

Research article

Mechanoelectric feedback does not contribute to the Frank-Starling relation in the rat and guinea pig heart

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Abstract: Mechanoelectric feedback (MEF) is the process by which mechanical forces on the myocardium can alter its electrical properties. The effect can be large enough to induce ectopic beats or fibrillation. However, the role of MEF at physiological levels of mechanical stress is not clear. We have investigated alteration in action potential morphology in rat and guinea pig ventricle and in rat atrial tissue at levels of stretch near the plateau of the Frank-Starling curve. Stretch of >100 mm.Hg End Diastolic Left Ventricular Pressure (EDLVP) or rapidly applied stretch (EDLVP increased by 25 mm.Hg within 100 ms) often triggered ectopic beats in isolated rat and guinea-pig hearts. However, ventricular epicardial monophasic action potentials (MAPs) recorded during stretch to EDLVP up to 30 mm. Hg showed no consistent changes in action potential duration (at APD₂₀, APD₅₀ or APD₈₀) in either species. MAP recording detected APD prolongation with very small concentrations of 4-AP (10 μ M), confirming the discrimination of the recording technique. In isolated rat atrial strips, no changes in intracellular action potential morphology or membrane potential were seen when stretched to levels producing an optimum increase in contractility. We conclude that alteration in action potential morphology with stretch does not contribute to the Frank-Starling relation in ventricle of rat or guinea-pig isolated heart, or in rat atrial tissue.

Keywords: Mechano-electric feedback; Frank-Starling relation; Cardiac electrophysiology; Stretch

1. Introduction

Nearly a century after Frank, Starling, and colleagues demonstrated that an increase in ventricular filling (sarcomere length) promotes an increase in developed pressure (tension), the cellular and molecular mechanisms underlying this effect remain elusive. A sudden increase in myocardial stretch produces an immediate (within a beat or two) increase in force that is not due to

an increase in the calcium transient [1], followed by a slower increase in tension accompanied by a rise in the calcium transient [39]. The rapid change in force is larger than can be accounted for by the change in overlap of the contractile filaments, and this extra increase in force appears to be due, in large part, to an increase in sensitivity of the contractile proteins. The mechanisms of this are still being investigated, but it has been suggested that a closer myofilament lattice spacing is one of the major underlying factors [13].

However, as well as these intracellular cellular responses to stretch, stretch produces electrophysiological effects on myocardial cells through modulation of stretch-sensitive ion channels in the sarcolemmal membrane [21]. For example, as early as 1915, it was reported that heart rate is increased when the right atrium is distended [3] and later studies showed this to be a direct (ie non-reflex mediated) effect [4,24]. Mechanical stretch also produces electrical responses in ventricles [14,33]. The responses are complex, and depend upon the timing of the stretch relative to the cardiac cycle; stretch produces a rapid hyperpolarisation if applied during systole but a depolarisation if applied during diastole [43]. Again, these responses are not due to reflex loops or other extracardiac effects, since they can be demonstrated in isolated tissues [14], and indeed at the level of single myocytes [41]. This electrophysiological response to stretch is called mechano-electric feedback (MEF).

The physiological role of MEF in the heart is not clear. It has been proposed that MEF may aid in the beat to beat regulation of contraction in the face of haemodynamic perturbations [22]. Alternatively, it has been suggested that it acts to reduce the dispersion of repolarisation that would otherwise occur because of regional inhomogeneities in action potential propagation velocity arising as a consequence of, for example, ischaemia [22]. Fundamental to these ideas is the idea that stretch can alter action potential morphology essentially instantaneously, and that this in turn alters contractility. Note that stretch has been reported to either prolong, shorten, or produce a “cross over” of the AP [21], presumably depending on which ion channels are activated and their current density. Hence, the effect of MEF on the Frank-Starling relation could potentially be additive (a prolongation of the action potential acting to add further tension increases) or negative (shortening of the action potential with stretch attenuating the increase in force produced by other mechanisms). An important condition for either effect of MEF on the Frank-Starling relation is that MEF, in the form of action potential alterations, should be demonstrable at levels of stretch which are normally encountered by the heart, i.e. levels of stretch that produce a maximal increase in contractility (ie, near the plateau of the Frank-Starling relation). Whether changes in action potential occur over this range of stretch is still equivocal. Therefore, in the present study we have examined whether action potential morphology is altered in rat and guinea-pig cardiac muscle at levels of stretch within the range of the Frank-Starling relation.

2. Methods

2.1. Isolated hearts

Animals used throughout this study were cared for according to the Australian National Health and Medical Council Guidelines for the Care and Use of Animals. The University of Adelaide Animal Ethics Committee approved all experimental procedures.

Male Sprague-Dawley rats weighing 350 to 450 g were anaesthetized by I.P injection of 30 mg/kg sodium pentobarbitone with 2000 units of heparin. Guinea pigs weighing 850 to 950 g were anaesthetized by I.P injection of 60 mg/kg Ketamine and 10 mg/kg Xylazine with 2000 units of heparin. Under full anesthesia animals were killed by exsanguination and hearts from either species were rapidly excised and placed in ice cold (5 °C) HEPES buffer consisting of (in mmol/L) NaCl 133.5, NaH₂PO₄ 1.2, KCl 4, HEPES 10.0, MgCl₂ 1.2, and D-glucose 11 (pH 7.4). The aorta was cannulated with an 18 gauge needle and retrogradely perfused with bicarbonate buffered solution (average time to perfusion <3 min). Perfusate was equilibrated with 95% O₂ and 5% CO₂ and consisted of (in mmol/L) CaCl₂ 1.5, NaCl 111.0, KCl 4.0, MgCl₂ 0.6, NaHCO₃ 23.9, NaH₂PO₄ 1.2, D-glucose 12.0 at 37°C. Through an incision in the left atrium a deflated thin latex balloon was anchored within the left ventricle. The balloon was then inflated with water until the desired diastolic pressure (typically 5 to 30 mmHg) was attained. The balloon was designed to have a considerably larger volume than the ventricle, so that its compliance did not contribute to the diastolic pressure recorded at any volume used in the experiments (figure 1). The “zero pressure” volume of the left ventricle was about 200 µl and the compliance was considerably greater than that reported by some other groups e.g. [31], indicating that abnormal stiffness of the ventricular wall was not a confounding factor in our experiments. Intraventricular pressure was measured with a force transducer (ADInstruments, Australia) connected to the balloon via a 38 mm long 18 gauge needle. Hearts were perfused at a constant coronary perfusion pressure in the range of 50–80 mmHg and paced at 4 Hz via the left atrium at twice threshold with 10 ms bipolar pulses.

