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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).

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