Effects of contraction-excitation feedback on electrophysiology and arrhythmogenesis in rabbits with experimental left ventricular hypertrophy

W Jauch, M N Hicks, and S M Cobbe

Objective: The aim was to investigate the influence of contraction-excitation feedback on myocardial electrophysiology and arrhythmia susceptibility in the setting of experimental left ventricular hypertrophy. Methods: New Zealand White rabbits with perinephritis hypertension were used. With the hearts perfused in vitro, left ventricular monophasic action potential duration and local effective refractory periods were determined at three sites, namely the anterior, apical, and posterior wall, together with ventricular tachycardia inducibility and ventricular fibrillation threshold under different loading conditions. Results: The left ventricular dry weight to body weight ratio was increased by 31% in the hypertrophied group (3.863 × 10⁻⁴, v 2.955 × 10⁻⁴ in the controls). Left ventricular hypertrophy was associated with prolongation of action potential duration when the left ventricle was not loaded and under normal loading conditions. Changing from unloaded Langendorff to baseline working heart perfusion resulted in a consistent decrease in action potential duration and effective refractory period at all left ventricular sites in both hypertrophied and control hearts. Subsequent manipulations of myocardial loading resulted in decreases in action potential duration and effective refractory period in both groups of hearts. Ventricular tachycardia could not be induced in any heart in Langendorff mode. Under different increased loading conditions, a total of four hypertrophied hearts (44%) became inducible, while control hearts remained non-inducible. The ventricular fibrillation threshold under conditions of increased load tended to be lower in the hypertrophied hearts than the control hearts; in the setting of increased preload the hypertrophied group showed significantly increased vulnerability to ventricular fibrillation (median threshold currents 35 mA v > 100 mA, p < 0.05). Conclusions: Left ventricular hypertrophy is associated with a prolongation of action potential duration and effective refractory period and an increased arrhythmia susceptibility in the setting of increased myocardial loading. There were no marked differences between the groups in the magnitude of the changes in action potential duration, effective refractory period, or dispersion of repolarisation and refractoriness resulting from manipulations of myocardial loading that could have been implicated in the increased arrhythmia susceptibility of the hypertrophied hearts during changes in load.

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Hypertrophy of the left ventricle is known to carry a poor prognosis, with a fivefold increase in cardiac mortality. Most of these deaths occur suddenly and are likely to be attributable to lethal arrhythmias. Subjects with left ventricular hypertrophy have been shown to have an increased frequency and complexity of spontaneous ventricular arrhythmias and an increased susceptibility to arrhythmias induced by programmed stimulation in some, but not all studies. Furthermore those subjects with ventricular arrhythmias have an increased mortality.

The major aetiological factor for left ventricular hypertrophy is hypertension, which imposes chronically increased loading conditions on the myocardium. These loading conditions may be further influenced by the acute reduction in blood pressure resulting from antihypertensive therapy. The change in loading conditions in this setting could alter myocardial electrophysiology by the process of contraction-excitation feedback, which is inferred when changes in mechanical stress or strain cause or precede cardiac electrophysiological changes. Contraction-excitation feedback has been demonstrated both in the human setting and in experimental animals. An influence of contraction-excitation feedback has also been shown experimentally in abnormal hearts with previous myocardial infarction. Experimental heart failure, produced by a combination of pulmonary artery banding and tricuspid regurgitation, resulted in increased ventricular excitability thresholds.

The aim of this study was to investigate whether alterations in contraction-excitation feedback, resulting in consequent alterations in myocardial electrophysiology and susceptibility to arrhythmias, occur in the setting of experimental left ventricular hypertrophy.

Methods

Animal model
Male New Zealand White rabbits, weight 2.5-3.2 kg, were pre-medicated with fentanyl citrate 0.095 mg kg⁻¹ and flunisolide 3 mg kg⁻¹ (Hynnorm, Janssen) and anaesthetised with a mixture of halothane, nitrous oxide, and oxygen. The left kidney was exposed via a flank incision and wrapped in cellophane. The right kidney was exposed via a separate right flank incision and excised. In sham operated animals the left kidney was manipulated but not wrapped and the right kidney was excised. Postoperatively 20 ml 0.9% NaCl was given intravenously, 50 mg ampicillin was given intramuscularly, and analgesia was provided by 150 mg buprenorphine intramuscularly over two days. Care of the animals was in accordance with United Kingdom Home Office guidelines.

Blood pressure was measured prior to surgery and at four-weekly intervals after surgery. During measurements the rabbits were rested in a quiet room in a custom made wooden box. The base of the ear was infiltrated with 2% lignocaine, the central ear artery was cannulated, and mean arterial pressure was measured with a transducer and recorded after obtaining steady state conditions.