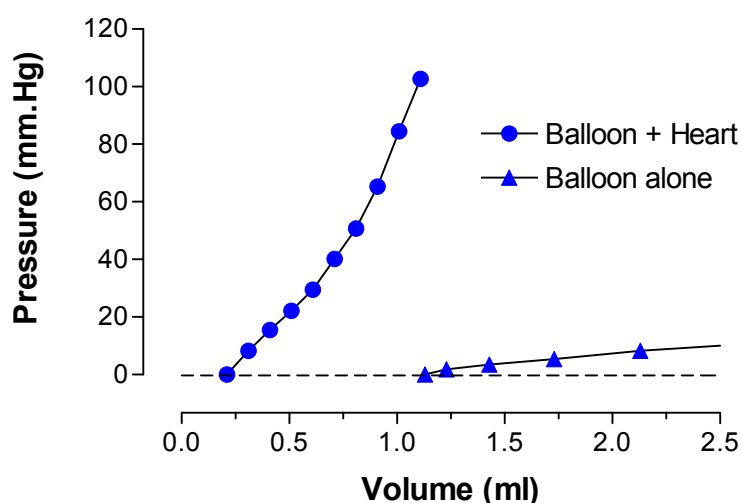


Figure 1. Compliance of left ventricle of isolated rat hearts and the balloon alone. For a typical sized rat heart, pressure was measured in the intraventricular balloon for small increments in volume, either with (circles) or without (triangles) the balloon being placed in the left ventricle. The balloon is partially collapsed until slightly over 1 ml is injected, and so generates no pressure at volumes less than this.

2.2. Ventricular monophasic action potential recordings:

Monophasic action potential (MAP) recordings were made using a modified floating suction

MAP catheter consisting of a small AgCl ball (~1 mm in diameter) in an outer suction cup held on the epicardial surface with ~50 mm.Hg suction. The MAP electrograms were amplified, digitised at a rate of 2 kHz and analysed using Chart V and peak parameter software (ADInstruments, Australia). Recordings were considered reproducible and acceptable for analysis only if they had stable base lines and amplitudes with a variation of less than 10%, as well as a stable action potential duration during the control period.

2.3. *Rat atrial and ventricular strips*

Whole rat left atria and epicardial rat left ventricular strips cut from the apex to the base of the left ventricle were paced at 0.5 Hz at twice threshold with 1 ms bipolar pulses. Tissue was then stretched between a fixed point and a micro-tension transducer attached to a micro-manipulator. Action potentials were recorded during intracellular impalements performed on areas under tension using a modified floating glass microelectrode (1–3 M) filled with 3 M KCl.

3. Results

3.1. *Ventricle*

In isolated rat hearts, MEF, in the form of ectopic beats, could be readily demonstrated by increasing end-diastolic left ventricular pressure (EDLVP). An increase in the volume of the balloon in the left ventricle sufficient to produce an increase in EDLVP from about 10 mmHg to about 100 mmHg (an injected volume of approx 750 μ l) within 2 to 3 seconds typically induced a series of ectopic beats lasting up to 10 seconds, after which the rhythm returned to normal (figure 2A). Although this pressure is obviously beyond the physiological range, it did not cause damage to the heart since the contractility at normal LVEDP appeared unaffected even after repeated applications of this pressure. Lower pressures could evoke arrhythmias if applied more rapidly: an increase in diastolic pressure from near zero to approx 20 mm.Hg (an injection volume of approx 300 μ l) within about 250 ms produced a single ectopic beat (figure 2B). Intriguingly, a sudden release of stretch from approx 20 mm.Hg to near zero also produced an ectopic beat (figure 2C). Smaller changes in pressure, even if very rapid, did not induce ectopic beats. When EDLVP was increased stepwise in short steps of a few seconds each from 0 mm.Hg to between 25 and 30 mm.Hg and then reduced once more, a substantial increase in contractility of the ventricle was seen, as evidenced by an increase in pulse pressure and dP/dt (figure 3A). An EDLVP of 25 to 30 mm.Hg was well into the plateau phase of the Frank-Starling relation (figure 3B). Ectopic beats were very rarely observed at these levels of ventricular stretch with this protocol and within this pressure range there were no obvious differences in MAPs recorded at <5 mm.Hg and >20 mm.Hg duration (figure 3C). Measurement of APD at 20%, 50% and 80% repolarisation and AP amplitude at number of pressures over this range of LVEDP showed no change in either rat or guinea-pig isolated hearts (figure 4). Superimposition of individual action potentials recorded at near zero and at 25 to 30 mm.Hg in these hearts showed that they were almost identical for both species (figure 4B and 4D). Stable amplitude MAP recordings obtained from animals were also observed over time by looking at control, 20–25 mm.Hg EDLVP and re-control conditions following the completion of a Frank-Starling curve. The data is summarised for 4 rat and 4 guinea pig hearts at these EDLVPs in figure 5. There was no

significant difference in MAP duration at any level of repolarisation during stretch, compared to either control or recontrol, in either species.

