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Influence of ethnic background on left atrial markers of inflammation, endothelial function and tissue remodelling

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ABSTRACT

Background: It has been suggested that ethnicity can make a significant difference to the likelihood of thromboembolic stroke related to atrial fibrillation. Ethnic differences have been shown to alter inflammatory and haemostatic factors; however, this may all be confounded by differences in cardiovascular risk factors between different ethnicity. The impact of different ethnicities on the thrombogenic profile is not known. The aim of this study was to investigate differences in markers of inflammation, endothelial function and tissue remodelling between Caucasian and Indian populations with supraventricular tachycardia (SVT).

Methods: Patients with structurally normal hearts undergoing catheter ablation for SVT were studied. This study included 23 Australian (Caucasian) patients from the Royal Adelaide Hospital, Adelaide, Australia and 24 Indian (Indian) patients from the Christian Medical College, Vellore, India. Blood samples were collected from the femoral vein, and right and left atria. Blood samples were analysed for the markers of endothelial function (ADMA, ET-1), inflammation (CD40L, VCAM-1, ICAM-1), and tissue remodelling (MMP-9, TIMP-1) using ELISA.

Results: The study populations were well matched for cardiovascular risk factors and the absence of structural heart disease. No difference in the echocardiographic measurements between the two ethnicities was found. In this context, there was no difference in markers of inflammation, endothelial function or tissue remodelling between the two SVT populations.

Conclusion: Caucasian and Indian populations demonstrate similar inflammatory, endothelial function or tissue remodelling profiles. This study suggests a lack of an impact of different ethnicity in these populations in terms of thrombogenic risk.

1. Introduction

Ethnicity can alter cardiovascular risk factors, risk of atrial fibrillation (AF) and stroke risk [1,2]. The Indian population is known to have an altered disease risk profile compared to that of the Caucasian population [3,4]. According to the World Health Organization, cardiovascular disease is the foremost cause of morbidity and mortality in the world and that the Indian population is one of the most at risk ethnic groups [5]. Current data suggests that each year in India approximately 1.5 persons per 1000 individuals suffer a stroke and up to 41% (male, 38%; women, 43%) of stroke victims die acutely following a stroke [6].

AF incidence, which is associated with an increased risk of stroke have also been shown to differ between ethnicities [7]. Furthermore, ethnic differences in some inflammatory and haemostatic factors have previously been demonstrated [8].

Caucasians, have been shown to have an increased risk of AF when compared to African Americans, Asians or Hispanics [9]. However, the treatment of stroke risk in AF through

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anticoagulation has been reported to be less efficacious in preventing strokes in non-Caucasian patients with AF, potentially due to different thrombotic processes [10].

Previous studies have shown that AF is associated with increased left atrial (LA) inflammation, endothelial dysfunction and tissue remodelling [7,11,12]. In contrast, we have shown that Australian Caucasians patients with supraventricular tachycardia (SVT) do not have intra-cardiac regional differences in inflammation or endothelial function [13]. However, there are no studies which have directly compared inflammation, endothelial function and tissue remodelling in patients with SVT from different ethnic groups.

Therefore, the aim of the current clinical study was to evaluate the impact of ethnicity alone on stroke risk factors. We selected patients with structurally normal hearts (SVT) and undertook intracardiac sampling to evaluate the potential differences in markers of inflammation, endothelial function and tissue remodelling between a Caucasian population and Indian population.

2. Methods

This study population consisted of 47 patients with structurally normal hearts, undergoing ablation of left-sided accessory pathway. Twenty three patients were Caucasian recruited from the Royal Adelaide Hospital, Adelaide, Australia, and 24 patients of Indian origin were recruited from the Christian Medical College, Vellore, India. The following exclusion criteria were used: age less than 18 years; previous clinical evidence of AF; any structural abnormality on echocardiography; and any symptoms of arrhythmia in the 48 h prior to the study. All patients underwent echocardiography prior to the procedure to determine left and right atrial and ventricular dimensions, to verify normal parameters of atrial size and function. Any patients who had abnormal cardiac dimensions via echocardiography were also excluded. No patients were taking antiarrhythmic or anticoagulant/platelet medication at the time of procedure.

