AN EXAMINATION OF THE ROLE OF ATRIAL STRETCH IN THE GENESIS OF ATRIAL FIBRILLATION AND THE ANTIARRHYTHMIC EFFECTS OF DIETARY FISH OIL

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1 Abstract

This thesis is submitted as a PhD by portfolio of publications. It explores the role of atrial stretch in the pathogenesis of atrial fibrillation and the modulating effect of dietary fish oil.

Atrial fibrillation is more common in conditions associated with atrial stretch. This relationship is thought to be due to changes in activity of stretch-sensitive ion channels and alterations in calcium handling. Increasing atrial pressure in isolated rabbit hearts shortens atrial refractoriness and enhances the inducibility and sustainability of atrial fibrillation.

The first of the publications in this thesis[1] describes the effect of pericardial constraint on the isolated rabbit heart model which uses increasing atrial pressure as a surrogate for increasing stretch. Reproducing the original description of this model but with an intact pericardium, increasing atrial pressure did not result in the electrical changes seen with marked atrial dilatation. When the pericardium was removed, the relationship between increasing atrial pressure and susceptibility to atrial fibrillation was restored.

The second publication[2] reports the effect of streptomycin and intracellular acidosis on the rabbit heart atrial fibrillation model. Stretch-activated channel blockers gadolinium and Grammostola toxin have been shown to limit atrial fibrillation with stretch in the rabbit model. We further explored the role of the non-specific cation stretch-activated channel using streptomycin. Streptomycin reduced the stretch-related vulnerability to atrial fibrillation without altering the drop in refractory period associated with stretch. We proposed that the drop in refractoriness might be related to activation of stretch-activated potassium channels. These channels have also been shown to be sensitive to intracellular pH. We therefore investigated the interaction between intracellular pH and stretch in the induction of atrial

fibrillation. Intracellular acidosis, induced with propionate, amplified changes in refractoriness and inducibility of atrial fibrillation with stretch.

The third publication[3] examines the effect of dietary fish oil on the rabbit model of atrial fibrillation. Changes in membrane fluidity and fatty acid composition could alter the stretch response. We proposed that changing the phospholipid membrane composition could alter the mechano-electric feedback in this model. Comparing rabbits fed for 12 weeks with fish oil or sunflower oil supplemented diets, we reported protection from the stretch induced vulnerability to atrial fibrillation in the fish oil fed rabbits. This was associated with an increase in n-3 omega fatty acids in the atrial tissue which was reflected in changes in erythrocyte membrane composition.

The last publication[4] measured the effect of a 12 week dietary fish oil supplement on the heart rate variability of 46 overweight adults. This was a substudy of a larger randomised double-blinded placebo controlled study of fish oil and exercise on cardiovascular health. Frequency domain analysis was performed before and after the 12-week intervention. Fish oil increased the high frequency component of heart rate variability in keeping with increased parasympathetic activity and improved autonomic function.

The outcome of this research has been to further the understanding of the complex interplay between stretch and atrial arrhythmias and to raise the possibility of using dietary fish oil to treat atrial fibrillation.

2 Signed Declaration

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. I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis (as listed below) resides with the copyright holders of those works.

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Passive pericardial constraint protects against stretch-induced vulnerability to atrial fibrillation in rabbits.
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[4]Ninio DM, Hill AM, Howe PR, Buckley JD, Saint DA.
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Lastly I would like to dedicate my thesis to my wonderful wife, Kathryn and my three little distractions from writing: Joseph, Jeremy and Sarah.

Melius tarde, quam nunquam.

4 Statements of Contributions of Jointly Authored Papers

NOTE: Statements of authorship appear in the print copy of the thesis held in the University of Adelaide Library.