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Mechanoelectric feedback in the atrium of the isolated guinea-pig heart

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Abstract

Objectives: Atrial arrhythmias are prevalent during clinically abnormal myocardial loading, e.g. when the atrium is dilated or stretched. The initiating cause of the first premature beat that leads to this arrhythmia is unclear, as are the reasons for sustaining it. One possibility is that abnormal mechanical factors induce electrophysiological changes conducive to arrhythmia via 'mechanoelectric feedback'. The aim of this study is to investigate the concept that atrial stretch modulates the electrophysiological properties of the atrium via mechanoelectric feedback, and that mechanoelectric feedback can produce atrial arrhythmias. **Methods**: Guinea-pigs were humanely killed by cervical dislocation and the hearts removed and perfused with oxygenated Krebs-Henseleit solution by the Langendorff method. The heart was paced at an atrial site near the sinus node. Monophasic action potentials and electrocardiograms were recorded from the left atrium and left ventricle with suction electrodes. Transient stretch was induced by inflating a fluid-filled intra-atrial latex balloon catheter. **Results**: Increase in atrial volume produced several significant changes in the epicardial monophasic action potentials. It produced (i) decreases in the amplitude; (ii) a decrease in duration from 62.55 to 51.95 ms measured at 50% repolarisation (10.6 ± 3.6 ms, $P < 0.05$, $n = 6$); (iii) an increase in duration from 122.45 to 140 ms measured at 90% repolarisation (17.55 ± 4.5 ms, $P < 0.05$, $n = 6$) — due to the presence of early afterdepolarisations. (iv) These load-induced electrophysiological changes coincided with the occurrence of arrhythmia or premature atrial beats. **Conclusions**: Load changes in the atrium can produce electrophysiological changes of a kind that may be relevant to clinical atrial arrhythmia.

Keywords: Mechano-electric feedback; Stretch; Guinea-pig, heart; Monophasic action potential; Atrial arrhythmias

1. Introduction

The initiating cause of the first premature beat that leads to atrial fibrillation is unclear, as are the reasons for sustaining it. As reviewed by Murgatroyd and Camm [1], it is the commonest sustained cardiac arrhythmia. Featuring among its aetiologies are mechanical factors such as valvular disease and hypertension. Diagnosis and treatment of atrial arrhythmias are often based on abnormal atrial electrical behaviour. This appears logical, for the electrical activity of the heart triggers its mechanical activity by a process known as excitation–contraction coupling. However, drug treatment on the whole has been disappointing, and is usually aimed at blocking atrioventricular conduction to slow the ventricular rate. The search for new therapeutic avenues for the management of atrial rhythm disturbances continues.

Atrial enlargement, for example resulting from heart valve lesions, is frequently associated with atrial fibrillation. It is possible that the increased volume per se is arrhythmogenic. Evidence has been accumulating to show that mechanical changes can initiate electrophysiological changes. This suggests that in addition to excitation–contraction coupling, the unidirectional system controlling mechanical activation in the heart, there is a feedback system, whereby mechanical changes during contraction modulate electric activity [2]. This system is often referred to as mechanoelectric feedback (MEF).

Mechanoelectric feedback has been extensively studied in the thick-walled ventricles, for example by Lab and colleagues [2,3], Franz et al. [4], Hansen et al. [5], where it

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plays a role in ventricular rhythm disturbances [2–5]. The thick left ventricular wall is anatomically and functionally complex. One cannot be certain what is being stretched: Purkinje fibres, contractile myocardium, nerve terminals. One of the mechanisms that could explain mechanoelectric feedback is the stretch-activated channel as described by Yang and co-workers [6] and reviewed by Kim [7–9], who concentrated on atrium to a large extent. Most studies have focused on patch clamping in general and Morris [10] has suggested that these stretch-activated channels are artefact. However, mechanoelectric feedback in the thin-walled atrium has yet to be firmly established, although it has been demonstrated to exist in the atrial myocardium by Kaseda and Zipes [11], and our own preliminary observations [12,13].