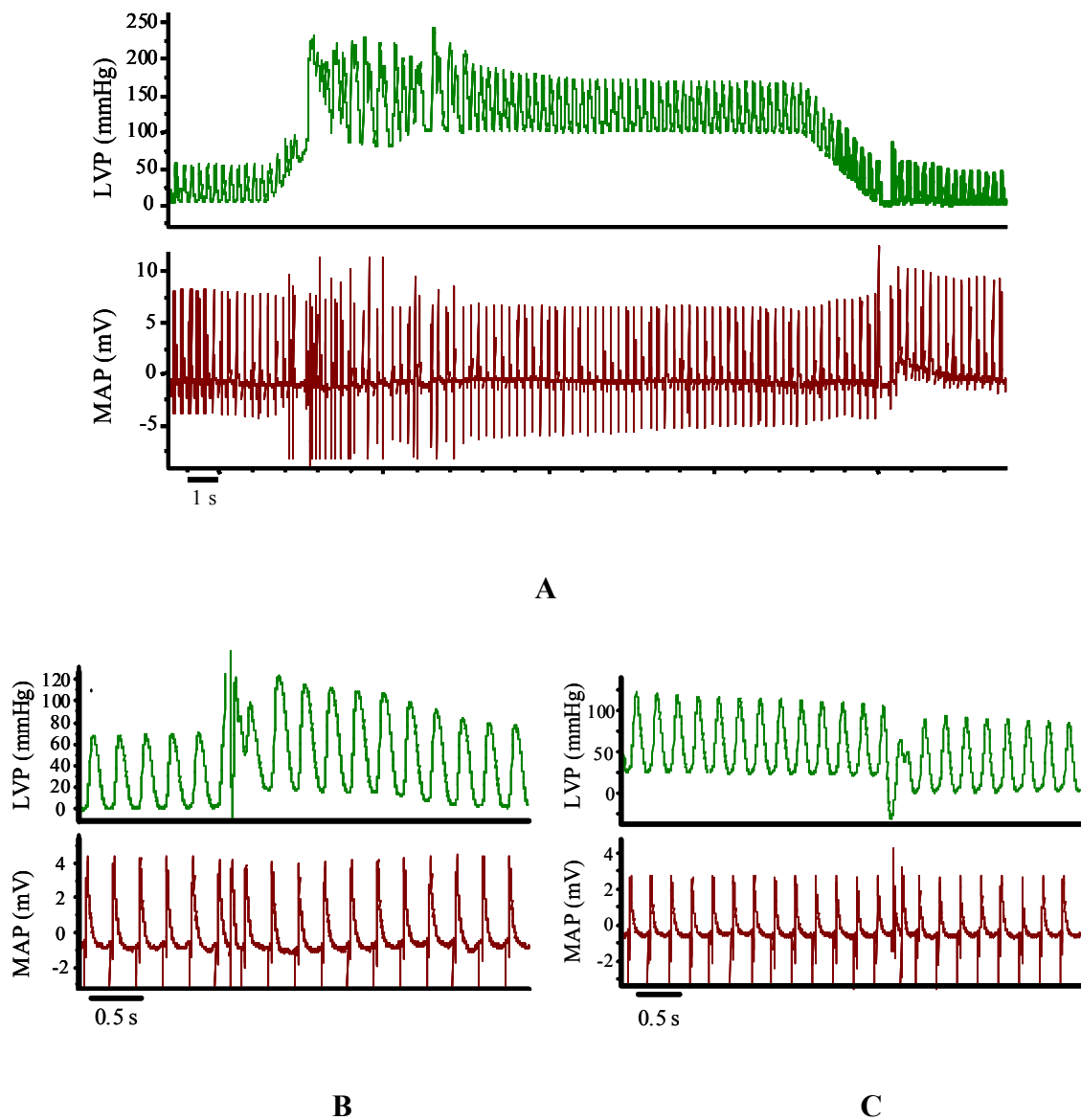


Figure 2. Ectopic beats evoked in isolated rat heart by stretch. Panel A: Top trace; intraventricular pressure, lower trace; MAP recorded from the epicardial surface. Heart paced at 4 Hz. Increase in EDLVP from near 0 to ≈ 100 mm.Hg over 2 to 3 seconds produced a series of ectopic beats. Panel B: effect of a sudden increase in EDLVP pressure from near zero to 20 mm.Hg. Upper trace; ventricular pressure, lower trace is ECG recording from surface electrodes. Pressure was increased at the arrow. Panel C: Effect of sudden release of stretch (at arrow). Traces as in Panel B.

