MECHANOELECTRIC FEEDBACK IN THE MAMMALIAN HEART

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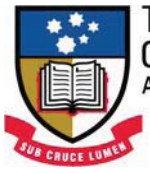

THE UNIVERSITY OF ADELAIDE
AUSTRALIA

Margaret Helen Kelly

(Sept 6, 1944 – May 30, 2001)

This thesis is dedicated in loving memory of my mother who without I would not have been here

General Table of Contents

Abbreviations:

APD	Action Potential Duration
CICR	Calcium-induced Calcium Release
DAD	Delayed After Depolarisation
EAD	Early After Depolarisation
ECG	Electrocardiogram
EDLVP	End Diastolic Left Ventricular Pressure
EDV	End Diastolic Volume
ESLVP	End Systolic Left Ventricular Pressure
HR	Heart Rate
KSAC	Potassium-selective SAC
LV	Left Ventricle
LVP	Left Ventricular Pressure
MAP	Monophasic Action Potential
MEF	Mechano-electric feedback
NSAC	Non-selective SAC
RMP	Resting Membrane Potential
SAC	Stretch Activated ion Channel
SR	Sarcoplasmic Reticulum
VF	Ventricular Fibrillation
Vm	Membrane Potential

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Lastly, I would like to thank my family and friends for putting up with my behavioural fluctuations over the past years, not to mention the divergent music tastes.

ABSTRACT

Stretch of cardiac muscle is known to activate various physiological processes that result in changes to cardiac function, contractility and electrophysiology. To date, however, the precise relationship between mechanical stretch and changes in the electrophysiology of the heart remain unclear. This relationship, termed mechano-electric feedback (MEF), is thought to underlie many cardiac arrhythmias associated with pathological conditions. These electrophysiological changes are observed not only in the whole heart, but also at the single cardiomyocyte level, and can be explained by the presence of stretch-activated ion channels (SACs). Most investigations of the actions of stretch have concentrated on these sacrolemmal ionic currents thought responsible for the proposed MEF-induced changes in contractility. While these studies have provided some useful insight into possible mechanisms, the inappropriate use of solutions and non-physiological degrees of stretch, may have caused somewhat misleading results. Currently, little is known about the involvement or contribution of non-selective or K^+ selective SACs to the normal cardiac cycle. Here, I investigate the concept that stretch-induced changes in cardiac electrophysiology (MEF) are important in normal cardiac cycle and demonstrate the effects of stretch on the Frank-Starling mechanism (stretch induced increases in cardiac contractility) while pharmacologically manipulating stretch-activated ion currents. Experiments were conducted using a number of agents known to influence stretch-activated channels either in a positive or antagonistic manner. Results proved somewhat negative toward MEF theory with only substantial or pathological levels of stretch being able to elicit any electrophysiological change in the heart. Furthermore, where electrophysiological changes were associated with pathological stretch they were not consistently modulated by stretch-activated ion channel activators or blockers. Of equal importance was the observation that smaller levels of myocardial stretch associated with positive changes in contractility via the Frank-Starling mechanism were not associated with any electrophysiological changes in the Langendorff perfused heart (as observed by monophasic action potentials) nor in isolated muscle preparations (as observed through transcellular membrane potential recordings). As such, the present research undertaken in this thesis confirms an absence of electrophysiological changes with stretch except under extreme conditions suggesting that MEF is not a robust and necessarily repeatable phenomenon in the mammalian heart.

Declaration

I declare that this thesis does not incorporate, without acknowledgment, any material previously submitted for a degree or diploma in any university. I also declare that to the best of my knowledge it does not contain any materials previously published unless noted below, or written by another person except where due reference is made in the text.

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Declaration

Some of the material in this thesis has been published in the following papers and presentations:

An introduction of the ideas covered in this thesis appeared in

Kelly, DR (2003). Investigation of mechano-electric feedback and the Frank-Starling relationship in the heart: The function of stretch-activated ion channels in the heart, University of Adelaide Report & Presentation.

Parts of the isolated atrial and papillary muscle chapter have been presented;

Kelly, DR and Saint DA (2004). Absence of Mechano-Electric Feedback in isolated rat atrial tissue. Findings presented at the International Society for Heart Research (ISHR) Conference, Brisbane

Some of the Endocardial-Epicardial chapter appeared in;

Kelly, DR, Mackenzie L and Saint DA (2005). Effect of temperature on stretch-induced cardiac action potential shortening in the rat heart: involvement of TREK-1. Findings presented at the Australian Physiological Society, Canberra.

Mackenzie L, Kelly, DR and Saint DA (2005). More than one type of stretch activated channel contributes to the action potential duration in guinea pig. Findings presented at the Australian Physiological Society, Canberra.

Some of the Endocardial-Epicardial chapter appeared in;

Kelly D, Mackenzie L, Hunter P, Smaill B, Saint DA (2006). Gene expression of stretch-activated channels and Mechano-electric feedback in the heart. Clin Exp Pharmacol Physiol. 2006 Jul;33(7):642-8.

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