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Whole heart preparation

The whole heart was perfused using apparatus permitting retrograde perfusion by the Langendorff method, and perfusion in working mode with the heart pumping and performing external work. The rabbits were heparinised (2000 IU intravenously) and killed by an overdose of sodium pentobarbitone (100 mg/kg). The heart was excised and immersed in ice cold Tyrode solution. The aorta was cannulated rapidly and the heart was perfused retrogradely with modified Tyrode solution (composition in mmol-litre\(^{-1}\): Na\(^+\) 142.0, K\(^+\) 5.4, Ca\(^{2+}\) 1.0, Cl\(^{-}\) 121.4, HCO\(_3\)\(^{-}\) 28, HPO\(_4\)\(^{2-}\) 1.4, Mg\(^{2+}\) 1.0, glucose 11.0), equilibrated with 95%\(\text{O}_2/5\%\text{CO}_2\) to provide a pH of 7.4. The left atrium was cannulated to permit filling of the left side of the heart for the performance of external work. The right atrium was paced using a square wave electrical stimulus of constant duration at a cycle length of 300 ms and a pulse width of 2 ms using an isolated stimulator. The preparation was perfused retrogradely for a 15 min period before starting recordings. The epicardial surface temperature of the preparation was monitored throughout the experimental protocol and maintained at 35°C. Water jacketed glassware for the apparatus comprising the Langendorff and working heart circuits was heated and thermostatically controlled independently, and adjusted to ensure that temperature variations did not occur when changing from Langendorff to working heart mode. Regional variations in epicardial temperature were minimised by enclosing the heart in a temperature controlled chamber.

Electrophysiological measurements

Monophasic action potentials and local effective refractory periods were recorded. Monophasic action potentials were recorded from three left ventricular sites, anterior, apical, and posterior wall, using custom made suction electrodes. The signals obtained were amplified by a high input impedance amplifier, filtered at 100 Hz to 3 kHz, and sampled every 91 μs. Monophasic action potentials were recorded from three left ventricular sites with a cycle length of 300 ms, an extrastimulus (S\(_1\)) was introduced decrementally, followed by the introduction of a third extrastimulus (S\(_3\)) if prior stimulation did not result in a ventricular arrhythmia or which degenerated into ventricular fibrillation.

If a sustained ventricular tachycardia was not provoked, a second extrastimulus (S\(_2\)) was introduced late in diastole and the conduction delay was incremented at a constant cycle length of 300 ms and a pulse width of 2 ms using an isolated stimulator. The preparation was perfused retrogradely for a 15 min period before starting recordings. The epicardial surface temperature of the preparation was monitored throughout the experimental protocol and maintained at 35°C. Water jacketed glassware for the apparatus comprising the Langendorff and working heart circuits was heated and thermostatically controlled independently, and adjusted to ensure that temperature variations did not occur when changing from Langendorff to working heart mode. Regional variations in epicardial temperature were minimised by enclosing the heart in a temperature controlled chamber.

In vitro protocol

In order for a preparation to be used for the study, a minimum baseline atrioventricular conduction delay of 80 cm/min, measured using an inline flow meter, was required when the heart was pumping with the preload set at 10 cm H\(_2\)O and the afterload set at 75 cm H\(_2\)O (baseline working heart mode). The preload and afterload could be independently adjusted by altering respectively the height of the atrial reservoir and the aortic return reservoir above the level of the aortic cannula. Initial recordings were performed under unloaded Langendorff perfusion. The heart was then switched to baseline working heart mode, and the recordings repeated. Subsequent manipulation of loading conditions consisted of an increase in the afterload to 115 cm H\(_2\)O, an increase of the preload to 25 cm H\(_2\)O, and a simultaneous increase in both the preload and the afterload. Following each manipulation the heart was returned to the baseline working heart condition, thereby permitting the recordings obtained during the intervention to be compared with the recordings obtained from the baseline working heart mode sandwiching the intervention. At least 2 min were allowed to elapse after any change in the loading condition before recordings were taken to ensure that steady state had and had been achieved. Ventricular monophasic action potentials were recorded and effective refractory periods were determined after each change in load. The inducibility of ventricular tachycardia was then determined under the Langendorff condition followed by baseline working heart mode, increased preload, and finally the combination of increased afterload and preload. This sequence was repeated for the determination of ventricular fibrillation thresholds. Following the induction of any sustained arrhythmia requiring direct current cardioversion, a 5 min period for recovery was allowed before the protocol was continued.

Statistical methods

Data are expressed as mean(SEM). Electrophysiological data from hypertrophied and control hearts were compared using unpaired \(t\) tests. The response to altering loading conditions was analysed using paired \(t\) tests. Comparison of ventricular fibrillation data was performed using the non-parametric Kruskal-Wallis test. A p value of less than 0.05 was taken as significant.