The overall purpose of this study is to investigate the possibility that atrial stretch modulates its electrophysiological properties, i.e. to see whether (i) atrial stretch modulates action potentials, and (ii) it contributes to the genesis of atrial arrhythmias.

2. Methodology

2.1. Langendorff-perfused guinea-pig hearts

Twelve guinea-pigs of either sex, weighing between 400 and 500 g were humanely killed by cervical dislocation. The hearts were retrogradely perfused with modified Krebs-Henseleit solution, consisting of (in mM): NaCl 115.3, KCl 4.6, $MgSO_4$ 1.1, $NaHCO_3$ 22.1, KH_2PO_4 1.1, $CaCl_2$ 2.5, and glucose 11.1 (Sigma Chemical Co.). The perfusate was equilibrated to 37°C ± 0.5°C through a temperature control system (Techne Circulator C100) and bubbled continuously with 95% O_2/5% CO_2 (pH 7.4) to maintain normoxia and pH.

A fluid-filled latex balloon was inserted into the left atrium, via a stiff catheter, and used to stretch it (Fig. 1). The balloon was larger than the mitral valve to prevent it herniating into the ventricle. The balloon was attached to a pressure transducer (Linten instruments). The distance between the transducer and the balloon was minimised to prevent dampening of the system. Coronary flow, pH, and temperature of the perfusate were measured at least every 15 min. Experiments in which pH varied more than 0.5, and experiments in which temperature varied more than 0.5°C were excluded from analysis. Experiments were also excluded if sinus frequency was higher than the chosen paced frequency. Absolute values of spontaneous rate for the isolated guinea-pig heart was 210–220 beats/min, consequently hearts were paced at 240 beats/min.

2.2. Protocol

2.2.1.1. Pacing. The heart was paced at an atrial site near the sinus node by a suction electrode. It was performed at

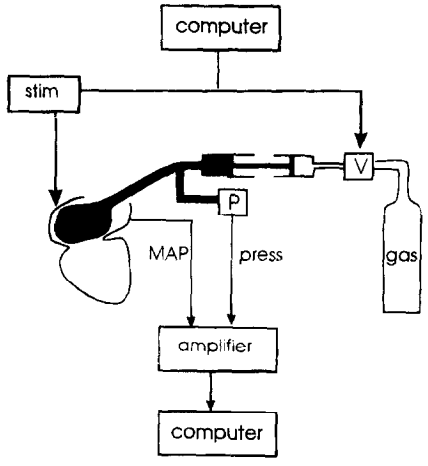

Fig. 1. Diagram of atrial inflation apparatus. V = valve; Stim = stimulator; MAP = monophasic action potential; press = intra-atrial pressure. Shading represents fluid-filled region of the system.

20 beats/min above its intrinsic rate using 2-ms rectangular pulses at twice diastolic threshold. Electrical pacing was performed with a Digitimer Stimulator Model DS2 controlled directly by custom software and a computer.

2.2.1.2. Atrial stretch. (see Fig. 1) The atrial wall is thin and compliant. A servocontrolled pump mechanism is not necessary to inflate the atrium. A simple gas-operated pump system provided constant rates of inflation and deflation of the balloon at predetermined volumes and times. It consisted of two syringes whose plungers were attached back to back. One calibrated fluid-filled syringe was attached to a cannula and pressure transducer via a three-way tap. The mechanical effector mechanism (as well as the stimulus) was controlled by computer which triggered a solenoid-operated valve. This allowed compressed air to drive the plunger mechanism to inflate the balloon. The inflation was maintained for 5 s.

Balloon inflation was timed relative to the pacing spike. The atrium was stretched 100 ms after the pacing stimulus. As judged from the monophasic action potential recordings, repolarisation was usually complete at this point in the cardiac cycle (i.e. electrical diastole). Although isovolumic relaxation of the atrium was not always complete at the onset of stretch, we chose to apply stretch early in diastole, since arrhythmia induction is similar to ventricular preparations for early versus late diastolic stretch [5]. Atrial beats occurring under unloaded conditions in the Langendorff preparation can be assumed to be ejecting in nature (i.e. the muscle shortens).

