ELECTRICAL REMODELLING OF THE ATRIA AND PULMONARY VEINS DUE TO STRETCH IN RHEUMATIC MITRAL STENOSIS

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A thesis submitted to the Faculty of Health Science, University of Adelaide

in total fulfilment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

Discipline of Medicine - Royal Adelaide Hospital

University of Adelaide,

Adelaide, South Australia

Australia

July 2008

To my wife Rebecca and children Joshua and Hazel

Abstract

Atrial fibrillation is the most common sustained arrhythmia; however, its mechanism is not well understood. Several conditions such as valvular disease, heart failure, and hypertension predispose to atrial fibrillation. Identifying the electrophysiological substrate in these clinical conditions would yield insight into the mechanism of atrial fibrillation and aid in developing strategies to prevent or cure it.

Rheumatic mitral stenosis is associated with high prevalence of atrial fibrillation. While atrial stretch itself may be adequate to explain the occurrence of atrial fibrillation in this population, it is not known if the disease process would remodel the atria so as to increase its propensity. Chapters 2 and 3 present the results of the studies evaluating the substrate for atrial fibrillation in both the left and right atria in rheumatic mitral stenosis. These studies have demonstrated extensive conduction abnormalities both regional and site specific associated with low voltage area and scar. Despite the prolonged atrial refractoriness, the propensity for atrial fibrillation was increased; lending support to the theory that structural remodelling associated with conduction abnormalities plays a greater role in the substrate predisposing to atrial fibrillation. Chapters 4 and 5 present the results of the studies evaluating the immediate effects of chronic atrial stretch reversal on the atrial electrical remodelling. These studies demonstrated that immediately after percutaneous mitral commissurotomy there was decrease in P wave duration, improvement in site specific conduction delay and conduction velocity associated with increase in the voltage. However, there was no change in atrial refractoriness. Chapter 6 studies the substrate long-term after reduction of stretch. There was further increase in conduction velocity and voltage

associated with decrease in atrial refractoriness and conduction delay across the crista terminalis. These observations suggest that strategies aimed at reducing atrial stretch in different disease conditions would potentially decrease the burden or prevent atrial fibrillation.

There is mounting evidence of the effect of stretch on the atria; however, the effect of stretch on the triggers of atrial fibrillation has not been evaluated before. Chapter 7 and 8 present the results of the study examining the effect of acute and chronic stretch on human pulmonary veins. Simultaneous pacing of the right ventricle and pulmonary vein induced acute stretch. The effect of chronic stretch was evaluated in patients with mitral stenosis. The atrial refractoriness was abbreviated in acute stretch while it was prolonged in the chronic form. Nevertheless, both resulted in marked pulmonary vein conduction abnormalities that were pronounced with chronic stretch and extra-stimuli. Additionally, structural remodelling was seen with chronic stretch. These abnormalities implicate stretch in the milieu for re-entry and pulmonary vein arrhythmogenesis in conditions predisposed to atrial fibrillation.

In summary, this thesis has evaluated the effects of stretch on the substrate and triggers of atrial fibrillation. It provides evidence for the importance of structural changes and the associated abnormalities in conduction in predisposing to atrial fibrillation. These observations may be important in the development of tools to treat, cure and prevent atrial fibrillation.

Declaration

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Bobby John

July 2008

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John B, Stiles MK, Kuklik P, Chandy ST, Young GD, Mackenzie L, Szumowski L, Joseph G, Jose J, Worthley SG, Kalman JM, Sanders P. Electrical remodelling of the left and right atria due to rheumatic mitral stenosis. Eur Heart J 2008; 29:2234-2243

Acknowledgements

I would like to thank Professors Prashanthan Sanders, Sunil Chandy and Stephen Worthley for their guidance, support, friendship and encouragement as my supervisors and mentors over this exciting period. It has indeed been a privilege to work side by side with world renowned clinical researchers particularly, Professor Sanders. His dedication to work and research continues to inspire me. I am grateful to Professor Chandy for his insightful direction which culminated in undertaking this thesis.

I am grateful to Biosense-Webster for affording me a scholarship through the University of Adelaide for the duration of my PhD studies. These studies could not have been performed if not for the many patients, who often at times of significant illness, participated in our understanding of the disease.

I want to acknowledge the important role Professor Jose has had in inspiring my career direction to train in Cardiology and further the needs of my institution. I have appreciated the constant encouragement and teaching of Professor George Joseph and Dr Glenn Young, who also provided many of the patients and session times for study protocols. My gratitude to Professor Jonathan Kalman for his guidance and encouragement. My sincere thanks to Professor George Chandy, who constantly prodded me to achieve greater heights. I am indebted to Professor Derek Frewin, former dean of Medicine, University of Adelaide for initiating me into the PhD program. I am greatly indebted to Professor Ian Roberts-Thomson and Daryl Teague, Friends of Vellore, Adelaide who financially supported me as well as encouraged me during the course of the PhD. My sincere gratitude to Dr Yash Lokhandwala for giving me a better understanding of the complexities of cardiac electrophysiology. I am thankful to the many cardiology fellows and registrars who made the Department of Cardiology a place of comradeship, especially to Drs Martin Stiles, Dennis Lau, Hany Dimitri, Viji Samuel, John Roshan, Shashidar, Gautam Sharma, Han Sung Lim and Muayad Alasady. A special thanks to Dr Pawel Kuklik who spent many hours in the development of software to enable my data analysis. Special thanks to Dr Anthony Brooks and Thomas Sullivan for the statistical advice and to Dr Nicholas Shipp for his help in editing the manuscript. My sincere appreciation to Mr Graydon Beatty for technical support and help in understanding the complexities of three dimensional mapping system. I would also like to thank the staff of the Cardiac Catheterisation Laboratory at Christian Medical College and Royal Adelaide Hospital, without whom this research could not have taken place.