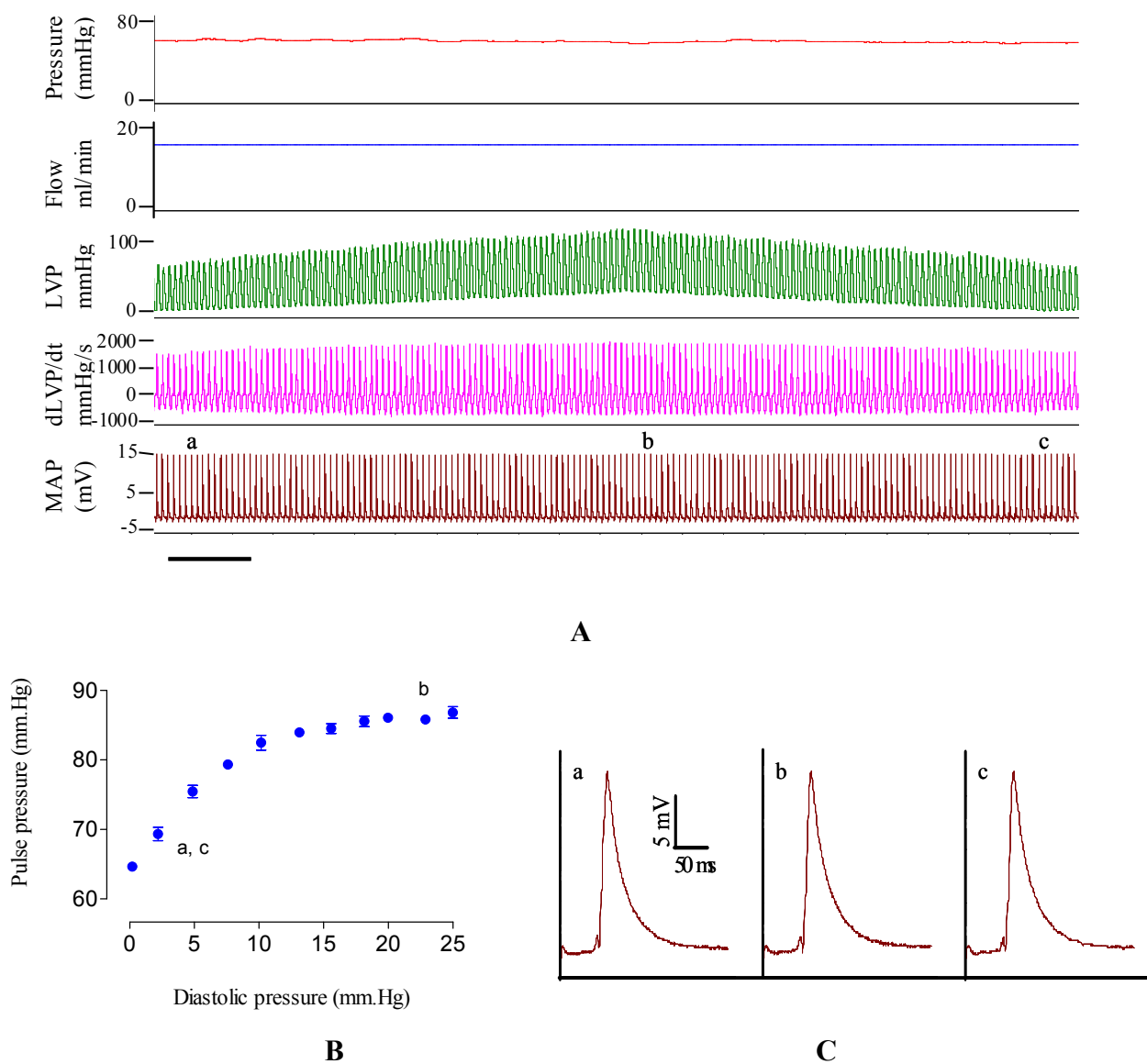


Figure 3. Effect of increasing Left Ventricular End Diastolic Pressure on contractility and Monophasic action potential in rat heart. Panel A: from top down: Coronary perfusion pressure (≈ 62 mm.Hg), coronary flow (maintained at 15.5 $\text{ml}\cdot\text{min}^{-1}$ by feedback control), Left ventricular pressure, left ventricular dP/dt , MAP recording. The horizontal scale bar indicates 5 seconds. Panel B: plot of pulse pressure against LVEDP. 5 pressure pulses were measured at each LVEDP and plotted as mean \pm SEM. Panel C: MAPs recorded at the times indicated by a,b,c in the upper section (at LVEDP of <5 , >20 and <5 mm.Hg respectively).

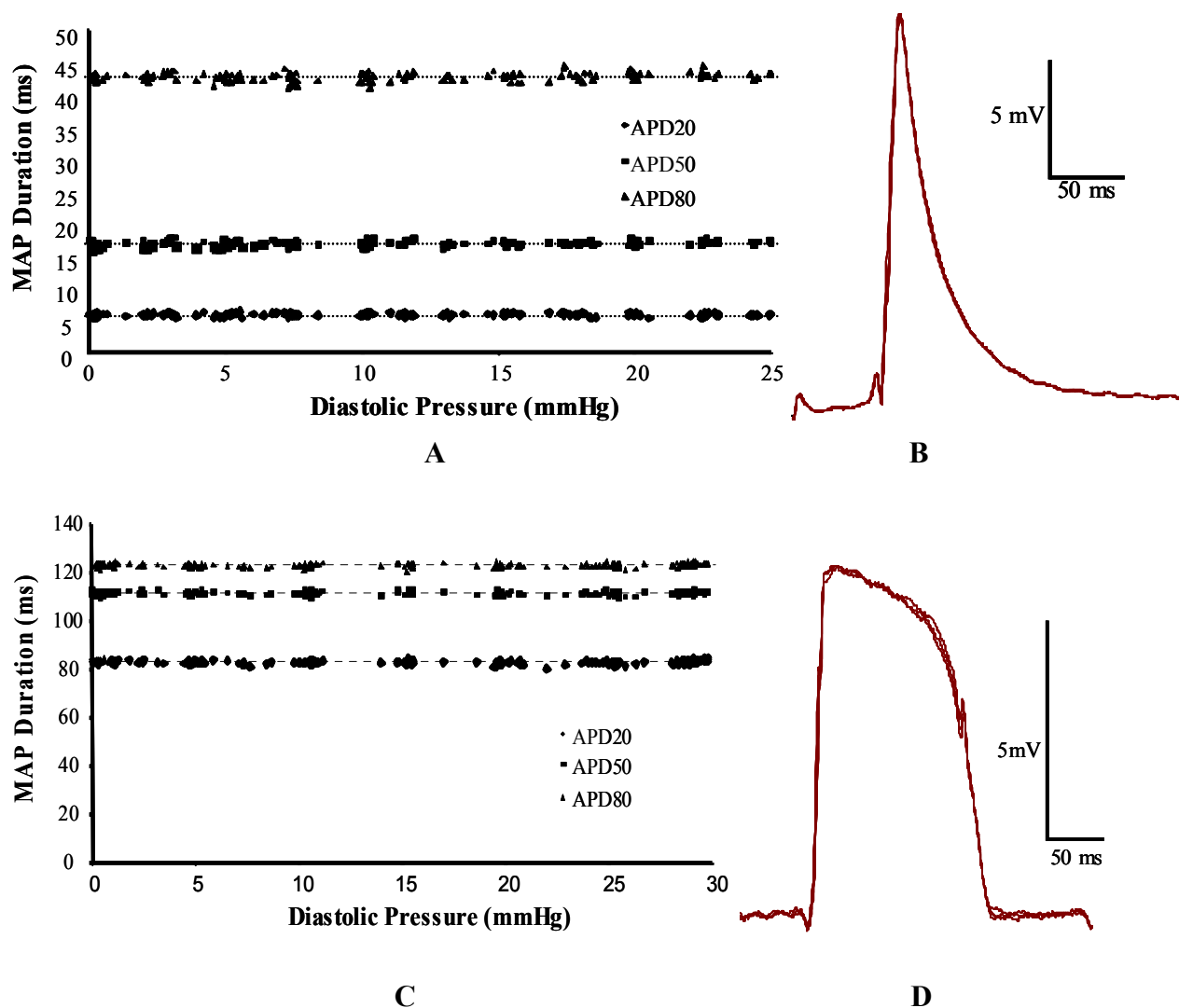
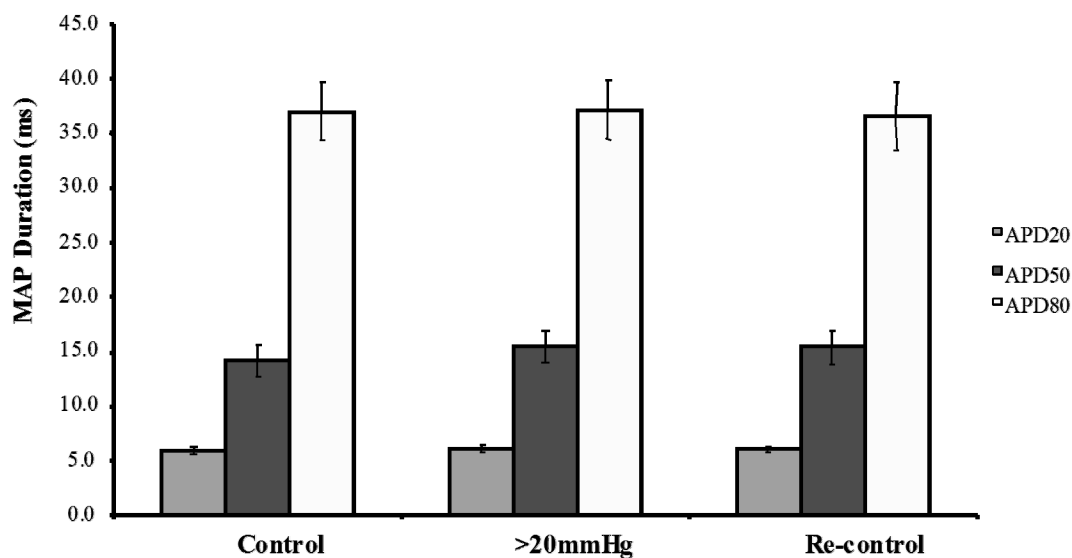
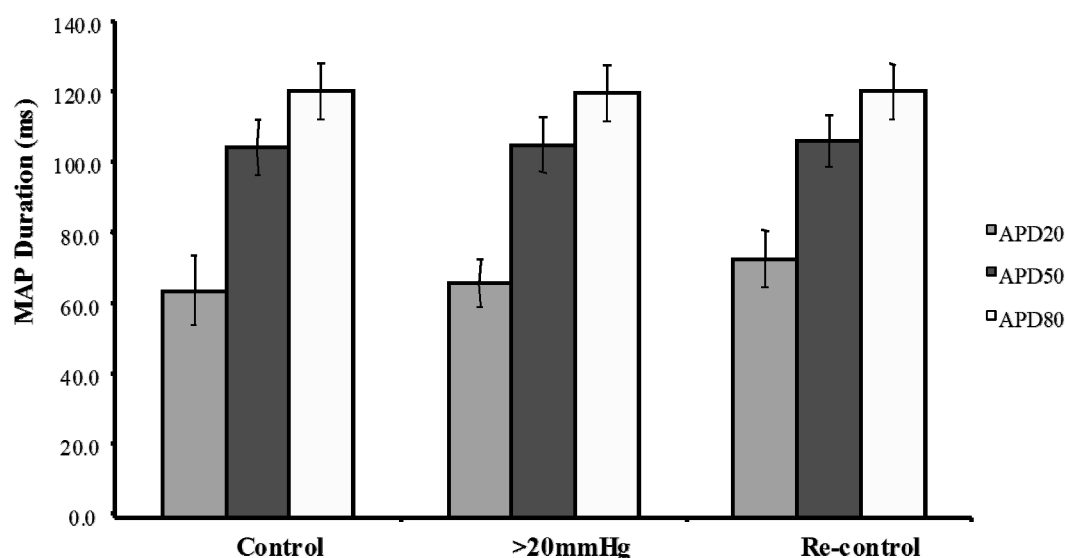