The heart was stabilised for 15 min, its intrinsic heart rate calculated and pacing initiated. Curves analogous to Starling curves were constructed (plot of the number of premature atrial beats (PABs) against inflation volume) to determine the maximum balloon inflation necessary to keep stretch within physiological limits. Inflation was started at zero volume and moved up to 0.5 ml in 0.1 ml

increments. At each volume three recordings were taken and the number of premature atrial beats counted. Our laboratory has found, in ventricular preparations, that a second stretch following the first within 30 s produced fewer premature beats than the first stretch. Thus, the hearts were allowed to recover for 2 min between inflations to avoid this 'mechanical adaptation' of the heart [14].

2.3. Electrophysiological measurements

2.3.1.1. Epicardial monophasic action potential. Monophasic action potentials (MAPs) were recorded from the epicardial surfaces of the left atrium, and left ventricle by means of suction electrodes [15]. The waveform resembles the excursion in transmembrane potential [16] and follows the shape and duration of the intracellular action potential as well as relative changes in action potential amplitude. However, the absolute amplitude of the action potential is less than the transmembrane potential.

2.3.1.2. Epicardial ECG. This was obtained from the indifferent wick electrodes of the monophasic action potential recording electrode.

2.3.1.3. Signal processing. The electrical signals from the suction electrodes and pressure transducer (Linten Instruments) were amplified using high impedance DC and AC preamplifiers (Lectromed, MT8). The signals were displayed onto an oscilloscope (Tektronic 5103 N) during the experiment and fed into a digitisation and data acquisition module (Cambridge Electronic Design, 1401) and monitored on-line using software ('Chart' Cambridge Electronic Design). The data were digitised at 1000 Hz and passed to a PC (486DX66) with 1 Gb hard disk. Back-up analogue signals were stored onto magnetic tape by a TEAC XR-501 cassette tape recorder.

2.4. Experimental analysis

2.4.1.1. Action potential duration / amplitude. Monophasic action potential durations (MAPDs) and amplitude were analysed using customised software (Cambridge Electronic Design). Action potential duration was measured at 50% and 90% repolarisation. The amplitude of the action potential was taken as the difference in mV between the diastolic baseline and the crest of the plateau.

2.4.1.2. Identification of premature atrial beats. The timing with respect to the stimulation spike was the most important criterion. Normally, the position of the atrial action potential has a consistent time relationship with the pacing spike. A premature atrial beat is characterised when its upstroke was not consistent with the stimulation spike: usually when the upstroke of the action potential occurred before the stimulation spike. The guidelines of the Lambeth convention [17] were used to classify and define premature ventricular contractions. They were identified by inspecting the QRS complex of the ECG for an extended QRS complex duration or an activation vector change, or altered repolarisation vector, for example, 'flattened' or inverted T-wave.

2.5. Statistical analysis

Analysis of variance for repeated measures was employed to determine whether atrial loading conditions influenced the electrophysiological variables for each of the various experimental stages. When a significant treatment was indicated by the F statistic, Student's paired *t*-test was used to analyse the data. Statistical significance was taken as $P < 0.05$.

The investigation was performed in accordance with the Home Office *Guidance on the operation of the Animals (Scientific Procedures) Act 1986*, published by HMSO, London.

3. Results

Throughout the recording period, in the absence of any alteration in myocardial load, monophasic action potentials remained stable in amplitude and configuration, and action potential duration measures remained constant during the first 30 min of continuous recording. After the first 30 min of continuous pacing the average MAPD shortened by approximately 2 ± 1 ms. Subsequently, the MAP signal deteriorates and the electrode needs to be repositioned. The electrode is placed adjacent to its preceding site. MAPD at this point did not differ significantly from its former location.

3.1. Effect of stretch volume on arrhythmia induction

The results depicted in Fig. 2 show the relationship between stretch-induced premature atrial beats and inflation volume. The results were derived from ten control preparations. For each preparation we repeated each specific volume inflation in triplicate. In four experiments we started stretching the atrium using a high volume (0.5 ml) and subsequently progressed to zero in 0.1 ml decrements. We found that there was no significant difference in the number of premature atrial beats induced using this protocol or using one in which stretch was initiated at zero volume with 0.1 ml increments.