All patients provided written informed consent to the study protocol that was approved by the Human Research Ethics Committees of the: Royal Adelaide Hospital, Adelaide, Australia; University of Adelaide, Adelaide Australia; and the Christian Medical College, Vellore, India.

2.1. Electrophysiology study

Electrophysiological studies were performed in a fasted conscious state. The following catheters were positioned: (i) 10-pole catheter was positioned within the coronary sinus; (ii) 4-pole catheter at the right ventricular apex; and (iii) 4-pole catheter at the His location. A conventional electrophysiology study was performed to determine the significance of the left sided accessory pathway. Only if clinically indicated, access was obtained to the left atrium. This was performed using a SLO sheath and BRK-1 needle (St Jude Medical, ST Paul, MN). Transeptal puncture was performed using fluoroscopic guidance and pressure monitoring and was confirmed using a contrast injection. The study protocol was performed immediately following transeptal access and prior to the administration of any anticoagulants.

2.2. Study protocol

Immediately following transeptal puncture and before the administration of heparin simultaneous blood samples (20 mls) were collected through the sheaths in the left (LA) and right atria (RA), and femoral vein (peripheral). Blood was collected utilizing a slow withdrawal technique (approximately 1 ml per second) and transferred into tubes containing 3.8% sodium citrate (ratio 1: 9). No ablation was performed prior to the study protocol sampling.

2.3. Analysis by enzyme-linked absorbance assay (ELISA)

The obtained blood samples were centrifuged at 2500 g for 15 min at 4 °C and stored at −80 °C for batch analysis utilizing enzyme-linked immunosorbent assay (ELISA). Endothelial function was measured through asymmetric dimethylarginine (ADMA, Immundiagnostik®) and Endothelin-1 (ET-1, Quantikine® R&D Systems). With inflammation being measured through soluble CD40 Ligand (CD40L, Quantikine® R&D Systems) and Vascular and Intracellular adhesion molecules (VCAM-1 and ICAM-1, Quantikine® R&D Systems) and tissue remodelling via matrix metalloproteinase-9 (MMP-9, Quantikine® R&D Systems) and tissue inhibitor of metalloproteinase-1 (TIMP-1 Quantikine® R&D Systems). All ELISAS were commercially available and completed according to the manufacturer's instructions.

2.4. Statistical analysis

Data are shown as mean difference in sample site and 95% confidence internals. Patient characteristics were compared using student's *t*-test for continuous data or a fisher's exact test for categorical data, all categorical data shown as mean ± SD. All data was tested for normality by a D'Agostino-Pearsons normality test. A one-way ANOVA was used to determine the difference between the two populations, with a Tukeys multiple comparisons to determine the comparison of the means of each site between the two populations. If appropriate, Bonferroni's post hoc analysis was used to compare each of the matching sample sites. Statistical analysis was performed using GraphPad Prism Version 7.0 (GraphPad Software). Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Baseline characteristics

There were no differences between the two populations with respect to demographic characteristics and cardiovascular risk factors (Table 1). There were no structural or functional differences in the echocardiographic characteristics between the groups (Table 1).

3.2. Endothelial function

Fig. 1 demonstrates the findings with regards to markers of endothelial function. There was no difference in these markers between the Caucasian and Indian populations. This result was consistent for both ADMA ($p = 0.369$, 95% CI [P-0.08-0.31: RA: -0.16-0.22, LA: 0.11-0.028]) and ET-1 concentrations and irrespective of sampling site ($p = 0.393$, 95% CI [P: -0.64-0.22, RA: -0.51-0.35, LA: -0.56-0.30]).

3.3. Inflammation

There were no differences in the levels of platelet derived inflammation (CD40L $p = 0.938$, 95% CI [P: -305.7-217.1, RA: -216.6-306.3, LA: -315.7-207.1]) or vascular and intracellular inflammation between the P, RA and LA between Caucasian and Indian populations. (VCAM-1 $p = 0.923$, 95%CI [P: -136.7-93.0, RA: -89.3-140.3, LA: -110.3-119.4]) (ICAM-1, $p = 0.212$, 95%CI [P: -46.5-240.2, RA: -67.8-219.4, LA: -98.5-185.7]) (Fig. 2).