Figure 4. Effect of increasing Left Ventricular End Diastolic Pressure on Monophasic action potentials in rat and guinea pig heart. Panel A: MAP durations in a rat heart measured at 20%, 50% and 80% repolarisation plotted against the EDLVP at the time of recording. Dotted lines show best fit linear regression lines for each data set: none of these lines has a slope significantly different from zero. Panel B: MAPs recorded at EDLVP of 0, 25 and 0 mm.Hg shown superimposed. Panel C and D: as in Panel A and Panel B, for Guinea pig heart (again, slopes of regression lines not significantly different from zero).



A



B

Figure 5. Effect of increasing Left Ventricular End Diastolic Pressure on Monophasic action potential durations at different levels of repolarisation in rat and guinea pig hearts. MAP durations at 20%, 50% and 80% repolarisation plotted for control (close to zero EDLVP), EDLVP >20 mm.Hg and re-control (EDLVP returned to close to zero). Error bars indicate \pm SEM, n = 4 hearts (each measurement in each heart is an average of at least 15 action potentials at each level of stretch). There are no significant differences in MAP durations between control, >20 mm.Hg and re-control. Panel A: data for rat and Panel B: data for Guinea pig.

Similar experiments in which intracellular action potentials were recorded in rat ventricular

strips also revealed no consistent differences in action potential morphology when the tissue was stretched (table 1). This result is consistent with that previously reported by Kiseleva et al [20], who also reported afterdepolarisations (presumably the correlate of our ectopic beats) at higher levels of stretch.

Table 1. Changes in intracellular action potential parameters in rat atrial and ventricular strips.

Atrial	APD ₂₀	APD ₅₀	APD ₈₀	RMP	Amplitude	Ventricular	APD ₂₀	APD ₅₀	APD ₈₀	RMP	Amplitude
NoChange	20(11)	14(9)	8(7)	9(8)	6(6)	NoChange	2(2)	2(2)	-	2(2)	1(1)
Increase	-	1(1)	-	8(7)	6(5)	Increase	-	-	-	-	-
Decrease	4(3)	9(7)	14(8)	7(5)	12(8)	Decrease	1(1)	1(1)	1(1)	1(1)	2(2)

Table 1. Results from “x” experiments and (y) rats. Data show variation observed in Action Potential Duration (APD) measurements following a minimum 0.3 g step in resting tension (from 0–0.5 g to 0.8 g). Decreases in Resting Membrane Potential (RMP) denote hyperpolarization while increases in RMP represent depolarisation. $P < 0.05$ (un-paired t-tests for separate impalements, paired for continuous impalements). Multiple steps in resting tension were made in each preparation. Where differences were observed in response, the number of preparations and animals that exhibited the response is also shown.

3.2. Atria

In intact rat atria, previous studies have shown that showed that modest stretch alters action potential morphology [17,38]. We attempted to reproduce this observation in rat atrial strips. Although increasing the tension over the range 0.5 to 3 g produced an obvious increase in dT/dt , no clear change in action potential morphology could be seen (figure 6A and 6B). In a single impalement retained for over 2 minutes, no obvious change in action potential morphology could be seen at stretches up to 4 g (which produced an increase in developed tension of about 50%), although a small depolarisation of resting membrane potential could be discerned (figure 6C). The passive tensions that we used in these experiments, although apparently within the range of the Frank-Starling relation, are much higher than those used by Kamkin et al (1.7 mN) [17]. It may be that this is because of the different orientation of the tissue relative to the stretch axis (ie stretch is not being applied axially to the muscle fibres). Nevertheless, for levels of stretch that produced obvious changes in contractility, we recorded no change in action potential morphology. The results of our recordings of intracellular action potentials in isolated atrial tissue are also summarised in table 1. Since the action potential morphology remains essentially constant throughout the experiment, and contractility is similarly maintained, we conclude that tissue ischaemia is not affecting the data (rat atrial wall is about 200 μm thick so diffusion of oxygen should not be a limiting factor).