In general, small stretch volumes (less than 0.1 ml) failed to trigger a premature atrial beat. An increase in balloon volume triggered premature atrial beats. Volume was increased in 0.1 ml increments until no further increase in the number of premature atrial beats was observed. Starling curves were constructed of inflation volume and developed pressure. Curves analogous to these

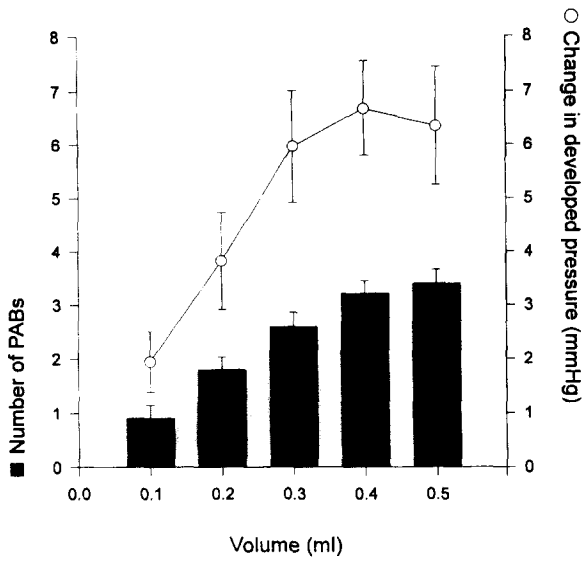

Fig. 2. Bar graph to illustrate the relationship between balloon volume and the number of stretch-induced premature atrial beats (PABs) in the left atrium of isolated, Langendorff-perfused guinea-pig hearts. Line plot describes the relation between balloon volume and change in developed pressure in the atrium. The hearts were paced at a constant rate. Results are displayed as means ± standard error of the means. The plots were used to determine a physiological inflation volume. This was approximately 75% of the volume/pressure that produced the maximum number of premature beats.

Starling curves were also constructed, consisting of a plot of the number of premature atrial beats against inflation volume (Fig. 2). The Starling curves were scrutinised to ensure physiological inflation volumes. The volume which produced 75% of the maximum number of premature atrial beats and/or 75% of the maximal developed pressure was selected as the experimental volume to induce premature atrial beats. We used this volume as the optimal volume which was usually between 0.25 and 0.35 ml.

Fig. 3 is a slow playout of atrial and ventricular action potentials. Stretch produced a premature atrial MAP (first asterisk) which conducted to the ventricles producing an early ventricular MAP (vertical arrow). The next atrial premature beat (second asterisk) did not excite the ventricle, producing a pause following the arrowed ventricular MAP. Premature atrial excitation (*) occurred at the beginning and at the end of the inflation period. Pressure increases produced complex arrhythmias, whilst pressure reductions produced simple atrial ectopics.

3.2. Effect of left atrial stretch on action potential amplitude

The amplitude of the monophasic action potential was defined as the difference in millivolts between the diastolic baseline and the crest of the systolic plateau. Figs. 3 and 4 depict the changes in monophasic action potential amplitude observed during transient atrial stretch. An increase in

