

# MECHANO-ELECTRIC FEEDBACK IN THE MAMMALIAN HEART

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NOTE:

This picture is included in the print copy of the thesis held in the University of Adelaide Library.

*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***

|  |     |          |
|--|-----|----------|
| General Table of Contents  | I   |          |
| <i>Abbreviations</i>   | IX  |          |
| ACKNOWLEDGEMENTS   | X   |          |
| ABSTRACT   | XI  |          |
| DECLARATION  | XII |          |
| <b>CHAPTER 1: INTRODUCTION</b>                                       |     | <b>1</b> |
| INTRODUCTION   | 2   |          |
| MOTIVATION   | 2   |          |
| STRUCTURE  | 5   |          |
| RESEARCH CONTRIBUTION & AIMS   | 6   |          |
| <b>CHAPTER 2: LITERATURE REVIEW</b>                                  |     | <b>7</b> |
| INTRODUCTION   | 9   |          |
| <i>Ventricular Loading as a Trigger for Arrhythmia</i>               | 10  |          |
| <i>Excitation-Contraction Coupling</i>                               | 11  |          |
| METHODS OF OBSERVING MEF   | 12  |          |
| <i>The various electrode techniques</i>                              | 12  |          |
| <i>MEF at the Cellular Level</i>                                     | 14  |          |
| <i>Simple Electrophysiological Theory</i>                            | 15  |          |
| <i>Non-Selective Stretch-Activated Cation Channels (NSACs)</i>       | 17  |          |
| <i>Potassium-Selective Stretch-Activated Cation Channels (KSACs)</i> | 21  |          |
| METHODS USED TO VISUALISE SACS                                       | 22  |          |
| <i>NSAC Modulators</i>   | 22  |          |
| <i>Methods of Demonstrating SACS</i>                                 | 24  |          |
| Relevance to Pathological Conditions                                 | 25  |          |
| CONCLUSION   | 26  |          |

|  |           |
|--|-----------|
| <b>CHAPTER 3: GENERAL METHODS</b>  | <b>29</b> |
| INTRODUCTION   | 31        |
| BACKGROUND   | 32        |
| <i>Langendorff Perfused Heart</i>  | 32        |
| LANGENDORFF SETUP & CALIBRATION  | 34        |
| <i>Intra-ventricular Balloon Construction</i>                              | 34        |
| <i>Calibration of Pressure and Flow Recordings</i>                         | 35        |
| <i>Ethics and Animal Care</i>  | 36        |
| <i>Anaesthetisation of Animals</i>   | 36        |
| <i>Surgical Preparation Of The Heart</i>                                   | 37        |
| <i>Measurement of Contractile Force</i>                                    | 38        |
| <i>Pacing</i>  | 39        |
| <i>Perfusate Solutions</i>   | 39        |
| <i>Perfusion of the Heart</i>  | 41        |
| <i>Statistical Analysis</i>  | 43        |
| <b>CHAPTER 4: PRELIMINARY EXPERIMENTS</b>                                  | <b>45</b> |
| <b>Preliminary Experiment 1: Intrinsic Heart Rate and Basic Conditions</b> | <b>47</b> |
| INTRODUCTION   | 47        |
| METHODS  | 47        |
| RESULTS  | 48        |
| DISCUSSION   | 51        |
| CONCLUSION   | 52        |

|   |           |
|---|-----------|
| <b>Experiment 2: MAP Recording Electrodes</b>                                 | <b>53</b> |
| INTRODUCTION  | 53        |
| <i>Surface Method</i>   | 54        |
| <i>Transmural Method</i>  | 58        |
| <i>Obtaining MAP recordings</i>   | 59        |
| METHODS   | 59        |
| RESULTS   | 59        |
| DISCUSSION  | 63        |
| <i>DATA ACQUISITION</i>   | 63        |
| CONCLUSION  | 65        |
| <i>Limitations</i>  | 65        |
| <i>DRUGS AND CONCENTRATIONS</i>   | 66        |
| <i>EXCLUSIONS</i>   | 66        |
| <br>  |           |
| <b>CHAPTER 5: CONTRIBUTION OF MEF TO THE<br/>FRANK-STARLING RELATION</b>      | <b>67</b> |
| INTRODUCTION  | 69        |
| BACKGROUND  | 70        |
| BACKGROUND  | 70        |
| <i>Frank-Starling Response</i>  | 70        |
| <i>Changes in lattice spacing and myofilament Ca<sup>2+</sup> sensitivity</i> | 71        |
| <i>Changes in the intracellular Ca<sup>2+</sup></i>                           | 72        |
| METHODS   | 73        |
| RESULTS   | 74        |
| DISCUSSION:   | 83        |
| <i>Considerations</i>   | 88        |
| <i>Summary</i>  | 90        |
| CONCLUSION  | 91        |