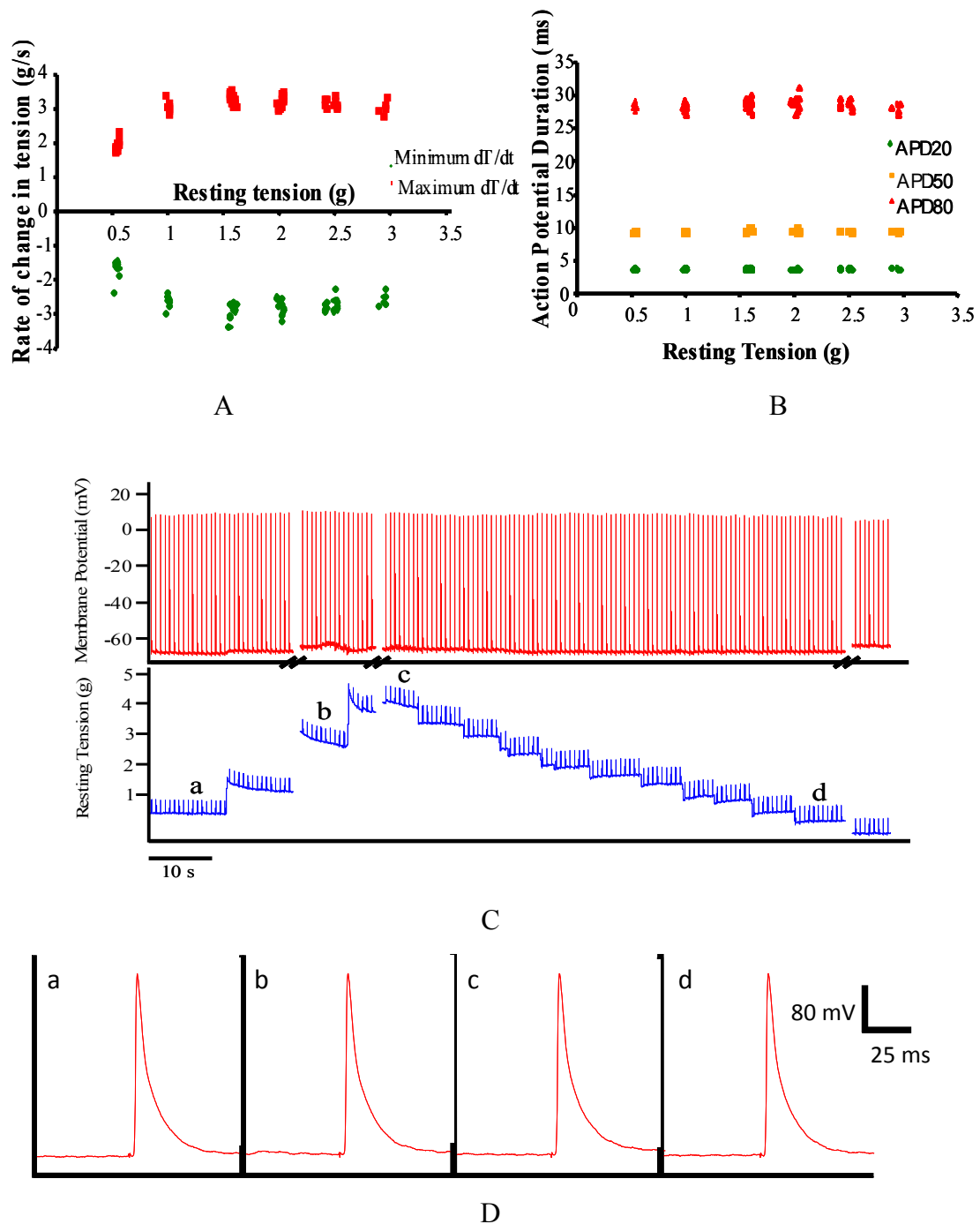


Figure 6. Effect of stretch on contractility and intracellular action potential morphology in rat atrial strips. Panel A: dT/dt (both positive and negative) recorded in a rat atrial strip plotted against the level of resting tension. **Panel B:** Action potential duration for intracellular action potentials in the same tissue as Panel A at 20%, 50% and 80% repolarisation at different levels of resting tension. Each point represents an action potential from a continuous impalement. **Panel C:** example of a record in which a single impalement was maintained in an atrial strip. Top panel shows the intracellular membrane potential, below it is the tension record. Action potentials recorded at points a, b, c and d are shown in Panel D.

3.3. Discrimination of the recording technique

We were concerned that the failure to see changes in action potential morphology at low levels of stretch may have been due to poor discrimination of the recording technique. We tested this by recording the action potential changes produced by 10 μM 4-AP, a concentration which would be expected to produce barely perceptible changes in action potential morphology (EC_{50} for 4-AP to block I_{to} in rat heart is 1 mM [40]). We find that even with this very low concentration of 4-AP we can record significant differences in APD (figure 7). This confirms that the failure to see changes in APD with stretch is not due to poor discrimination of the recording technique.