Table 1
Patient characteristics for Caucasian and Indian SVT patients.

	Caucasian population N = 23	Indian population N = 24	P Value
Age (years)	40 ± 12	36 ± 9	0.278
Sex (M: F)	13: 10	16: 8	0.148
Comorbidities			
Heart Failure	0	0	–
Coronary artery disease	0	0	–
Diabetes mellitus	0	0	–
Smoking	1	0	0.359
Hyperlipidaemia	0	3	0.055
Medications			
Beta blockers	7	11	0.120
ACEI/ARB	2	0	0.208
Echocardiographic Parameters	Caucasian population	Indian population	P Value
LA Area (cm^2)	20.4 ± 4.7	24.1 ± 7.8	0.115
RA Area (cm^2)	18.7 ± 3.9	20.6 ± 4.5	0.086
LA diameter (mm)	34.0 ± 3.8	36.4 ± 5.1	0.151
LVEF (%)	63.3 ± 6.8	60.8 ± 9.7	0.309

Data shown as Mean ± SD.

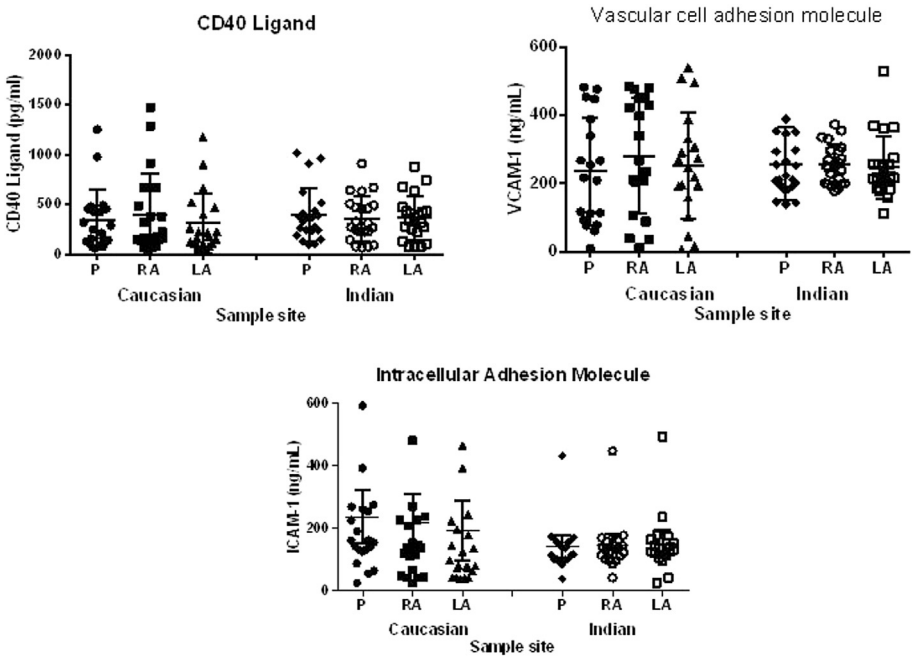

Fig. 1. Endothelial Function (all graphs show Mean 95% CI).
ADMA was not altered at any of the samples sites between the two SVT groups (p = 0.369, 95% CI [P-0.08-0.31: RA: -0.16-0.22, LA: 0.11-0.028]). There were no differences in ET-1 levels between Caucasian and Indian SVT patients (=0.393, 95% CI [P: -0.64-0.22, RA: -0.51-0.35, LA: -0.56-0.30]) this was consistent for each of the sample site at multiple comparison.

3.4. Atrial remodelling

There was no change in atrial structural remodelling as assessed by levels of MMP-9 (p = 0.868, 95% CI [P: -323.4-333, RA: -225.7-282, LA: -182.6-473.8]) and TIMP-1 (p = 0.649, 95% CI [P: -62.1-48.1, RA: -47.2-63.0, LA: -75.5-34.7]), between the Caucasian and Indian populations (Fig. 3).