|   |            |
|---|------------|
| <b>CHAPTER 6: FURTHER INVESTIGATIONS OF MEF</b>                           | <b>93</b>  |
| INTRODUCTION  | 95         |
| BACKGROUND  | 95         |
| METHODS   | 96         |
| RESULTS   | 96         |
| DISCUSSION  | 98         |
| CONCLUSION  | 100        |
| <b>MEF IN THE GUINEA PIG HEART</b>  | <b>100</b> |
| INTRODUCTION  | 100        |
| METHODS (GUINEA PIGS)   | 101        |
| RESULTS   | 101        |
| DISCUSSION  | 105        |
| CONCLUSION  | 107        |
| <b>MEF IN THE RAT HEART</b>   | <b>108</b> |
| INTRODUCTION  | 108        |
| METHODS   | 108        |
| RESULTS   | 109        |
| DISCUSSION  | 110        |
| SUMMARY   | 111        |
| CONCLUSION  | 111        |
| <b>CHAPTER 7: MEF IN SUB-EPICARDIAL AND ENDOCARDIAL MYOCARDIAL LAYERS</b> | <b>113</b> |
| INTRODUCTION  | 115        |
| BACKGROUND  | 115        |
| <i>The involvement of SACs in Beat-to-Beat Regulation</i>                 | 116        |
| METHODS   | 116        |
| RESULTS   | 117        |
| <i>Effect of stretch on sub-epicardial and endocardial MAPs</i>           | 117        |
| DISCUSSION  | 125        |
| <i>Effect of Stretch on Sub-epicardial and Endocardial MAPs</i>           | 125        |
| <i>Effect of Pharmacological Modulation of SACs</i>                       | 127        |
| SUMMARY   | 128        |
| CONCLUSION  | 129        |
| ACKNOWLEDGEMENTS  | 129        |

|  |            |
|--|------------|
| <b>CHAPTER 8: FURTHER INVESTIGATIONS INTO<br/>TRANSMURAL MEF</b> | <b>131</b> |
| <b>TEMPERATURE MODULATION OF MEF</b>                             | <b>133</b> |
| INTRODUCTION   | 133        |
| <i>Temperature modulation of SAC response</i>                    | 133        |
| METHODS  | 135        |
| RESULTS  | 136        |
| SUMMARY  | 142        |
| DISCUSSION   | 142        |
| CONCLUSION   | 143        |
| <b>STREPTOMYCIN MODULATION OF SAC<br/>RESPONSE IN GUINEA PIG</b> | <b>145</b> |
| INTRODUCTION   | 145        |
| METHODS  | 145        |
| RESULTS  | 147        |
| <i>Sub-Epicardial Effect of Stretch</i>                          | 148        |
| DISCUSSION   | 150        |
| CONCLUSION   | 153        |
| <b>TEMPERATURE MODULATION OF MEF IN THE<br/>GUINEA PIG</b>       | <b>153</b> |
| INTRODUCTION   | 153        |
| RESULTS  | 154        |
| DISCUSSION   | 155        |
| <b>GLIBENCLAMIDE MODULATION OF STRETCH<br/>RESPONSE</b>          | <b>157</b> |
| INTRODUCTION   | 157        |
| METHODS  | 158        |
| RESULTS  | 158        |
| DISCUSSION   | 161        |
| SUMMARY  | 162        |
| CONCLUSION   | 163        |