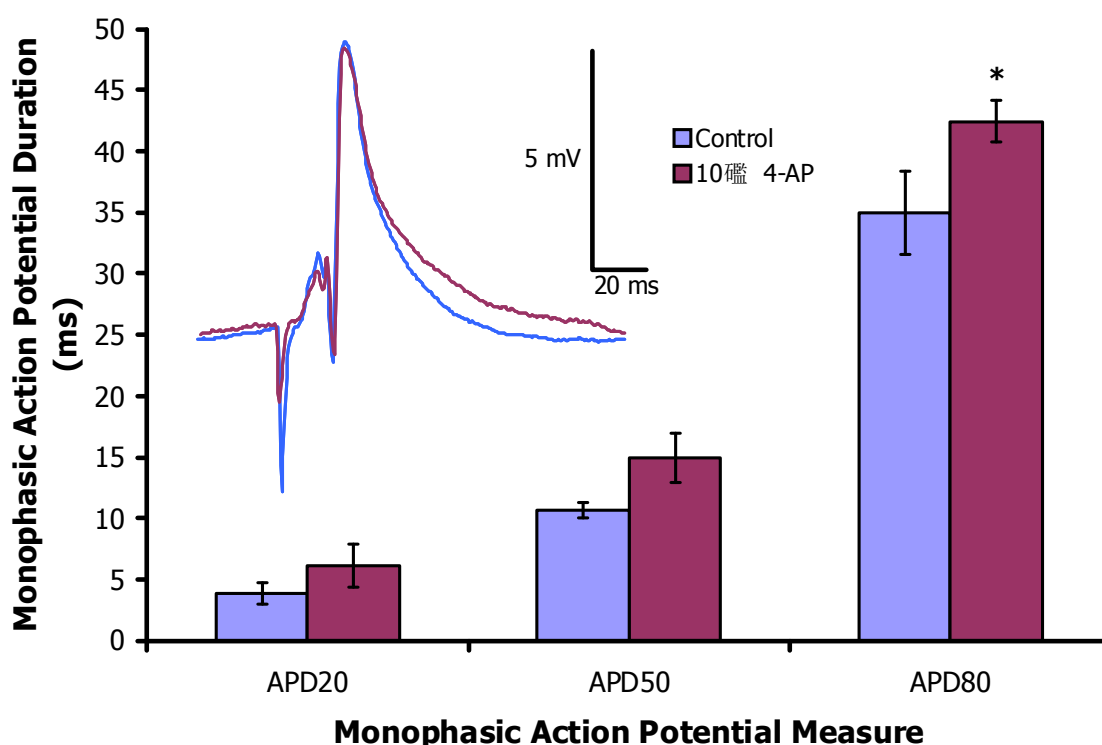


Figure 7. Sensitivity of MAP recording to detect change in action potential duration with low dose 4-AP. Main Panel: Action potential duration measured by monophasic action potential recording in an isolated rat heart paced at 5 Hz at 20%, 50% and 80% repolarisation in control (open bars) and in the presence of 10 μM 4-AP (shaded bars) ($n = 4$). * indicates significant difference ($P < 0.05$). Inset—superimposed typical traces of MAP recording in control and in the presence of 10 μM 4-AP.

4. Discussion

Many experimental and theoretical studies have sought to demonstrate a role for MEF in cardiac physiology [21]. One of the more consistent observations is that stretch produces slight depolarisation [20] and a rise in intracellular calcium [42], presumably by activation of non-selective cation channels, and this appears to be involved in the slow inotropic response and possibly the

hypertrophic response to stretch [6–8]. However, these responses do not involve changes in action potential morphology, and do not appear to contribute to the immediate increase in contractility with stretch. We find that, in isolated heart preparations and isolated tissues, it is difficult to demonstrate MEF at levels of tissue stretch comparable to those normally encountered by the myocardium. This result reflects the inconsistencies in the literature; some studies have demonstrated shortening of the action potential with stretch [10,12,29], an effect also seen in human heart [35], while others report no effect [15,17] or a “crossover” effect [17,26]: see reviews [28] and [11]. Similar inconsistencies can be seen in experiments examining MEF at the cellular level [30]. This lack of clear MEF at “physiological” levels of stretch is a perplexing result, since there is no doubt that stretch activated channels are present in the membrane of both ventricular and atrial cardiac myocytes [16,23,32,36]. This failure to demonstrate MEF in our experiments may be related to the observation that it appears to be necessary to rapidly stretch the myocardium in order to elicit obvious electrophysiological changes (figure 2B). This suggests that the rate of stretch is more important than the degree of stretch per se, as suggested by Calkins, Levine and Kass [9], perhaps due to the visco-elastic properties of the myocardium, or perhaps due to MEF being elicited by sheer stress between planes of muscle fibres [25]. More intriguingly, ectopic beats can be elicited by rapid release of the myocardium from stretch (figure 2C), and observation made some time ago [18] but still not fully understood. The mechanism may be related to the dissociation of calcium from the unloaded myofilaments, due to the tension-dependence of the affinity of troponin for calcium [2], the consequent rise in intracellular calcium accelerating sodium-calcium exchange or other electrogenic calcium dependent processes which in turn result in afterdepolarisations [22,23]. If such changes in calcium handling are occurring at physiological levels of stretch, they are not prominent enough to alter action potential morphology, as might be predicted by effects on calcium dependent channels or the sodium-calcium exchanger.

5. Conclusion

There are other possible reasons why we may fail to see MEF in these experiments. MEF may be a labile process, subject to continuous modulation by hormonal or biochemical influences [5,37] and, in the process of preparing the isolated heart or tissues, this influence is lost. Perhaps more importantly, MEF is not uniform throughout the myocardium. It has been shown that the distribution of stretch activated channels is heterogeneous in the myocardium [34,36] and that the distribution of strain is also inhomogeneous [27]. Consistent with this, we have previously shown in rat ventricle that sub-epicardial action potentials (recorded with a different electrode technique) are much less affected by stretch than are sub-endocardial [19]. One might also expect similar regional disparities between apex and base [10]. Hence, it may be that our recordings do not reveal AP changes because we are recording from the epicardial surface near the equator, whereas more obvious changes may be occurring elsewhere in the myocardium. These considerations also apply to guinea-pig heart, although the subtleties of MEF in this species is less well understood.

