

Passive pericardial constraint protects against stretch induced vulnerability to atrial fibrillation in the rabbit

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Abstract

Atrial Fibrillation is more common in conditions with elevated atrial pressure and can be induced experimentally with acute increases in atrial pressure. We examined the effect of increased atrial pressure with and without pericardial constraint to better separate the effects of increased pressure and atrial stretch. In Langendorff perfused rabbit hearts with intact pericardium, after ligating the pulmonary and caval veins, intra-atrial pressures were increased in a stepwise manner by adjusting the pulmonary outflow cannula. Rapid burst pacing was applied to induce atrial fibrillation at increasing intra-atrial pressures from 0 to 24cm H₂O. The atrial refractory period was recorded at each pressure using a single extra stimulus. The protocol was repeated after the pericardium was removed. When the pericardium was intact, atrial stretch was limited by passive constraint and sustained atrial fibrillation could not be induced despite atrial pressures in excess of 20cm H₂O. In contrast, when the pericardium was removed, atrial fibrillation could be reliably induced when atrial pressure exceeded 15cm H₂O. This suggests that the electrophysiological effects of acute atrial volume loading rely on atrial stretch rather than increased atrial pressure alone.

Key Words

Atrial refractory period, mechano-electric feedback, Langendorff

Introduction

The rabbit model of stretch-induced vulnerability to atrial fibrillation (AF) has provided insight into the mechanisms by which acute elevations in atrial pressure change atrial electrophysiology(15). In this model, the elevation in atrial pressure causes marked atrial dilatation and this is associated with a drop in atrial refractoriness, changes in conduction and an increased propensity to atrial fibrillation(7, 15). It has been proposed that the electrophysiological changes associated with increased atrial pressure are due to the activation of stretch induced ion channels and altered calcium handling(2, 3). If this were the case, increased atrial pressure alone (without increased atrial stretch) should not alter atrial electrophysiology. We tested this hypothesis comparing the effects of increasing atrial pressure in the rabbit Langendorff heart model with and without an intact pericardium.

Materials and Methods

All animal care procedures and experiments were approved by the University of Adelaide Animal Ethics Committee.

Experimental Protocol

Nine adult semi-lop rabbits of either sex weighing >3kg were used for this study. Rabbits were anaesthetised with intravenous pentobarbitone with heparin and the hearts were removed with great care taken to leave the pericardium intact. The hearts were perfused on a Langendorff apparatus with a perfusion pressure of 60mm Hg at 37°C. The perfusion fluid contained (in mMol) NaCl 130, KCl 4.0, NaHCO₃ 24.2, NaPO₄ 1.2, MgCl 0.6, CaCl 2.2, glucose 12, and was bubbled with Carbogen to maintain a pH between 7.35 and 7.4.

The AV node was ablated using DC current and the interatrial septum was perforated. Ventricular fibrillation was induced with burst pacing. The superior vena cava and one

pulmonary vein were connected to a single “Y”- shaped manometer and the inferior vena cava and other pulmonary veins were ligated. The pulmonary artery was cannulated and biatrial pressure was controlled by adjusting the height of the pulmonary outflow catheter. Atrial pressure was increased in 3cm H₂O steps to a maximum of 24cm H₂O and burst pacing was applied at each step to induce atrial fibrillation. The protocol was repeated after the pericardium was removed.

If the pericardium was damaged prior to data collection (and hence would not provide passive constraint), the pericardium was removed and the heart was used as a control. Data from these control experiments were combined with 6 historical controls where the pericardium had been removed intentionally.

Electrophysiological Measurements

Hook electrodes were placed on the pericardium overlying the left atrium to record the epicardial electrogram. Signals were amplified through a Powerlab (AD Instruments, Australia) and recorded and analysed using Chart 4 software (ADI). Atrial refractory periods (ARP) were determined using single extra stimuli to the right atrium at a basic cycle length of 250ms at 3 times the pacing threshold. Atrial fibrillation was induced 5 times at each pressure with burst pacing at 50 Hz for 1 second at 3 times the pacing threshold. Atrial fibrillation was defined as “inducible” when a fast irregular rhythm longer than 2 seconds followed burst pacing and the term “sustained atrial fibrillation” was applied to episodes that lasted longer than 1 minute.