|   |            |
|---|------------|
| <b>CHAPTER 9: MEF IN ISOLATED MUSCLE PREPARATIONS</b>             | <b>165</b> |
| INTRODUCTION  | 167        |
| BACKGROUND  | 168        |
| <i>Intracellular Recordings</i>                                   | 168        |
| METHODS   | 170        |
| RESULTS   | 172        |
| <i>Preliminary Experiments</i>                                    | 172        |
| <i>Effect of Stretch</i>  | 174        |
| <i>Effect of SAC Modulators</i>                                   | 178        |
| DISCUSSION  | 180        |
| CONCLUSION  | 182        |
| ACKNOWLEDGEMENTS  | 183        |
| <b>EFFECT OF TEMPERATURE ON MEF IN ISOLATED PAPILLARY MUSCLES</b> | <b>184</b> |
| INTRODUCTION  | 184        |
| RESULTS   | 185        |
| DISCUSSION  | 187        |
| CONCLUSION  | 188        |
| <b>CHAPTER 10: INTRACELLULAR RECORDINGS IN LEFT ATRIAL TISSUE</b> | <b>189</b> |
| BACKGROUND  | 191        |
| METHODS   | 191        |
| RESULTS   | 192        |
| DISCUSSION  | 199        |
| CONCLUSION  | 200        |



|  |            |
|--|------------|
| <b>CHAPTER 11: THE CONTRIBUTION OF MEF TO THE GREGG EFFECT</b>                   | <b>201</b> |
| INTRODUCTION   | 203        |
| BACKGROUND   | 203        |
| <i>Effect of Contraction on Coronary Flow</i>                                    | 204        |
| <i>Involvement of SACs</i>   | 205        |
| METHODS:   | 206        |
| RESULTS  | 207        |
| <i>Gregg Effect Observations with Suction MAP Electrode</i>                      | 208        |
| <i>Gregg Effect Observations with Surface Contact Electrode</i>                  | 211        |
| <i>Gregg Effect Observations with Transmural MAP Electrode</i>                   | 212        |
| DISCUSSION   | 215        |
| CONCLUSION   | 218        |
| <b>CHAPTER 12: INTRACELLULAR RECORDINGS OF ISOLATED PERFUSED RIGHT VENTRICLE</b> | <b>219</b> |
| BACKGROUND   | 221        |
| METHODS  | 222        |
| RESULTS  | 223        |
| DISCUSSION   | 226        |
| CONCLUSION   | 228        |
| <b>CHAPTER 13: CONTRIBUTION OF MEF TO RAPID-STRETCH INDUCED ECTOPIC BEATS</b>    | <b>229</b> |
| INTRODUCTION   | 231        |
| BACKGROUND   | 231        |
| <i>Other Effects of Stretch</i>  | 232        |
| <i>Importance of Na<sup>+</sup>-Ca<sup>2+</sup> exchanger</i>                    | 233        |
| METHODS  | 234        |
| RESULTS  | 235        |
| DISCUSSION   | 238        |
| CONCLUSION   | 241        |
| ACKNOWLEDGEMENTS   | 242        |