Acknowledgments

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References

1. Allen DG, Kentish JC (1985) The cellular basis of the length-tension relation in cardiac muscle. *J Mol Cell Cardiol* 17: 821–840.
2. Babu A, Sonnenblick E, Gulati J (1988) Molecular basis for the influence of muscle length on myocardial performance. *Science* 240: 74–76.
3. Bainbridge FA (1915) The influence of venous filling upon the rate of the heart. *J Physiol* 50: 65–84.
4. Blinks JR (1956) Positive chronotropic effect of increasing right atrial pressure in the isolated mammalian heart. *Am J Physiol* 186: 299–303.
5. Bockenhauer D, Zilberberg N, Goldstein SA (2001) KCNK2: reversible conversion of a hippocampal potassium leak into a voltage-dependent channel. *Nat Neurosci* 4: 486–491.
6. Bustamante JO, Ruknudin A, Sachs F (1991) Stretch-activated channels in heart cells: relevance to cardiac hypertrophy. *J Cardiovasc Pharmacol* 17 Suppl 2: S110–113.
7. Calaghan SC, Belus A, White E (2003) Do stretch-induced changes in intracellular calcium modify the electrical activity of cardiac muscle? *Prog Biophys Mol Biol* 82: 81–95.
8. Calaghan SC, Le Guennec JY, White E (2004) Cytoskeletal modulation of electrical and mechanical activity in cardiac myocytes. *Prog Biophys Mol Biol* 84: 29–59.
9. Calkins H, Levine JH, Kass DA (1991) Electrophysiological effect of varied rate and extent of acute in vivo left ventricular load increase. *Cardiovasc Res* 25: 637–644.
10. Dean JW, Lab MJ (1990) Regional changes in ventricular excitability during load manipulation of the in situ pig heart. *J Physiol* 429: 387–400.
11. Franz MR (1996) Mechano-electrical feedback in ventricular myocardium. *Cardiovasc Res* 32: 15–4.
12. Franz MR, Cima R, Wang D, et al. (1992) Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. *Circulation* 86: 968–978.
13. Fuchs F, Martyn DA (2005) Length-dependent Ca(2+) activation in cardiac muscle: some remaining questions. *J Muscle Res Cell Motil* 26: 199–212.
14. Hansen DE, Craig CS, Hondeghem LM (1990) Stretch-induced arrhythmias in the isolated canine ventricle. Evidence for the importance of mechano-electrical feedback. *Circulation* 81: 1094–1105.
15. Hennekes R, Kaufmann R, Lab M (1981) The dependence of cardiac membrane excitation and contractile ability on active muscle shortening (cat papillary muscle). *Pflugers Arch* 392: 22–28.
16. Hu H, Sachs F (1997) Stretch-activated ion channels in the heart. *J Mol Cell Cardiol* 29: 1511–1523.
17. Kamkin A, Kiseleva I, Wagner KD, et al. (2000) Mechano-electric feedback in right atrium after left ventricular infarction in rats. *J Mol Cell Cardiol* 32: 465–477.
18. Kaufmann RL, Lab MJ, Hennekes R, et al. (1971) Feedback interaction of mechanical and electrical events in the isolated mammalian ventricular myocardium (cat papillary muscle). *Pflugers Arch* 324: 100–123.
19. Kelly D, Mackenzie L, Hunter P, et al. (2006) Gene expression of stretch-activated channels and mechano-electric feedback in the heart. *Clin Exp Pharmacol Physiol* 33: 642–648.
20. Kiseleva I, Kamkin A, Wagner KD, et al. (2000) Mechano-electric feedback after left ventricular infarction in rats. *Cardiovasc Res* 45: 370–378.
21. Kohl P, Bollensdorff C, Garny A (2006) Effects of mechanosensitive ion channels on ventricular electrophysiology: experimental and theoretical models. *Exp Physiol* 91: 307–321.

22. Lab MJ (1999) Mechanosensitivity as an integrative system in heart: an audit. *Prog Biophys Mol Biol* 71: 7–27.
23. Lab MJ, Allen DG, Orchard CH (1984) The effects of shortening on myoplasmic calcium concentration and on the action potential in mammalian ventricular muscle. *Circ Res* 55: 825–829.
24. Lange G, Lu HH, Chang A, et al. (1966) Effect of stretch on the isolated cat sinoatrial node. *Am J Physiol* 211: 1192–1196.
25. Legrice IJ, Hunter PJ, Smaill BH (1997) Laminar structure of the heart: a mathematical model. *Am J Physiol* 272: H2466–2476.
26. Nazir SA, Lab MJ (1996) Mechanoelectric feedback in the atrium of the isolated guinea-pig heart. *Cardiovasc Res* 32: 112–119.
27. Nickerson D, Niederer S, Stevens C, et al. (2006) A computational model of cardiac electromechanics. *Conf Proc IEEE Eng Med Biol Soc* 1: 5311–5314.
28. Ravens U (2003) Mechano-electric feedback and arrhythmias. *Prog Biophys Mol Biol* 82: 255–266.
29. Reiter MJ, Synhorst DP, Mann DE (1988) Electrophysiological effects of acute ventricular dilatation in the isolated rabbit heart. *Circ Res* 62: 554–562.
30. Riemer TL, Tung L (2003) Stretch-induced excitation and action potential changes of single cardiac cells. *Prog Biophys Mol Biol* 82: 97–110.
31. Rozenberg S, Tavernier B, Riou B, et al. (2006) Severe impairment of ventricular compliance accounts for advanced age-associated hemodynamic dysfunction in rats. *Exp Gerontol* 41: 289–295.
32. Sackin H (1995) Mechanosensitive channels. *Annu Rev Physiol* 57: 333–353.
33. Stacy GP, Jr, Jobe RL, Taylor LK, et al. (1992) Stretch-induced depolarizations as a trigger of arrhythmias in isolated canine left ventricles. *Am J Physiol* 263: H613–621.
34. Stones R, Calaghan SC, Billeter R, et al. (2007) Transmural variations in gene expression of stretch-modulated proteins in the rat left ventricle. *Pflugers Arch* 454: 545–549.
35. Taggart P (1996) Mechano-electric feedback in the human heart. *Cardiovasc Res* 32: 38–43.
36. Tan JH, Liu W, Saint DA (2004) Differential expression of the mechanosensitive potassium channel TREK-1 in epicardial and endocardial myocytes in rat ventricle. *Exp Physiol* 89: 237–242.
37. Tan JH, Liu W, Saint DA (2002) Trek-like potassium channels in rat cardiac ventricular myocytes are activated by intracellular ATP. *J Membr Biol* 185: 201–207.
38. Tavi P, Han C, Weckstrom M (1998) Mechanisms of stretch-induced changes in $[Ca^{2+}]_i$ in rat atrial myocytes: role of increased troponin C affinity and stretch-activated ion channels. *Circ Res* 83: 1165–1177.
39. Todaka K, Ogino K, Gu A, et al. (1998) Effect of ventricular stretch on contractile strength, calcium transient, and cAMP in intact canine hearts. *Am J Physiol* 274: H990–1000.
40. Volk T, Nguyen TH, Schultz JH, et al. (1999) Relationship between transient outward K^+ current and Ca^{2+} influx in rat cardiac myocytes of endo- and epicardial origin. *J Physiol* 519 Pt 3: 841–850.
41. White E, Boyett MR, Orchard CH (1995) The effects of mechanical loading and changes of length on single guinea-pig ventricular myocytes. *J Physiol* 482 (Pt 1): 93–107.
42. Wilhelm J, Kondratev D, Christ A, et al. (2006) Stretch induced accumulation of total Ca and Na

in cytosol and nucleus: a comparison between cardiac trabeculae and isolated myocytes. *Can J Physiol Pharmacol* 84: 487–498.

43. Zabel M, Koller BS, Sachs F, et al. (1996) Stretch-induced voltage changes in the isolated beating heart: importance of the timing of stretch and implications for stretch-activated ion channels. *Cardiovasc Res* 32: 120–130.

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