4. Discussion

This study undertook intra-cardiac and peripheral sampling to evaluate differences in endothelial, inflammatory and structural markers between Caucasian and Indian SVT populations to characterise the potential sources of ethnic variability in stroke risk. We found that these two diverse ethnic groups had;

(i) No difference in markers of endothelial function
(ii) No difference in markers of inflammation
(iii) No difference in markers of tissue remodelling

The current study has shown that mechanisms potentially leading to thrombus formation in the LA (endothelial function, inflammation and remodelling) are not altered between the Caucasian and Indian populations. This study directly compares potential ethnical differences between atrial parameters of endothelial function, inflammation and structural remodelling in two populations with structurally normal hearts.

The patients in this study did not have differences in

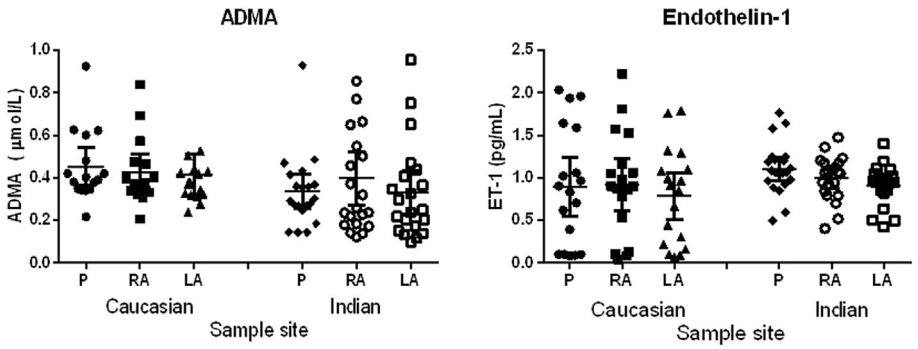

Fig. 2. Inflammation (all graphs show Mean 95% CI).
There was no change in CD40L or V-CAM levels between any of the sample sites, between each the two populations. (CD40L p = 0.938, 95% CI [P: -305.7-217.1, RA: -216.6-306.3, LA: -315.7-207.1]). (V-CAM p = 0.923, 95%CI [P: -136.7-93.0, RA: -89.3-140.3, LA: -110.3-119.4]). As well as for I-CAM-1 (p = 0.212, 95%CI [P: -46.5-240.2, RA: -67.8-219.4, LA: -98.5-185.7]]).

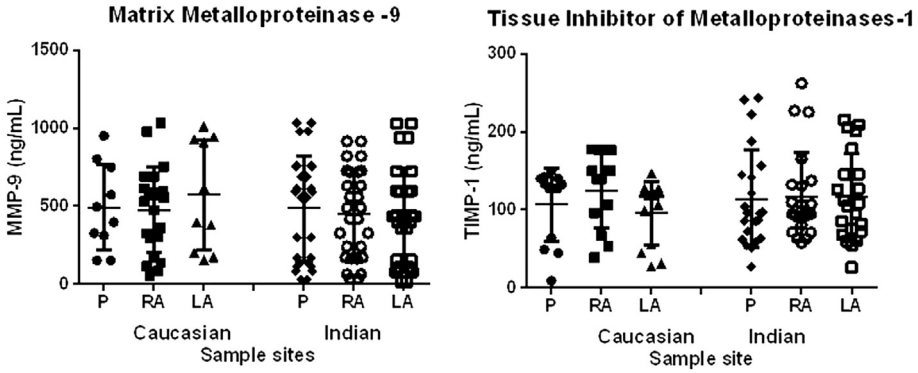

Fig. 3. Tissue Remodelling (all graphs show Mean 95% CI).
There was no difference in the levels of MMP-9 (Fig. 3A, p = 0.868, 95% CI [P: -323.4-333, RA: -225.7-282, LA: -182.6-473.8]) or TIMP-1 (Fig. 3B, p = 0.649, 95% CI [P: -62.1-48.1, RA: -47.2-63.0, LA: -75.5-34.7]) concentrations between any of the sample sites between the Caucasian and Indian SVT populations.

cardiovascular risk factors, or to the structure and function of the heart, as expected in an SVT population (Table 1). There was also no alteration found in markers of structure remodelling in the periphery or with in the atrium which could relate to previously noted risk factors (Fig. 3). Therefore, the underlying disease profile between these two ethnically diverse (Caucasians and Indians) populations was not a compounding factor in this study.