Statistics

Data are presented as mean \pm SEM unless indicated otherwise. A two-way analysis of variance was used to test the interaction between the presence of the pericardium and atrial

pressure on AF inducibility and ARP. AF inducibility, duration and ARPs at different degrees of atrial dilatation were statistically evaluated with the two-tailed unpaired Student's t tests, corrected for multiple comparisons. Values of $P < 0.05$ were taken to indicate statistical significance.

Results

Setting up the experiment with the pericardium intact was technically demanding. On 3 occasions, the pericardium was cut or torn during the dissection and the atria would prolapse through the tear when atrial pressures were increased. In these cases, the pericardium was removed prior to data collection and these 3 hearts were used as controls.

In the 9 control experiments, increasing atrial pressure produced a significant, reproducible reduction in ARP ($P < 0.05$ Figure 1) and this corresponded with an increased vulnerability to atrial fibrillation. AF was induced with a single extra stimulus when the ARP reached 50ms (the shortest coupling interval tested). Inducibility and duration of atrial fibrillation increased progressively with increasing pressure until atrial fibrillation was sustained with atrial pressures over 15cm H₂O (Figure 2).

In the remaining 6 rabbits, the hearts were dissected with the pericardium intact and it therefore acted as a passive constraint, limiting the distention of the atria when the atrial pressure was elevated. With the pericardium intact, the drop in ARP with increasing atrial pressure demonstrated in control experiments was not observed (Figure 1). Despite marked increases in atrial pressure (over 20cm H₂O), we were unable to induce sustained atrial fibrillation (Figure 2).

In contrast, when the pericardium was removed, all hearts demonstrated a drop in ARP with increasing atrial pressure and sustained atrial fibrillation could be reliably induced with burst pacing at atrial pressures comparable to those needed to induce AF in the control experiments.

Discussion

This study supports the hypothesis that acute increases in atrial pressure can predispose to atrial fibrillation via mechanically induced electrical changes (mechano-electric feedback). It is clear from catheter induced atrial ectopics during cardiac catheterisation that mechano-electric feedback exists in the human atrium. Whether acute stretch plays an important role in the initiation and maintenance of atrial fibrillation in conditions of elevated atrial pressure remains controversial. Antoniou et al studied a group of patients with lone atrial fibrillation during high and low atrial pressures using acute fluid loading(1). They found it was easier to induce atrial fibrillation and that the atrial fibrillation was more sustained with higher atrial pressure. Acute changes in atrial electrophysiology have been recorded following the drop in atrial pressure with mitral balloon commissurotomy for mitral stenosis(18) and non-invasive manoeuvres during atrial flutter(14). Several groups have tried to demonstrate acute changes in atrial electrophysiology in humans during short term dual chamber pacing with conflicting results(4-6, 11, 20).

Our results suggest that the electrophysiological effects of acute atrial volume loading rely on atrial stretch rather than increased atrial pressure alone. ANP release is similarly dependent on atrial stretch rather than atrial pressure and the pericardium attenuates the release of ANP with acute increases in atrial pressure(19). Experiments using ultrasonic crystals have shown that the pericardium alters the atrial pressure-diameter relationship by providing pericardial restraint(9, 10, 16, 19).

Tyberg recently reviewed the role of the pericardium in cardiac pathophysiology and the need to consider the transmural pressure gradient to understand stretch-related mechanical and electrical phenomena in the heart.(21) While patients without an intact pericardium have satisfactory cardiac function, the intact pericardium is a major determinant of ventricular

filling. Our data further support his proposition that, by providing constraint against abrupt changes in volume, the pericardium may also protect against stretch related electrical phenomena. These findings are particularly interesting in light of the current interest in passive ventricular restraint devices(12, 13, 17).In addition to the anticipated benefits on mechanical functioning and remodelling, these may also limit the adverse electrical responses associated with elevated intracardiac pressures that would predispose to arrhythmias. Another mechanical intervention, intra-aortic balloon counterpulsation, was effective in controlling refractory ventricular tachycardia (8).