|  |            |
|--|------------|
| <b>IN VIVO DEMONSTRATION OF MEF</b>                                    | <b>243</b> |
| BACKGROUND   | 243        |
| METHODS  | 243        |
| PRELIMINARY RESULTS  | 244        |
| DISCUSSION   | 246        |
| RESULTS  | 247        |
| DISCUSSION   | 248        |
| CONCLUSION   | 249        |
| ACKNOWLEDGEMENTS   | 250        |
| <br>   |            |
| <b>CHAPTER 14: CONCLUSION</b>  | <b>252</b> |
| INTRODUCTION   | 254        |
| SUMMARY OF RESULTS   | 254        |
| <i>Chapter 5 - Contribution of MEF to the Frank-Starling Relation:</i> | 254        |
| <i>Chapter 6 - Further Investigations of MEF in the Rat Heart</i>      | 254        |
| <i>Chapter 7 – Epicardial and Endocardial MEF Responses:</i>           | 255        |
| <i>Chapter 8 – Further Investigations into Transmural MEF:</i>         | 255        |
| <i>Chapter 9 – MEF in Isolated Muscle Preparations</i>                 | 256        |
| <i>Chapter 10 – MEF in the Isolated, Stretched Left Atrium</i>         | 256        |
| <i>Chapter 11 – Contribution of MEF to the Gregg Effect</i>            | 256        |
| <i>Chapter 12 – MEF in the Isolated, Perfused Right Ventricle</i>      | 256        |
| <i>Chapter 13 – MEF in response to rapid stretch</i>                   | 256        |
| <br>   |            |
| DISCUSSION   | 257        |
| <i>Involvement of SACs</i>   | 258        |
| <i>Effect of Experimental Conditions</i>                               | 258        |
| <i>Regulation and Modulation of SAC Activity</i>                       | 259        |
| <i>Stretch and the Gregg Effect</i>                                    | 260        |
| <i>Other Sources of MEF</i>  | 261        |
| <i>Sensitivity of Stretch Responses</i>                                | 261        |
| <i>Other Mechanisms of MEF</i>   | 263        |
| <i>Suitability of MAP Recordings for Observing MEF</i>                 | 265        |
| <i>SACs and Ischaemia</i>  | 265        |
| <i>Methods of Demonstrating SAC Responses</i>                          | 266        |
| <i>Modulation of SAC-mediated MEF Responses in the Heart</i>           | 266        |
| <br>   |            |
| CONCLUDING REMARKS   | 268        |
| FUTURE DIRECTIONS:   | 269        |
| <i>Involvement of SACs in MAP Generation</i>                           | 269        |
| <i>Involvement of TREK-1 in MEF</i>                                    | 270        |
| <i>Involvement of SACs in Pathological Conditions</i>                  | 270        |
| <br>   |            |
| REFERENCE LIST   | 271        |
| List of Figures & Tables   | 302        |
| Index  | 306        |

## Abbreviations

### ***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                |
| V <sub>m</sub> | Membrane Potential                      |

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## **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 sarcolemmal 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.

Signed:

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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;

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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.

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## ***List of Figures & Tables***

|            |   |     |
|------------|---|-----|
| Figure 1:  | Cellular Regulation Invoking MEF  | 12  |
| Figure 2:  | Cardiac Action Potential  | 17  |
| Figure 3:  | Raw Chart Recording   | 42  |
| Figure 4:  | Balloon Placement in Langendorff Perfused Heart   | 43  |
| Figure 5:  | Intrinsic Heart Rate  | 48  |
| Figure 6:  | Effect of Frequency of Stimulation on Contractility   | 49  |
| Figure 7:  | Effect of Frequency of Stimulation on Pulse Pressure  | 50  |
| Figure 8:  | Effect of Perfusion on Contractility  | 51  |
| Figure 9:  | Spring Electrode Design   | 56  |
| Figure 10: | Suction Electrode   | 57  |
| Figure 11: | Contact Electrode   | 57  |
| Figure 12: | Epicardial-Endocardial MAP electrode  | 58  |
| Figure 13: | MAPs Obtained With Spring Electrode   | 60  |
| Figure 14: | MAPs Obtained With Suction Electrode  | 61  |
| Figure 15: | Effect of Stimulation Frequency on MAP durations  | 62  |
| Figure 16: | Filtering MAP Signals   | 64  |
| Figure 17: | Frank-Starling Response   | 70  |
| Figure 18: | Effect of Stepwise increases in EDLVP on MAP Morphology   | 75  |
| Figure 19: | Effect of EDLVP on MAP Durations  | 76  |
| Figure 20: | Effect of EDLVP and Time on MAP Amplitude   | 76  |
| Figure 21: | Effect of Stretch on APD20 at Different Perfusion Pressures   | 78  |
| Figure 22: | Effect of Coronary Perfusion Pressure on MAP APD50  | 79  |
| Figure 23: | Effect of Coronary Perfusion Pressure on MAP APD80  | 80  |
| Figure 24: | Effect of Coronary Perfusion Pressure on MAP Amplitude  | 81  |
| Figure 25: | Effect of EDLVP on MAP Duration at Constant Perfusion Pressure  | 82  |
| Figure 26: | MAP overlay at different EDLVP  | 83  |
| Figure 27: | Effect of a Single Step in EDLVP on MAP Morphology  | 97  |
| Figure 28: | Effect of 4-AP on MAP Morphology  | 98  |
| Figure 29: | Effect of Changes in EDLVP on MAP Morphology in the Guinea Pig Isolated Perfused Heart (CP = 60 mmHg) | 102 |