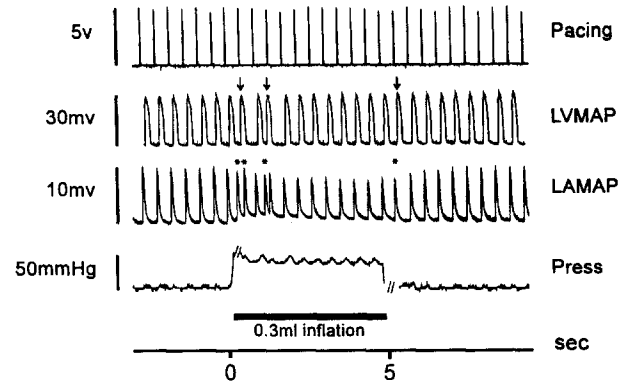

Fig. 3. Change in left atrial (LAMAP) and left ventricular (LVMAP) monophasic action potential with rapid increases in left atrial volume. Timing and inflation volume is indicated by the horizontal bar. Dynamics of stretch are represented by the pressure trace (press). Top trace is the pacing stimulus. Stretch shifts the diastolic and systolic potential of LAMAP to reduce the overall amplitude of the action potential. The alterations in amplitude were reversible on deflation. Premature atrial beats were consistently observed (*) during volume changes (see text for identification of premature atrial beats). Changes in action potential amplitude were not observed in the unloaded left ventricle (LV). Hash lines interrupt pump-associated mechanical artefact.

left atrial volume resulted in simultaneous shifts in diastolic and systolic levels of monophasic action potentials (Fig. 3) recorded from the left atrium. The diastolic depolarisation of resting potential was largest at the onset of inflation, and it gradually dissipated despite the continuous presence of inflation. In contrast, the amplitude reduction of the systolic potential continued throughout the entire inflation period. This sudden change in amplitude of the monophasic action potential did not occur in the left

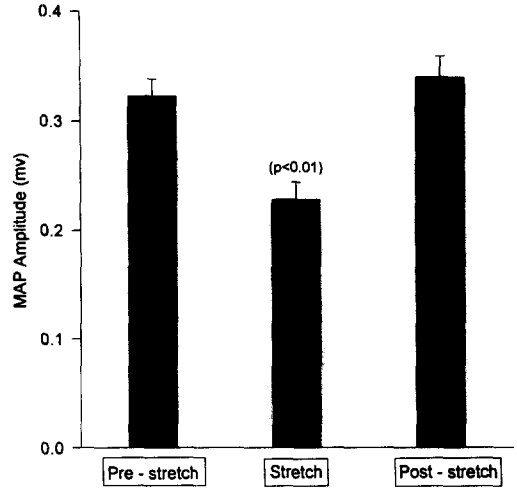

Fig. 4. Bar graph to illustrate decrease in monophasic action potential (MAP) amplitude during left atrial stretch in Langendorff-perfused guinea-pig hearts ($n = 6$). The hearts were paced at 240 beats/min (250 ms interval), and atrial stretch was induced by inflation of an intra-atrial balloon. Results are displayed as means ± standard error of means. Atrial stretch significantly decreased MAP amplitude ($P < 0.01$) in all preparations. Post-stretch data were collected when amplitude values resumed a stable baseline. This was normally 1–2 beats after stretch.

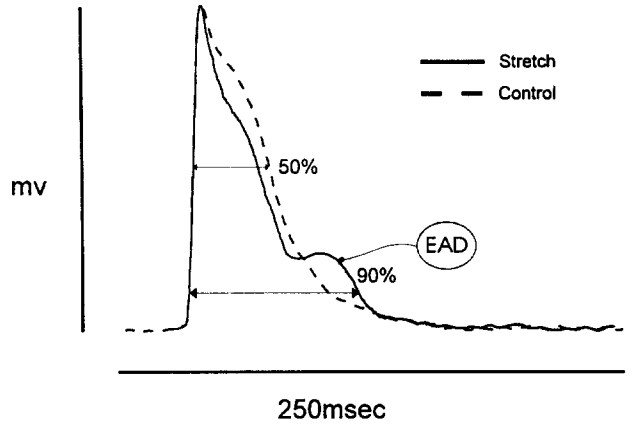

Fig. 5. Typical monophasic action potentials digitised from the stretched (solid line) and unstretched (dashed line) left atrium recorded by a suction electrode. MAPs have been normalised to depict the effect of left atrial volume increase on duration at repolarisation levels of 50% ($MAPD_{50}$) and 90% ($MAPD_{90}$). A simultaneous decrease and increase in $MAPD_{50}$ and $MAPD_{90}$ was observed respectively during stretch. A mechanically induced early afterdepolarisation (EAD) on the action potential associated with the stretched atrium reflected the increase in $MAPD_{90}$.

ventricle, and the observed change in amplitude is exclusively a stretch-induced response.

