have smaller LA size and therefore increased LA function.

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.

Keywords Left atrial volume; Left atrial function; cardiovascular magnetic resonance imaging; ethnicity; atrial fibrillation

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It has an estimated prevalence of 3% in adults aged 20 years or older[1] and this figure is expected to rise further, potentially doubling over the next 50 years[2]. AF is associated with a 1.5-to1.9-fold increase in mortality[3], increases the risk of morbidity that results from stroke or heart failure[4] and can significantly impair patients' quality of life[5]. Risk factors for AF include hypertension, diabetes mellitus, coronary artery disease and obesity[6]. The South Asian population, an ethnic group that originates from the Indian sub-continent and comprises more than a fifth of the world's population, have a high prevalence of these risk factors[7-9] and so it would be reasonable to expect for this population to have high rates of AF. However, studies have consistently shown that South Asians have a lower prevalence of AF compared with Caucasians[7, 8, 10] and the cause of this disparity remains unclear.

It is possible that South Asian atria are 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[11-14]. 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[14, 15]. Although echocardiographic studies have previously suggested that South Asian atria may be proportionally smaller to Caucasian atria[16, 17], the atrial size and function of South Asians has not been formally assessed using the reference technique of cardiovascular MRI.

Therefore, in this study, we aimed to use MRI to investigate atrial morphology and function in a retrospectively selected cohort of South Asian and Caucasian patients. We hypothesized 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.

METHODS

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 1). Patients were identified retrospectively from the local MRI database. 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[18]) with no evidence of cardiomyopathy and patients had been discharged from further cardiology follow-up.

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).

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.

Image analysis

Using the same software (CVI 42, Circle Cardiovascular Imaging, Calgary, Canada), post-processing analysis was performed by JO'N (1 years' experience) and reviewed by PS (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 2). The atrial appendage was included in the analysis but the pulmonary veins were excluded. LA volume was calculated using the disk summation method.

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.

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

- Total LA emptying fraction (LAEF): $(LAV_{max}–LAV_{min})/LAV_{max}$
- Passive LAEF: $(LAV_{max}–LAVpre\text{-}a)/LAV_{max}$
- 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[19].

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.

For the regression model, the following independent variables were used. Age[17, 20, 21], male gender[17, 21], BMI[22] and the presence of hypertension[23-25] or diabetes[26, 27] 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[28-33], 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.

RESULTS

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 1. 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.

Variations in cardiac structure and function

A comparison of LA and LV morphology and function in South Asians and Caucasians is shown in table 2. 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.

Univariable and multivariable regression analysis

Univariable and multivariable relationships of LAV_{min}, LAV_{max} and LA function are shown in table 3 and supplemental tables 1 and 2. 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 (see Supporting Information, Supplemental Table 1). South Asian ethnicity was also a univariable predictor of smaller LA volumes

(Supplemental Table 1). However, on multivariable linear regression, only age, South Asian ethnicity and BSA-corrected LV mass were independent predictors of LAV_{min} and LAV_{max} (Table 3).

Total LA function was negatively associated with age, BMI and LV mass corrected for BSA on univariable regression (Supplemental Table 2). Of these variables, age and LV mass/BSA had a significant association with reduced LA function on multivariable analysis (Table 3). Passive and active LA function demonstrated similar results (Supplemental Table 2).

DISCUSSION

To our knowledge, this is first study to compare LA volume and function between South Asians and Caucasians using the reference technique of cardiovascular MRI. We have 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[7, 8], diabetes mellitus[7, 8] and obesity[34]. Our 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 and these results support the findings of previous studies[21, 31].

We did not demonstrate a difference in LA function between South Asians and Caucasians although this is not entirely unexpected. Whilst a reduction in LA function has been shown to be independently associated with the development of AF, it would be unusual to see significant variations in LA function in cohorts without any known cardiac pathology and 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[21, 35]. 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[36] and lead to a reduction in LA function[37].

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)[16] whilst the EchoNoRMAL study showed that LA diameter, LV size and LV volume were lowest in the South Asian ethnic group[17]. The results of our study, using MRI, support these findings. However, volumetric analysis by MRI is superior to echocardiography[38, 39] and it is likely that our results will have greater reproducibility in future studies.

South Asian ethnicity and its relationship with body size

Our 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 stature[34, 40, 41]. Our 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[42]. 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[41]. They found similar growth trajectories in both groups, suggesting that genetic influences play a more important role than environmental factors.

South Asian atrial size and the risk of atrial fibrillation

South Asians have a lower prevalence of AF compared with Caucasians and this may well be related to their smaller LA size. It is well established that increasing LA size is an important independent predictor of AF[13]. This observation is likely to be related to the fact that increasing atrial size can facilitate the existence of multiple re-entrant circuits[43]. There is also an increased risk of developing atrial fibrosis with atrial enlargement which can subsequently alter atrial conduction and effective refractory periods[44]. 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.

Limitations

This study should be interpreted in the context of several 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, we 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.

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.

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Competing interests None.

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