THROMBOGENESIS IN SUBSTRATES OF ATRIAL FIBRILLATION

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ABSTRACT

Background: Atrial Fibrillation (AF) is the most common atrial arrhythmia affecting Australia and the world, with patients with AF known to be at a 5times higher risk of stroke than that of the normal population. The substrates of AF are also known to significantly impact of this risk of stroke. Mitral stenosis (MS) is one of the leading causes of valvular AF in the developing world. Enlargement of the LA is one of the most common structural changes that occurs in MS and is known to lead to fibrosis and oxidative stress. These alterations can also cause atrial electrical remodelling leading to the development of AF. Patients with MS have been shown to have an increase in thrombogenic properties which include platelet reactivity, inflammation and endothelial dysfunction.

The precise mechanisms which underlie this phenomenon of atrial thrombus formation in AF are still unknown, furthermore it is also unknown if the substrate (cause) of AF influences the thromboembolic profile in AF patients. This thesis aims to evaluate the peripheral and atrial thrombogenic profile of both AF and the major substrate MS and their differing disease states alter the thrombus potential.

Methods: A total of 166 patients were collected for this study, 55 patients undergoing a radiofrequency ablation as a curative procedure for paroxysmal AF, at the Royal Adelaide Hospital, Adelaide, 59 patients with mitral stenosis (MS)undergoing a balloon valvuloplasty at

the Christian Medical Centre in Vellore, India, and 52 with aged matched control subjects, diagnosed with left sided accessory pathway supraventricular tachycardia (SVT) undergoing a routine elective electrophysiological study. Blood samples were collected from the peripheral, RA and LA circulation, during each of these procedures, for further analysis through flow cytometry, platelet aggregation and ELISA tests. Echocardiographic studies were used for atrial structure measurements.

Results: We found that within the AF population there is increase in thrombogenic markers within the heart compared to the peripheral circulation. More interestingly when comparing the MS and AF populations each of the different factors involved in thrombogenesis is altered differently, with AF having an increase in platelet reactivity and endothelial function (ADMA and ET-1) and inflammation through VCAM-1 and ICAM-1. However of inflammation through MPO, CD40L and IL-6 and structural remodelling (MMP-9 and TIMP-1) were more pronounced within the MS population.

Conclusion: This study has shown that AF and the valvular AF substrate mitral stenosis (MS) have two distinctly different mechanisms leading to atrial thrombus formation. This shows that MS as a substrate for valvular AF impacts on atrial thrombus formation through remodelling and inflammation whereas non valvular AF affects endothelial function and tissue inflammation. This illustrates that the

pathophysiology of each of the diseases states is different when comparing it to the normal haemostatic properties of the heart within a control (SVT) population to determine if these factors are in fact altered from the norm.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Carlee D Schultz

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PRESENTATIONS AT NATIONALAND INTERNATIONAL SOCIETYS

C Schultz, S Willoughby, H Lim, S Kumar, S Nair, A Srivastava, S Chandy, D Lau, B John, P SandersEffects of Reversal of Chronic Atrial Stretch on Inflammation and Vascular Function, ***Heart Rhythm Society 2014***

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PUBLICATIONS ARRISING FROM THESIS

Chapter 3

Carlee D Schultz, Geetanjali Rangenker, Han S Lim; Angelique Fraudeau, Glenn Young, Kurt Roberts-Thomson, Bobby John, Matthew Worthley, Prashanthan Sanders, Scott R Willoughby. Characterization of Thrombogenic, Endothelial and Inflammatory Markers within the Normal Human Hearts. *Clinical and Experimental Pharmacology and Physiology, 2014*

Chapter 4

Schultz CD, Willoughby S, Lim H, Kumar S, Nair S, Srivastava A, Chandy ST, Lau D, John B, Sanders P. Influence of Ethnic Background on Inflammation, endothelial function and Thrombogenic Factors in Supraventricular Tachycardia.(To be submitted)

Chapter 5

Schultz CD, Willoughby S, Lim H, Kumar S, Nair S, Srivastava A, Chandy ST, Lau D, John B, Sanders P. Atrial Platelet Reactivity, Endothelial Function and Inflammation in Mitral Stenosis: Potential Thrombotic Risk. (To be submitted)

Chapter 6

Schultz CD, Willoughby S, Kumar S, Nair S, Srivastava A, Chandy ST, Lau D, John B, Sanders P. The Reversal of Chronic Atrial Stretch by Balloon Valvuloplasty Alters the Thrombogenic Profile of Patients with Mitral Stenosis. (To be submitted)

Chapter7

Schultz CD, Willoughby S, Lim H, Lau D, Sanders P. Atrial Endothelial Function, Inflammation and tissue remodelling in non-valvular Atrial Fibrillation: Potential Thrombotic Risk. (To be submitted)

Chapter 8

Schultz CD, Willoughby S, Lim H, Kumar S, Nair S, Srivastava A, Chandy ST, Lau D, John B, Sanders P. Atrial Endothelial Function and Inflammation between Atrial Fibrillation and its Substrate Mitral Stenosis (To be submitted)

PRIZES AND AWARDS DURING CANDIDTURE

Young Investigator Award

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  5th Annual Asia Pacific Heart Rhythm Society Scientific Sessions, Taipei, Taiwan, October 3-6, 2012.

Travel Awards

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  Awarded in October 2013.To aid in travel to the 6th Annual Asia Pacific Heart Rhythm Society Scientific Sessions, Hong Kong, October 3-6, 2013.

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