|            |   |     |
|------------|---|-----|
| Figure 30: | Effect of Changes in EDLVP on MAP Morphology in the Guinea Pig Isolated Perfused Heart (CP = 80 mmHg) | 103 |
| Figure 31: | Guinea Pig MAPs superimposed  | 103 |
| Figure 32: | Effect of Changes in EDLVP on Guinea Pig MAP Morphology   | 104 |
| Figure 33: | Testing Refractory Periods During Stretch   | 105 |
| Figure 34: | Rapid Stretch Induced Ectopic Beats   | 109 |
| Figure 35: | Rapid Inflation and Deflation Induced Ectopic Beats   | 109 |
| Figure 36: | Average Endocardial and Sub-epicardial MAP Durations  | 117 |
| Figure 37: | Endocardial and Sub-epicardial MAP Recordings   | 118 |
| Figure 38: | Effect of EDLVP on Sub-epicardial MAP Morphology  | 119 |
| Figure 39: | of EDLVP on Endocardial MAP Morphology  | 120 |
| Figure 40: | Effect of Stretch on Endocardial MAP APD50  | 121 |
| Figure 41: | Effect of Stretch on Sub-epicardial MAP APD50   | 122 |
| Figure 42: | Effect of Stretch on Endocardial MAP APD80  | 123 |
| Figure 43: | Effect of Stretch on Sub-epicardial MAP APD80   | 124 |
| Figure 44: | Effect of Temperature on TREK-1 Activity  | 134 |
| Figure 45: | Effect of Temperature on Contractility  | 136 |
| Figure 46: | Effect of Temperature on Sub-Epicardial MAP Morphology  | 137 |
| Figure 47: | Effect of Temperature on Endocardial MAP Morphology   | 138 |
| Figure 48: | Effect of Temperature on MEF in the Rat Heart (APD80)   | 139 |
| Figure 49: | Effect of Temperature on MEF in the Rat Heart (APD50)   | 140 |
| Figure 50: | Effect of Stretch on Rat Endocardial MAP  | 141 |
| Figure 51: | Endocardial and Sub-epicardial MAP Amplitude in the Guinea pig  | 147 |
| Figure 52: | Effect of Stretch on Endocardial and Sub-epicardial APD20 in the Guinea pig                           | 148 |
| Figure 53: | Effect of Stretch on Endocardial and Sub-epicardial APD50 in the Guinea pig                           | 149 |
| Figure 54: | Effect of Stretch on Endocardial and Sub-epicardial APD80 in the Guinea pig                           | 150 |
| Figure 55: | Effect of Temperature on MEF in the Guinea Pig Heart (APD80)  | 154 |
| Figure 56: | Effect of Temperature on MEF in the Guinea Pig Heart (APD50)  | 155 |
| Figure 57: | Modulation of Sub-epicardial Stretch Response by Glibenclamide  | 159 |