3.3. Effect of left atrial stretch on action potential duration

The effect of atrial stretch on monophasic action potential duration at two different levels of repolarisation is indicated in Figs. 5 and 6.

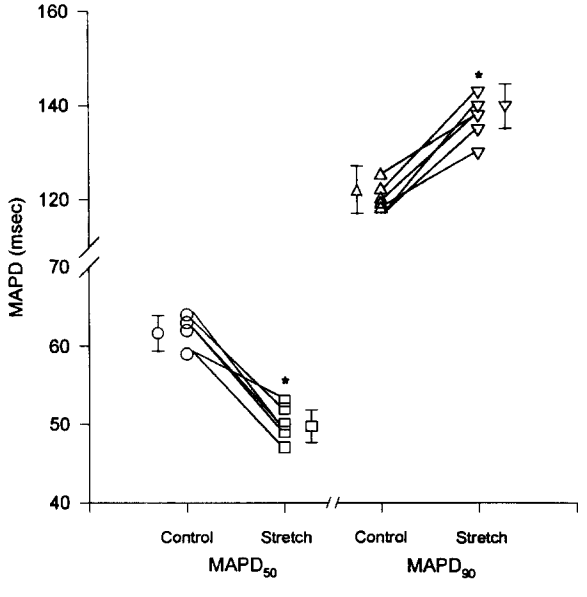

Fig. 6. Change in monophasic action potential duration during left atrial stretch. Mean action potential duration measured at 50% ($MAPD_{50}$) and 90% ($MAPD_{90}$) repolarisation are shown. Vertical bars represent standard errors. Atrial stretch induced a simultaneous decrease in $MAPD_{50}$ and increase in $MAPD_{90}$ (* denotes $P < 0.05$ with respect to control MAPD).

An increase in atrial volume resulted in: a significant decrease in action potential duration at 50% repolarisation by 10.6 ± 3.6 ms ($P < 0.05$), and a significant increase in action potential duration at 90% repolarisation by 17.55 ± 4.5 ms ($P < 0.05$). The increase in $MAPD_{90}$ was due to the development of 'hump-like' early afterdepolarisations (Fig. 5).

In all preparations, changes in monophasic action potential amplitude and duration occurred immediately after a volume increment.

4. Discussion

We show that sudden inflation, within physiological volume increases, produces electrophysiological changes in the isovolumetrically contracting atrium. Several significant changes were observed in the monophasic action potential as a consequence of increased load, and thus developed pressure. Atrial inflation (i) decreased the amplitude of the monophasic action potential, due to simultaneous shifts in both the maximum diastolic and systolic potential; (ii) shortened the monophasic action potential, particularly between phase 2 and 3 of repolarisation ($MAPD_{50}$); (iii) increased duration at $MAPD_{90}$: this took on the form of early afterdepolarisations; (iv) induced arrhythmia or premature atrial beats. These changes are consistent with contraction–excitation feedback, or mechanoelectric feedback: the phenomenon whereby changes in the mechanics of myocardial contraction precede and produce changes in membrane potentials. It has been proposed as a possible link between altered loading conditions and arrhythmias [2,3,18,19]. Although several workers have studied the phenomena in intact ventricle (including Lab [20] in frog, Franz et al. [4] in dog, Dean and Lab [3] in the in-situ pig preparation), this present study is the first of its kind systematically describing mechanically induced action potential changes in the intact atrium of isolated heart.

4.1. Atrial stretch induces arrhythmias

There were no spontaneous premature atrial contractions in hearts without atrial stretch. Transient dilation of the left atrial intracavitary balloon consistently elicits premature atrial beats. The above authors [3,4,20], as well as Hansen et al. [5], have made similar observations in isolated and in-situ ventricular preparations. Solti et al. [21] and a later pilot study by Nazir et al. [12] show similar results in in-situ atrial preparations. Although some investigators have demonstrated an association between volume expansions and premature beats, Calkins et al. [22] found no such correlation in the isolated ventricle. This discrepancy could be explained by the fact that they used gradual or static volume increases. Franz et al. [23] found that the faster the transient volume increase the more likely is the

production of premature ventricular contractions. Supporting this interpretation, Yamashita et al. [24] showed that it was the velocity of stretch of the atrium, by ventricular contraction, that altered the cycle length of atrial flutter.