A special thanks to my parents Dr John and Elzie Joseph whose prayerful support, love, encouragement and guidance have moulded me through out my life. My appreciation to my grandmother Annama Joseph for being always available with words of encouragement. To John and Mariamma Mathew for the love and support in each new endeavour. To my siblings, Asha, George, Anu, Geoby, Benjamin, Bobby and Chanchal for all their support. I would also like to thank our family from Unley Christian Chapel who have been so much a part of our lives in Adelaide.

Most importantly, I wish to thank my wife Becky and children Joshua and Diya who have remained patient, understanding and supportive through out the trying times while I prepared this thesis. I cannot help but thank my creator for the privilege given to learn more about his masterpiece, though it be in a small way.

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Publications and Communications to Learned Societies

Chapter 2: Electrical Remodelling of the Left and Right Atria in Rheumatic Mitral Stenosis

Chapter 3: Electroanatomic Remodelling of Left and Right Atria in Rheumatic Mitral Stenosis

(1) Manuscript. John B, Stiles MK, Kuklik P, Chandy ST, Young GD, Mackenzie L, Szumowski L, Joseph G, Jose J, Worthley SG, Kalman JM, Sanders P. Electrical remodelling of the left and right atria due to rheumatic mitral stenosis. European Heart Journal 2008; 29:2234-2243

(2) Presentation. 2nd Asia Pacific Atrial Fibrillation Symposium.2006 Tokyo, Japan.

First prize: Young Investigator Award- Asia Pacific Atrial Fibrillation Symposium.

(3) Presentation. 26th Annual Scientific Sessions of the North American Society of Pacing and Electrophysiology. Boston, Massachusetts, USA. 2006. [Abstract] Heart Rhythm 2006; 3: S194.

(4) Presentation. 54th Annual Scientific Sessions of the Cardiac Society of Australia and New Zealand. Canberra, Australia. 2006. [abstract] Heart Lung and Circulation 2006; 15S:107

Chapter 4: Acute Effects of Chronic Atrial Stretch on Left and Right Atrial Electrical Remodelling

Chapter 5: Acute Effects of Chronic Atrial Stretch on Left and Right Atrial Electroanatomic Remodelling

Chapter 6: Long Term Effects of Chronic Atrial Stretch Reversal.

(1) Manuscript: John B, Stiles MK, Kuklik P, Chandy ST, Young GD, Mackenzie L, Szumowski L, Joseph G, Jose J, Worthley SG, Kalman JM, Sanders P. Reverse remodelling of the atria after treatment of chronic stretch in humans: implications for the atrial fibrillation substrate. **Submitted.**

(2) Presentation. 3rd Asia Pacific Atrial Fibrillation Symposium. Taiwan, Republic of China. 2007.

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(4) Presentation. 55th Annual Scientific Sessions of the Cardiac Society of Australia and New Zealand. Christchurch, New Zealand. 2007. [Abstract] Heart, Lung and Circulation 2007; 6:S102.

(5) Presentation. American Heart Association 80th Scientific Sessions. Rolando, Florida, USA. 2007. Circulation 2007; 116 Supplement II-438.

(6) Presentation. 56th Annual Scientific Sessions of the Cardiac Society of Australia and New Zealand. Adelaide, Australia. 2008. [Abstract] Heart, Lung and Circulation 2008; 17:S126.

<u>Chapter 7:</u> Pulmonary Vein Remodelling due to Acute Stretch: Effect of Stretch on the Triggers of Atrial Fibrillation

(1) Presentation. 56th Annual Scientific Sessions of the Cardiac Society of Australia and New Zealand. Adelaide, Australia. 2008. [Abstract] Heart, Lung and Circulation 2008; 17:S125.

(2) Submitted for presentation at the American Heart Association 81st Scientific Sessions. New Orleans, Louisiana, USA

<u>Chapter 8:</u> Remodelling of Pulmonary Veins due to Chronic Atrial Stretch

(3) Presentation. 56th Annual Scientific Sessions of the Cardiac Society of Australia and New Zealand. Adelaide, Australia. 2008. [Abstract] Heart, Lung and Circulation 2008; 17:S130.

(4) Submitted for presentation at the American Heart Association 81st Scientific Sessions. New Orleans, Louisiana, USA

Abbreviations

CL	Cycle length
CS	Coronary sinus
CSNRT	Corrected sinus node recovery time
CT	Crista terminalis
ECG	Electrocardiogram
ERP	Effective refractory period
HLRA	High lateral right atrium
HSRA	High septal right atrium
ICE	Intracardiac echocardiography
LA	Left atrium
LAA	Left atrial appendage
LLRA	Low lateral right atrium
LSPV	Left superior pulmonary vein
LVEF	Left ventricular ejection fraction
MS	Mitral stenosis
MC	Mitral commissurotomy
NYHA	New York Heart Association
PV	Pulmonary vein
PWD	P wave duration
RA	Right atrium
RSPV	Right superior pulmonary vein
RV	Right ventricle