## List of Figures & Tables

|            |   |     |
|------------|---|-----|
| Figure 58: | Modulation of Endocardial response to Stretch by Glibenclamide                                  | 160 |
| Figure 59: | Effect of Stretch and Glibenclamide on MAP Amplitude  | 161 |
| Figure 60: | Effect of Stimulation Frequency on Papillary Muscle Contraction Force                           | 172 |
| Figure 61: | Effect of Perfusion Rate on Papillary Muscle Contractility                                      | 173 |
| Figure 62: | Effect of Stretch on Papillary Muscle Contractility   | 174 |
| Figure 63: | Effect of Stretch on Papillary Muscle Resting Membrane Potential                                | 175 |
| Figure 64: | Effect of Stretch on Papillary Muscle Action Potential Amplitude                                | 176 |
| Figure 65: | Effect of Papillary Stretch on Intracellular Action Potential Durations                         | 177 |
| Figure 66: | Effect of SAC Modulators on RMP in stretched Papillary muscles                                  | 178 |
| Figure 67: | Effect of SAC Modulators on Amplitude in stretched Papillary muscles                            | 179 |
| Figure 68: | Effect of SAC Modulators on Papillary Muscle APD80 During Stretch                               | 180 |
| Figure 69: | Effect of Reducing Bath Temperature on Action Potential Parameters                              | 185 |
| Figure 70: | Effect of Temperature on Stretch-induced Changes in Electrophysiology                           | 186 |
| Figure 71: | Stepwise changes in resting tension on atrial contractility and electrophysiology.              | 192 |
| Figure 72: | Effect of physiological tension on contractility in isolated left atrial tissue.                | 193 |
| Figure 73: | Continuous Atrial Appendage Impalement During Stretch Manipulations.                            | 194 |
| Figure 74: | Effect of Stretch on Atrial Appendage Action Potential Duration                                 | 195 |
| Figure 75: | Effect of Stretch on Atrial Appendage Action Potential Amplitude and Resting Membrane Potential | 195 |
| Figure 76: | Effect of Stretch on Atrial Appendage Action Potential Amplitude and Resting Membrane Potential | 196 |
| Figure 77: | Effect of Stretch on Atrial Appendage Action Potential Amplitude and Resting Membrane Potential | 197 |
| Figure 78: | Effect of Stretch on Action Potential Duration in Left Atrium of Rat                            | 198 |
| Figure 79: | Effect of Coronary Perfusion Pressure on Myocardial Contractility                               | 207 |

|            |   |     |
|------------|---|-----|
| Figure 80: | Preliminary Experiment Showing Effect of Flow on MAP durations  | 208 |
| Figure 81: | Effect of Coronary Flow Rate on MAP Durations   | 209 |
| Figure 82: | Effect of Coronary Flow Rate on MAP Amplitude in the Rat  | 210 |
| Figure 83: | Effect of Changes in Coronary Perfusion Pressure on MAP Amplitude   | 211 |
| Figure 84: | Effect of Coronary Perfusion Pressure on MAP Durations in Rat   | 212 |
| Figure 85: | Effect of Coronary Flow Rate on MAP APD50 in the Rat  | 213 |
| Figure 86: | Effect of Coronary Flow Rate on MAP APD20 in the Rat  | 214 |
| Figure 87: | Effect of Coronary Flow Rate on MAP APD80 in the Rat  | 215 |
| Figure 88: | Effect of Perfusion Rate on Perfusion Pressure in Isolated, Perfused Right Ventricle  | 224 |
| Figure 89: | Effect of Perfusion Rate on Action Potential Amplitude and RMP in Isolated, Perfused Right Ventricle                              | 225 |
| Figure 90: | Effect of Perfusion Rate on Action Potential duration in Isolated, Perfused Right Ventricle                                       | 226 |
| Figure 91: | Stretch-induced effects on the whole heart  | 232 |
| Figure 92: | Timing of Stretch-induced Ectopic Beat  | 236 |
| Figure 93: | Pharmacological Modulation of Stretch-induced Ectopic Beats   | 237 |
| Figure 94: | Effect of Aortic Occlusion on Heart Rate and Mean Arterial Pressure   | 244 |
| Figure 95: | Effect of Aortic Occlusion on HR in vivo  | 246 |
| Figure 96: | Effect of Aortic Occlusion on Endocardial and Sub-epicardial MAP APD80 immediately after occlusion and immediately after release  | 247 |
| Figure 97: | Effect of Aortic Occlusion on Endocardial and Sub-epicardial MAP APD50 immediately after occlusion and immediately after release  | 248 |
| Table 1:   | Summary of Endocardial and Sub-Epicardial MAP Changes in Response to Stretch at Physiological and Sub-Physiological Temperatures. | 142 |
| Table 2:   | Summary of Stretch-induced Electrophysiological Effects in Isolated Rat Atrial Preparations.                                      | 199 |