Atrial fibrillation and its associated risk of stroke differ between ethnicities [1,14]. A recent study showed that Black Africans, Chinese, and Japanese had lower incidence of AF compared to that of Europeans. This study also showed that in the case of Black Africans, the decreased incidence of AF occurred despite an increased prevalence of AF risk factors [15]. Further to this the prevalence of heart failure and AF in the under researched South Asian and Black African-Caribbean minority communities in the UK appears comparable to that of the general population. Heart failure and AF will continue to be a major cause of morbidity in all ethnic groups due to ageing of the population [16]. We have previously shown that in an Australian AF population there are atrial thrombotic alterations [7,17]. Although not within a SVT cohort of Australian patients [13].

In addition to the ethnic differences in the risk of AF, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) investigators found there are ethnic differences in the incidence of stroke. It has been shown that there is a significant difference in myocardial infarction and symptomatic intracerebral haemorrhage recurrence among different ethnic groups [18–21]. As hypertension and diabetes are highly prevalent among Asian Indian population, it is expected that this significantly contributes to the higher rate of strokes and heart attacks in India [22]. Our results are in contrast to a previous study by Bennett et al. that found ethnic differences in inflammatory and haemostatic factors, between a South Asian and African Caribbean's, where as we found no difference in inflammation or endothelial function in Caucasian and Indian populations (Figs. 1 and 2) [8]. This disparity suggests that further work is required to accurately determine the contribution of ethnicity to inflammatory and endothelial function responses in cardiovascular disease groups.

It has been shown despite the knowledge there is an ethnic related difference in rate of stroke; ethnicity does not alter the treatment of strokes. With the treatment of stroke risk in AF through anticoagulation (mainly warfarin) having previously been reported to be less efficacious in preventing strokes in non-Caucasian patients with AF [10]. However why this is it still currently unknown, with results form a study from Neurological Disorders and Stroke and the European Co-operative Acute Stroke III trials, finding that the interaction of tissue plasminogen activator with race ethnicity was non-significant [23]. This is consistent with our finding for inflammation and endothelial function, two major components in thrombus formation, with these not altering between Caucasian and Indian populations. Further there was no intra atrial difference as seen in AF, with these two populations having with normal heart and low cardiovascular risk factors.

4.1. Limitations

This study has a number of important limitations. Firstly, it was

conducted at two different locations: Adelaide, Australia and Vellore, India. Despite this limitation we obtained sufficient number of matched SVT subjects at each location. Secondly, this study did not have a specific clinical end point as these patients are not at a known risk of stroke. These populations were chosen as this is a comparison in ethnicity and not a study of disease modification. Due to this disease state being quite uncommon there was also a limitation to the sample size. A further limitation of this study is that patients with SVT have echographically and structural normal hearts and sinus rhythm with a normal resting heart rate, but still have a defined electrical abnormality which could potentially impact results. However, all subjects were sampled in sinus rhythm to avoid any confounding effects of elevated atrial rates.

4.2. Conclusion

This study analysed the differences in intra-atrial and peripheral markers of endothelial function, inflammation and remodelling between the Caucasian and Indian populations. We describe that these populations have similar inflammatory, endothelial function and tissue remodelling responses. This study suggests that comorbidities may account for differences in AF and stroke risk between Caucasians and Indians, rather than ethnicity alone.

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Conflict of interest disclosures

Dr Sanders reports having served on the advisory board of Biosense-Webster, Medtronic, St Jude Medical, Boston-Scientific and CathRx and having received lecture and/or consulting fees from Biosense-Webster, Medtronic, and St Jude Medical. Dr Sanders reports having received research funding from Medtronic, St Jude Medical, Boston Scientific, Biotronik and Sorin.

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