4.2. Mechanically-induced electrical artefact

Hoffman et al. [16] noticed afterdepolarisations in suction electrode records but not in the microelectrode record, dismissing the afterdepolarisation as a movement artefact. Lepeschkin [25] and Lab [20,26] later argued that these afterdepolarisations, including those induced by stretch, could be true membrane potentials. The possibility that the load changes produce mechanically induced artefact have been discussed [20] in relation to ventricular myocardium. It is worth entertaining and discussing in some detail mechanically induced artefact in the thin-walled atrium.

We believe that our recorded action potential changes, and afterdepolarisation events are not movement artefacts for the following reasons: (i) Isovolumetric beats exhibit less wall motion than ejecting beats, yet afterdepolarisations were greater in isovolumetric than in ejecting beats; (ii) Afterdepolarisations were often followed by premature atrial beats whose action potentials had a reduced amplitude as is expected when the membrane is partially depolarised; (iii) Our findings in the intact guinea-pig atrium are consistent with previous observations of mechanoelectric feedback, recorded by microelectrode or insulated gap technique in excised ventricular muscle preparations [20].

To test the hypothesis that action potential recordings of stretch-induced depolarisations were not merely motion artefacts, Stacy et al. [27] compared recordings acquired during normal perfusion with recordings from the same heart after K arrest with 154 mM K^+. They found that motion artefact was negligible at all stretch volumes that were used for stretch-induced depolarisations in normal perfusion.

Dudel and Trautwein [28] attributed their stretch-induced action potential changes to irreversible electrophysiological change. It is unlikely that our results can be attributed to overdistension of the atrial chamber, for first, we used inflation volumes that were within the physiological range (Fig. 2). Second, the effects of our stretch were fully reversible.

The atrial balloon was made from highly compliant latex rubber. Although the balloon corresponds very closely to the configuration of the cardiac chambers [29], it is possible that friction between the balloon and the inner atrial wall could be a source of experimental artefact. Hansen et al. [5] noted that stretch during the refractory period did not produce premature beats in isolated canine ventricles. Maintaining inflation at a static volume (minimal friction) did produce premature beats. Moreover, increases in intraventricular volume by aortic occlusion in the intact heart also produce premature beats [3,23] — that is, there is no question of intracavitary friction. We feel that the premature beats in our preparation were induced by myocardial stretch rather than by friction.

An acute increase in atrial wall stress in systole may compromise myocardial perfusion and cause our electrophysiological changes. However, the stretch-induced changes in action potential amplitude and duration occurred within a few seconds or just a few beats. Dilly and Lab [30] showed previously that coronary artery occlusion in the in situ working heart required at least a minute or so to produce significant changes in action potential amplitude and duration.

For all the foregoing reasons, we believe that the voltage changes observed in the monophasic action potential recordings during transient stretch of the thin-walled atrium represent stretch-induced membrane depolarisations, rather than motion artefacts, or perfusion deficits.

4.3. Mechanism of mechanoelectric feedback (MEF)

4.3.1.1. Stretch-activated channels (SACs). Patch clamp data have provided evidence that the myocardium contains channels which are regulated by membrane strain or tension. As reviewed by Yang et al. [6], Sachs [31] and Watson [32], these channels are linked to the cytoskeleton which may conduct the mechanical forces.

Kim [7–9] has demonstrated the existence of stretch-activated channels in the atrial myocardium. Bustamante et al. [33] estimated the reversal potential for these stretch-activated currents, produced mainly by Na^+, K^+ and Ca^{2+}, to be -40 mV. The role of SACs has been discussed extensively by Hansen [5,34] and colleagues. In brief, under normal conditions, stretch during early plateau, where the membrane potential is more positive than the equilibrium potential, would repolarise the membrane, i.e. increase speed of repolarisation to shorten action potential duration. We find APD_{50} shorten with stretch. Where the membrane potential is more negative than the reversal potential, stretch would induce an inward, depolarising current, to prolong action potential duration, subsequently producing afterdepolarisations. These would generate premature beats if the depolarisation reaches threshold potential.

