Passive pericardial constraint protects against stretch-induced vulnerability to atrial fibrillation in rabbits

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Ninio, Daniel M., and David A. Saint. Passive pericardial constraint protects against stretch-induced vulnerability to atrial fibrillation in rabbits. Am J Physiol Heart Circ Physiol 291: H2547–H2549, 2006. First published June 30, 2006; doi:10.1152/ajpheart.01248.2005—Atrial fibrillation is more common in conditions with elevated atrial pressure and atrial stretch. In Langendorff-perfused rabbit hearts with intact 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 24 cmH2O. 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 20 cmH2O. In contrast, when the pericardium was removed, atrial fibrillation could be reliably induced when atrial pressure exceeded 15 cmH2O. This suggests that the electrophysiological effects of acute atrial volume loading rely on atrial stretch rather than increased atrial pressure alone.

atrial refractory period; mechanoelectric feedback; Langendorff

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 AF (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 by 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 >3 kg, were used for this study. Rabbits were anesthetized with intravenous pentobarbital sodium 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 60 mmHg at 37°C. The perfusion fluid contained (in mmol) 130 NaCl, 4.0 KCl, 24.2 NaHCO3, 1.2 NaPO4, 0.6 MgCl, 2.2 CaCl, and 12 glucose and was bubbled with carbogen to maintain a pH between 7.35 and 7.4.

The atrioventricular node was ablated using direct 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 3-cmH2O steps to a maximum of 24 cmH2O, and burst pacing was applied at each step to induce AF. The protocol was repeated after the pericardium was removed.

If the pericardium was damaged before 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 six 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 Powerlab (AD Instruments) and recorded and analyzed by using Chart 4 software (AD). Atrial refractory periods (ARPs) were determined by using single extra stimuli to the right atrium at a basic cycle length of 250 ms at 3 times the pacing threshold. AF was induced 5 times at each pressure with burst pacing at 50 Hz for 1 s at 3 times the pacing threshold. AF was defined as "inducible" when a fast irregular rhythm longer than 2 s followed burst pacing, and the term "sustained AF" was applied to episodes that lasted longer than 1 min.

Statistics. Data are presented as means ± SE, unless indicated otherwise. A two-way ANOVA 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 unequal 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 three 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 before data collection, and these three hearts were used as controls.

In the nine control experiments, increasing atrial pressure produced a significant, reproducible reduction in ARP (P < 0.05; Fig. 1), and this corresponded with an increased vulnerability to AF. AF was induced with a single extra stimulus when the ARP reached 50 ms (the shortest coupling interval tested). Inducibility and duration of AF increased progressively with increasing pressure until AF was sustained with atrial pressures over 15 cmH2O (Fig. 2).
In the remaining six 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 (Fig. 1). Despite marked increases in atrial pressure (over 20 cmH2O), we were unable to induce sustained AF (Fig. 2).

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

DISCUSSION

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

Our results suggest that the electrophysiological effects of acute atrial volume loading rely on atrial stretch rather than increased atrial pressure alone. Atrial natriuretic peptide (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 (21) 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. Although 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 remodeling, 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. Because 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 recognize 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 AF and the impact of pericardial constraint in humans are likely to involve more complex mechanisms than those evident in this model.

In 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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REFERENCES