ATRIAL REVERSE REMODELING IN HYPERTENSIVE SUBSTRATE

Shivshankar Thanigaimani. MS.

Centre for Heart Rhythm Disorders
Royal Adelaide Hospital

&

School of Medicine
The University of Adelaide

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ABSTRACT

Hypertension is a major independent risk factor for atrial fibrillation (AF). Despite various clinical and experimental studies on atrial remodeling in hypertensive substrates, pre-clinical experimental studies involving the prevention and treatment of electrical and structural changes secondary to hypertension remain limited. Many antihypertensive drugs have been shown to reduce AF recurrence in patients with hypertension. Additionally, recent work suggests that anti-fibrotic drug, Tranilast, has beneficial effects in preventing AF. This thesis focuses on the electrophysiological and structural effects with anti-fibrotic and anti-hypertensive therapies in hypertensive large animal model.

Chapter 1 details the theoretical mechanisms involved in the initiation and maintenance of AF and various conditions that contributes to abnormal atrial substrate formation. Importantly, studies involving reverse remodeling of various substrates and possible prevention of pathological atrial remodeling are also discussed.

Chapter 2 details the histological, anatomical and molecular changes in the hypertensive atria. We demonstrated that hypertension resulted in structural remodeling through increased myocyte hypertrophy, endomysial and interstitial fibrosis and inflammation along with increased septal thickness, which was contributed by increased CTGF and TGF-$ß_1$ and reduced connexin43 expressions. Further, we showed that anti-hypertensive treatments could reverse all these pathological changes. This highlights the important

role of aggressive blood pressure lowering therapy in patients with AF and hypertension.

Chapter 3 illustrates the reverse electrical remodeling of hypertensive substrate using anti-hypertensive therapies. Significant improvement in conduction abnormalities and reduction in susceptibility to AF were seen with anti-hypertensive treatments. This further affirms the importance of blood pressure control in patients with hypertension and AF.

Chapter 4 details the histological, anatomical and molecular changes leading to the prevention of remodeling process in hypertensive atria. Tranilast (anti-fibrotic) treatment resulted in prevention of atrial structural remodeling by preventing myocyte hypertrophy, endomysial and interstitial fibrosis, inflammation, septal thickness and altered CTGF, TGF-$ß_1$ and connexin43 expression levels.

Chapter 5 illustrates the prevention of atrial electrical remodeling in hypertensive atria with tranilast treatment during the development of high blood pressure. The results showed a reduced susceptibility to AF by preventing conduction slowing and heterogeneity seen with hypertension. Importantly, the beneficial effects seen in chapter 4 & 5 with tranilast treatment were independent of blood pressure levels.

Chapter 6 examines the fibrillatory electrograms in hypertensive atria. Complex fractionated atrial electrograms (CFAE) and dominant frequency (DF) are thought to

represent substrate sites in AF. A novel index of spatio-temporal stability (STS) was used in this study. We found that STS of CFAE was able to better predict AF termination than absolute mean fractionation values.

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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PUBLICATIONS AND COMMUNICATIONS TO LEARNED SOCIETIES

Chapter 2 & 3:

Conference proceedings: Shivshankar Thanigaimani, Dennis H. Lau, Anthony G. Brooks, Pawel Kuklik, Rajiv Mahajan, Timothy Kuchel and Prashanthan Sanders. Reverse remodeling of the atrial substrate in hypertensive ovine model: Implications of conventional anti-hypertensive drugs. Cardiac society of Australia and New Zealand, Gold coast, Australia. Heart Lung and Circulation. 2013. Vol 22; Page – S99..

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Chapter 4 & 5:

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Chapter 6:

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