

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

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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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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.

First Prize: Young Investigator Award – Asia Pacific Atrial Fibrillation Symposium.

(3) **Presentation.** 27th Annual Scientific Sessions of the North American Society of Pacing and Electrophysiology. Denver, Colorado, USA. 2007 [abstract] Heart Rhythm 2007; 4(5):S178-9.

(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. Orlando, 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.

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

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Chapter 8: 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