Thesis title:

Obesity and Atrial Electrical and Mechanical Remodeling: Implications for Atrial Fibrillation.

Candidate name:

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Academic institution and discipline:

The University of Adelaide, Discipline of Medicine.

Thesis by publication structure and acknowledgements

The following thesis is the product of 5 years of work investigating the relationship between obesity and atrial fibrillation mechanisms and therapy. It is presented as a thesis by publication. The thesis abstract provides an overview of the research questions addressed and the hypotheses examined and summarizes the methodologies results and conclusions. The chapter 1 is an introductory review of the pertinent literature, forming the background for the following experimental work. The summary of the introductory chapter and the concluding chapter 5 has been presented in the form of a review paper to the peer reviewed journal, Obesity Reviews ("Obesity and Atrial Fibrillation", Article first published online: 24 JUL 2013 DOI: 10.1111/obr.12056).

Chapter 2 is the preclinical manuscript investigating the atrial structural, functional and electrical changes with progressive weight gain. The experiment utilizes cardiac magnetic resonance imaging, high density multi electrode epicardial electrophysiological measurements, histopathology and molecular analysis in an Ovine model of progressive weight gain. The paper was presented and awarded first prize at the Cardiac Society of Australia and New Zealand Ralph Reader Award 2011 basic sciences category and runner up at the Asia Pacific Heart rhythm society Young Investigator Award 2011. The manuscript has subsequently been published in the Heart Rhythm journal ("Obesity Results in Progressive Atrial Structural and electrical Remodeling: Implications for Atrial Fibrillation", Volume 10, Issue 1, January 2013, Pages 90–100). Chapter 3 is a single centre randomized and controlled clinical study into the

impact of lifestyle intervention, focusing on weight and cardio metabolic risk factor management, on atrial fibrillation symptoms, arrhythmia frequency, arrhythmia duration and cardiac structure. The manuscript has been presented and awarded first prize in 2012 at the American Heart Association Samuel Levine Young Investigator Award and is currently in the external peer review domain for publication. Chapter 4 is a study into the role of weight loss on pericardial fat burden and its relationship to semi-quantitative atrial fibrillation burden. The clinical study is a sub-study of the above, utilizing cardiac magnetic resonance imaging to quantify pericardial fat and cardiac chamber volumes, anthropometry and serum biochemistry. The paper was presented and awarded first prize in 2013 at the American College of Cardiology Young Investigator Award clinical category presentations. The paper will be submitted for peer review and publication.

This thesis could not be completed without the guidance, mentorship, patience and support of my supervisor, Professor Gary Wittert. In addition, to the support and contribution of all co-authors on each manuscript, a special mention is made to my friend and colleague Dr Darryl Leong. His insight, dedication and expertise have been immensely invaluable to seeing through the completing of each manuscript chapter.

Thesis declaration:

I certify that this work contains no material which has been accepted for the award of any other degree or diploma 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 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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Dr Hany Abed

Abstract

Background

Epidemiological evidence identifies obesity as an independent risk factor for atrial fibrillation (AF). Additionally, therapeutic outcomes for AF appear to be adversely affected by the presence of obesity.

Conditions associated with AF such as hypertension, obstructive sleep apnea, coronary disease and cardiac failure have common salient atrial electro-structural features, predisposing to arrhythmias. Many of these conditions are also associated with obesity and atrial hypertension. However, the degree by which obesity itself, independent of confounding hemodynamic changes, results in atrial electro-structural changes favoring arrhythmogenesis remains unknown.

Aims

The aim of our first study was to determine, using an ovine model, the electro-structural changes resulting from weight gain and obesity, and the contribution of the accompanying hemodynamic abnormalities. Following characterization of the obesity related atrial "substrate"; we investigated, in humans with atrial fibrillation, whether weight loss with cardio-metabolic risk factor management reduces arrhythmia burden, disease severity and structural correlates of reverse remodeling.

Hypotheses:

(I) Progressive weight gain promotes pro-arrhythmic atrial changes. (ii) Weight reduction combined with effective management of obesity-related co morbidities has favorable effects on AF severity and burden. (iii) Weight reduction and risk factor management has a favorable effect on atrial remodeling and pericardial fat volume (PFV).

Methods

Atrial structural (cardiac MRI), histological (tissue infiltrates and pro-fibrotic mediators) and electrical (tissue conduction and excitability) changes accompanying progressive weight gain over 8 months through ad-libitum calorie-dense feeding, were determined in male sheep sampled at baseline, 4 and 8 months (10/group).

The clinical study was conducted as a single center randomized prospective trial, to investigate the effect of weight and cardio-metabolic risk factor management on AF severity, AF burden, atrial structure, myocardial mass and pericardial fat volume. The study utilized a physician-led weight and risk factor management program. This was compared to a parallel control group provided with brief lifestyle counseling and daily supplementation with marine triglycerides.

Results

The pre-clinical work showed that diet-induced obesity was accompanied by a progressive increase in atrial size, tissue inflammatory, lipid and fibrotic infiltrates. Molecular markers of pro-fibrotic mediators were also increased. There was slowing in

conduction velocity, heterogeneity of conduction dispersion and greater AF burden. The electrical abnormalities persisted following statistical adjustment for systemic and atrial hypertension and the changes were more profound with greater increase in weight.

The clinical work demonstrated an effective reduction in AF burden and severity, using a standardized validated AF severity questionnaire and ambulatory rhythm monitoring. In addition, there was a reduction in atrial size and ventricular wall thickness accompanying a favorable cardio-metabolic risk profile. There was a favorable reduction in PFV, height-indexed atrial volumes and myocardial mass. On post-hoc analysis PFV was predictive of the reduction in AF severity scores.

Conclusion

Diet induced obesity resulted in atrial conduction and structural abnormalities independent of systemic and left atrial hypertension, suggesting an obesity-specific effect.

Our translational work shows that the burden of AF may be reduced through effective weight loss and appropriate management of the underlying metabolic derangement. Moreover, pericardial fat volume is independently predictive of AF severity and this depot is amenable to lifestyle intervention.

Subsequent investigation requires further analysis of inflammatory markers, molecular pathways regulating fibrogenesis and myocardial electrical activity and the effect of

pharmacological inhibition of key mediators. Long-term outcome studies to determine maintenance of benefit are also required.