The action potential changes observed in Fig. 3 could support this SAC hypothesis. These changes, purely by analogy, are compatible with this hypothesis. For example, immediately after balloon inflation, SACs open, permit ion flux, and cause membrane potential to move positively towards the SAC equilibrium potential. Threshold is reached to generate premature atrial beats. We require, however, more direct experimental evidence to draw a definitive conclusion. Pilot studies using streptomycin [13] and gadolinium [35] (SAC blockers) support the possibility that SACs are involved. Both streptomycin and gadolinium inhibit stretch-induced atrial arrhythmias. Whilst stretch is maintained premature atrial beats continue to arise (not shown in Fig. 3) despite gradual dissipation of diastolic

depolarisation and continued decrease of systolic potential. This suggests other mechanosensitive mechanisms could be responsible for mechanoelectric feedback.

4.3.1.2. Other mechanisms of mechanoelectrical feedback in intact preparations. Reduced mechanical loading (shortening) during myocardial contraction can reduce calcium binding to troponin-C (Tn-C) so that free intracellular calcium rises. The change in the calcium transient could change calcium-modulated transmembrane currents to trigger new action potentials [36,37]. This mechanism needs substantial inhomogeneous shortening in the atrial wall during isovolumic contraction where some segments shorten more at the expense of others. This may also result in a dispersion of atrial electrophysiology that may provide a substrate for re-entrant atrial arrhythmias. Because monophasic action potential recordings were obtained from only one epicardial site, the present study provided no information regarding how important inhomogeneity might be in this isolated Langendorff-perfused heart preparation.

Occasionally we find premature beats and a prolongation of action potential duration when the atrium is allowed to shorten abruptly (i.e. on deflation). This is strongly compatible with studies of Kaufmann [36] and James [38] who demonstrated that when muscle shortens suddenly, there is an immediate prolongation of the action potential duration sometimes with premature activation. However, PABs did not occur consistently with our protocol because the timing of deflation was unpredictable.

It is possible that premature beats could be explained by stretch-activated channels, calcium changes, and/or re-entrant mechanisms. As yet, there is no direct evidence for these possibilities.

4.4. Clinical relevance of mechanoelectric feedback

As reviewed by Murgatroyd and Camm [1], data from several studies suggest that atrial dilatation is an important predisposing factor in the pathogenesis of atrial tachyarrhythmias (atrial flutter, atrial fibrillation, paroxysmal atrial tachycardias). The appearance of atrial tachyarrhythmias can frequently be observed in conditions resulting in left or right atrial enlargement [39,40] — for instance during mitral valve stenosis, and congestive cardiac failure.

There is a possible, and curious, example of mechanically induced atrial arrhythmia without atrial enlargement. Conwell et al. [41] describe 'ectopic atrial tachycardia' (EAT) in a patient with a catheter in the atrium. They suggested that catheter whip produced the arrhythmia which was a 'lookalike' arrhythmia. Catheter whip could distort the atrial sacrolemma to open stretch-activated channels so that the membrane reaches threshold for a new action potential.

Our study concentrated on the effects of acute atrial stretch on the prevalance of atrial arrhythmias in the isolated guinea-pig heart. In contrast, clinically, the atrium is usually chronically dilated and under the influence of neurohormonal factors. Further clinical and experimental studies are required to reveal in more detail the mechanism of atrial arrhythmias due to atrial enlargement in this setting. However, we may have to seriously entertain the possibility that activation of some mechanoelectric transduction process, such as stretch-activated channels as a consequence of atrial distension are involved, and contribute to the genesis of clinical atrial tachyarrhythmias.

In summary, we have developed a reproducible model of stretch-induced arrhythmias to study the important relation between atrial dilatation and atrial arrhythmias. Our study provides the first evidence that transient stretch of the left atrium produces characteristic changes in the monophasic action potential which predispose to atrial arrhythmias.

Acknowledgements

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