ATRIAL FIBRILLATION AND OBESITY:

CHARACTERIZATION OF ELECTRO-STRUCTURAL ATRIAL SUBSTRATE WITH SUSTAINED OBESITY AND REVERSAL UPON WEIGHT REDUCTION

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To my parents Sabita and Bal,

my soulmate Kavita

and

my daughter Idhika

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Abstract

Atrial fibrillation (AF) is the most prevalent arrhythmia affecting humans. The identification of risk factors for AF has ushered a risk factor based approach for management. Obesity is a highly prevalent and novel risk factor for AF with a potential for reversibility. The epidemiological link between obesity and AF has been established in population based studies; however the atrial substrate remains to be fully characterized. Furthermore, mechanism and degree of reversibility with weight reduction has not been described. This thesis evaluates the various aspects of endocardial and epicardial atrial remodeling with sustained obesity and the underlying mechanisms in an ovine model. It also examines the endocardial atrial remodeling with obesity in humans and its relationship with epicardial adipose tissue. In addition, the reversal of obesity related atrial substrate with weight reduction has been characterized in a sustained obesity ovine model.

Chapter 2 examines the endocardial electrophysiological remodeling with sustained obesity in an ovine model. Sustained obesity was associated bi-atrial slow and heterogeneous atrial conduction with increased fractionation and greater vulnerability for AF. There is no significant alteration in endocardial atrial refractoriness. Although there was no difference in mean voltage there was increased voltage heterogeneity. Obesity was associated with overexpression of pro-fibrotic TGFβ1 and increased atrial fibrosis. Infiltration of the epicardial atrial musculature by the contiguous fat was seen and this could represent a unique substrate for AF in obesity.

Chapter 3 describes the reversal of the obesity related atrial substrate with weight reduction in an ovine model. Sustained obesity was associated with bi-atrial epicardial slow and heterogeneous conduction, reduced atrial refractoriness (epicardial) and increased propensity for AF. This was associated with hemodynamic stress and diastolic dysfunction. Histologically obesity was associated with atrial fibrosis, inflammation and fatty infiltration. There was up-regulation of atrial TGFβ1 expression and Endothelin receptor B. The TGFβ1 expression correlated with electrophysiological changes and atrial fibrosis, and this relationship persisted even after adjusting for left atrial pressure. There was decreased expression of atrial gap junction protein Connexin43 expression. The changes observed with sustained obesity were reversed with moderate weight reduction.

Chapter 4 describes the electrophysiological reverse remodeling with weight reduction in an ovine model. Weight reduction resulted in improvement in endocardial atrial conduction velocity and decrease in conduction heterogeneity. However, the atrial refractoriness from endocardial sites did not change with either obesity or weight reduction. This is in contrast to epicardial atrial refractoriness which shortened with sustained obesity and improved to control values with weight reduction. This endocardial- epicardial dissociation in atrial refractoriness may represent part of the unique substrate for AF in obesity.

Chapter 5 describes the validation of atrial pericardial fat assessment on cardiac magnetic resonance imaging against the gold standard of autopsy.

Chapter 6 describes the electroanatomic remodeling with obesity in humans and describes the association with atrial pericardial fat.

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Rajiv Mahajan
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Publications and Communications to Learned Societies

Chapter 2

1. **Presentation:** Presented at the Annual Scientific Sessions of the Heart Rhythm Society, May 2013, Denver, USA and published in abstract form (Heart Rhythm 2013:10: S259).
2. **Presentation:** Presented at the Annual Scientific Sessions of the Heart Rhythm Society, May 2012, Boston, USA and published in abstract form (Heart Rhythm 2012; 9: S185).
3. **Presentation:** Presented at the Annual Scientific Sessions of Cardiology Society of Australia, August 2012, Brisbane, Australia and published in abstract form New Zealand (Heart, Lung and Circulation 2012; 21;S125)

Chapter 3

1. **Young Investigator Award Presentation:** Presented at the Annual Scientific Sessions of the Heart Rhythm Society, May 2013, Denver, USA and published in abstract form (Heart Rhythm 2013; 10: S484).
2. **Young Investigator Award, Ralph Reader prize Presentation:** Presented at the Annual Scientific Sessions of Cardiology Society of Australia and New Zealand, August 2013, Goldcoast, Australia and published in abstract form (Heart, Lung and Circulation 2013; 22:S1-2)
3. **Best Oral Abstract Presentation:** Presented at the Annual Scientific Sessions of the Asia Pacific Heart Rhythm Society, October 2013, Hong

Kong, Hong Kong and published in abstract form (Journal of Arrhythmia 2013; 29:i1-130)

Chapter 4

1. **Presentation:** Presented at the Annual Scientific Sessions of Cardiology Society of Australia, August 2012, Brisbane, Australia and published in abstract form New Zealand (Heart, Lung and Circulation 2012; 21;S109-110)
2. **Presentation:** Presented at the Annual Scientific Sessions of the Heart Rhythm Society, May 2012, Boston, USA and published in abstract form (Heart Rhythm 2012; 9: S405).

Chapter 5

1. **Manuscript:** Mahajan R, Kuklik P, Grover S, Brooks AG, Sanders P, Selvanayagam JB. Cardiovascular magnetic resonance of total and atrial pericardial adipose tissue: A validation study and development of a 3 dimensional pericardial adipose tissue model. Journal of Cardiovascular Magnetic Resonance. 2013;15;73
2. **Presentation:** Presented at the Annual Scientific Sessions of Cardiology Society of Australia, August 2012, Brisbane, Australia and published in abstract form New Zealand (Heart, Lung and Circulation 2012; 21;S233)
3. **Presentation:** Presented at the Annual Scientific Sessions of the Heart Rhythm Society, May 2012, Boston, USA and published in abstract form (Heart Rhythm 2012; 9: S413).

Prizes and Awards during Candidature

1. Best Oral Abstract (First prize), Asia Pacific Heart Rhythm Society, 2013.
2. Ralph Reader Young Investigator Award (First prize), Cardiology Society of Australia and New Zealand, 2013.
3. Young Investigator Award (First prize), Heart Rhythm Society, Denver, 2013.
4. SA Heart Research Award (First prize), Adelaide Australia, 2013.
5. Cardiac Society of Australia and New Zealand Travelling Fellowship: 2013
6. First prize, Nimmo Prize, Royal Adelaide Hospital Research Forum, Adelaide Australia, 2012.
7. International Postgraduate Research Scholarship (2011). *University of Adelaide*.
8. Australian Post Graduate Award (2011). *University of Adelaide*.
9. Leo J Mahar Electrophysiology Scholarship (2011). *University of Adelaide*.