Limitations

As we did not measure atrial dimensions directly, we cannot comment on the precise effect of the pericardium on atrial pressure-volume relationship in this model. Without these measurements, it is possible that the atria could have dilated within the confines of the pericardium, although it was clear that the pericardium prevented the gross dilatation seen in the control experiments.

We recognise that there are problems extrapolating the results of this study to the clinical setting. There are inherent differences in the electrophysiology of the rabbit and humans. The electrical effects of chronic atrial stretch underlying atrial fibrillation and the impact of pericardial constraint in humans are likely to involve more complex mechanisms than those evident in this model.

Conclusion

Our results suggest that the electrophysiological effects of acute atrial volume loading rely on atrial dilatation rather than increased pressure alone and raise the possibility that limiting the dilatation might reduce these arrhythmogenic electrophysiological changes.

Grants

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Figure Legends

Figure 1 Atrial Refractory Period (ms) measured with a single extra stimulus as a function of atrial pressure recorded with no pericardium (Controls), with intact pericardium (Pericardium on) and then in the same hearts following removal of the pericardium (Pericardium off). Increasing atrial pressure had no significant effect on ARP when the pericardium was intact but the drop in ARP seen in controls with increasing pressure was restored when the pericardium was removed (* $p < .05$).

Figure 2a Atrial fibrillation inducibility (% of burst pacing stimuli resulting in AF > 2 seconds) as a function of atrial pressure. The Inducibility of atrial fibrillation with increasing pressures was significantly lower when the pericardium was intact (* $p < .05$)

Figure 2b Duration of atrial fibrillation induced as a function of atrial pressure. The progressive increase in AF duration with increasing pressure in control experiments is not seen until the pericardium is removed (* $p < .05$)

Figure 1

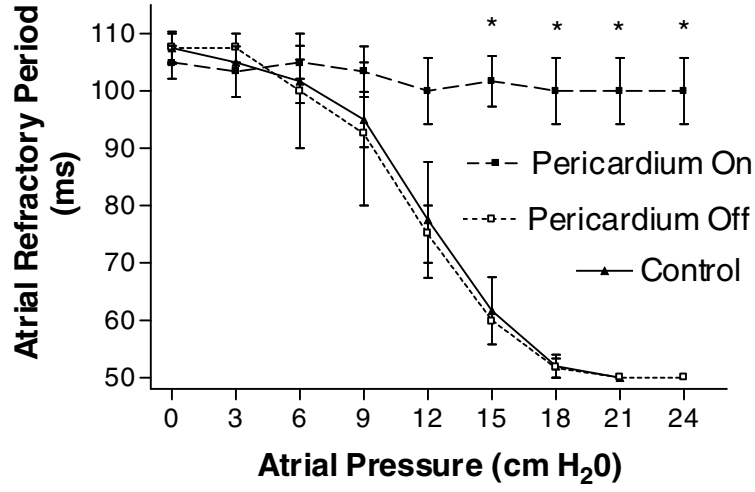


Figure 2

Figure 2a

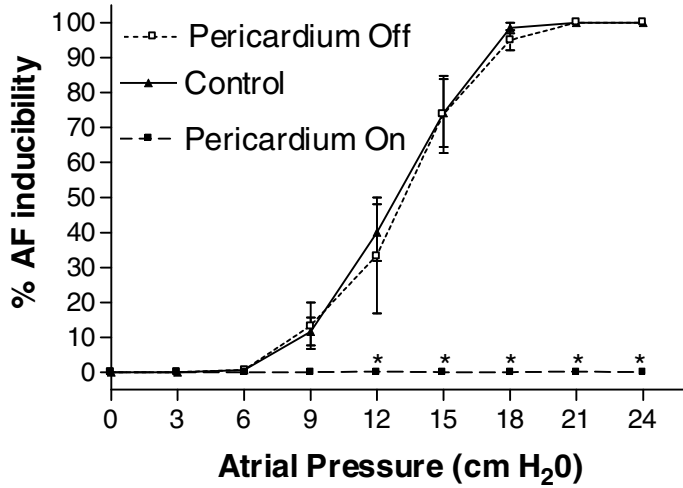


Figure 2b