Results

Experimental animals

The two groups of animals did not differ with respect to baseline mean arterial blood pressure prior to surgery: 71.0(SEM 2.3) mm Hg in the controls (n = 7) and 77.9(2.5) mm Hg in the animals undergoing renal wrapping (n = 9). During the postoperative period the highest mean arterial pressure developed in the wrapped group [119(1.3)] was significantly higher than that of the controls [88(3.2), \(p < 0.001\)]. The left ventricular dry weight to body weight ratio at 3.863 \(\times 10^3\) increased by 31% in the wrapped group compared to 2.955 \(\times 10^3\) in the controls, reflecting left ventricular hypertrophy in the wrapped animals, which will henceforth be described as the hypertrophied group.

Electrophysiological results

The action potential durations to 90% repolarisation and effective refractory periods under the unloaded Langendorff condition and in the baseline loaded condition in both groups are given in table I. The APD\(_{90}\) measured from the anterior left ventricular site was longer in the hypertrophied hearts than in the controls, at 158.9(2.4) \(\mu\)s compared to 147.6(3.0) ms, \(p < 0.05\). Under baseline working heart loading conditions, the action potential duration shortened significantly in both groups, remaining longer in the hypertrophied hearts than in the controls [147.0(1.9) \(\mu\)s compared to 138.0(3.1) ms, \(p < 0.05\)]. A similar trend was also seen at the apical and posterior sites.

There was always a significant shortening in action potential duration on changing from unloaded Langendorff condition to the baseline loaded working heart mode in both the...
control and left ventricular hypertrophy groups with a trend for longer action potential durations in the hypertrophied hearts under both conditions. There was a tendency for the effective refractory period to be longer in the hypertrophied hearts under both conditions. There was a tendency for the fAPD to be shorter in the hypertrophied groups at all sites and, as for APDoo, the values tended to be longer in the hypertrophied than in the control hearts.

The changes in APDoo and effective refractory period resulting from increases in loading are listed in Table I. Increasing the afterload resulted in no significant change in APDoo in either group of hearts. The effective refractory period in the setting of an increase in afterload shortened significantly by 4.4(1.7) ms at the anterior left ventricular site in hypertrophied hearts and by 9.6(3.2) ms at the posterior left ventricular site of control hearts. The effective refractory period was prolonged in the hypertrophied as against the control hearts in the setting of an increase in loading are listed in table I and illustrated in fig 1. Increasing the afterload resulted in no significant change in APDoo in either group of hearts. The effective refractory period in the setting of an increase in afterload shortened significantly by 4.4(1.7) ms at the anterior left ventricular site in hypertrophied hearts and by 9.6(3.2) ms at the posterior left ventricular site of control hearts. The effective refractory period was prolonged in the hypertrophied as against the control hearts in the setting of an increase in loading are listed in table I and illustrated in fig 1. Increasing the afterload resulted in no significant change in APDoo in either group of hearts. The effective refractory period in the setting of an increase in afterload shortened significantly by 4.4(1.7) ms at the anterior left ventricular site in hypertrophied hearts and by 9.6(3.2) ms at the posterior left ventricular site of control hearts. The effective refractory period was prolonged in the hypertrophied as against the control hearts in the setting of an increase in loading.

### Table I: Action potential duration to 90% repolarisation (APD90) and effective refractory period (ERP) in Langendorff and baseline working heart perfusion. Values are mean(SEM).

<table>
<thead>
<tr>
<th>Hypertrophy</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langendorff</td>
<td>BLWH</td>
</tr>
<tr>
<td>APD90 anterior LV</td>
<td>159.3±2.4</td>
</tr>
<tr>
<td>APD90 apex LV</td>
<td>152.4±2.3</td>
</tr>
<tr>
<td>APD90 posterior LV</td>
<td>151.4±1.8</td>
</tr>
<tr>
<td>ERP anterior LV</td>
<td>150.5±1.6</td>
</tr>
<tr>
<td>ERP apex LV</td>
<td>150.3±1.6</td>
</tr>
<tr>
<td>ERP posterior LV</td>
<td>[66.5±1.4]</td>
</tr>
</tbody>
</table>

BLWH = baseline working heart; LV = left ventricle. *p < 0.05 vs control hearts; †p < 0.05 vs Langendorff; ‡p < 0.005 vs Langendorff.

### Table II: Changes in action potential duration and effective refractory period under increased myocardial loading. Values are mean(SEM) plus [range].

<table>
<thead>
<tr>
<th>Controls</th>
<th>Increased preload</th>
<th>Increased afterload</th>
<th>Increased preload and preload</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔAPD (ms)</td>
<td>ΔERP (ms)</td>
<td>ΔAPD (ms)</td>
</tr>
<tr>
<td>Ant. LV</td>
<td>-0.1(2.5)</td>
<td>-0.7(3.3)</td>
<td>-7.8(2.1)*</td>
</tr>
<tr>
<td></td>
<td>[-9 to +9]</td>
<td>[-13 to +15]</td>
<td>[-17 to -11]</td>
</tr>
<tr>
<td>Apical LV</td>
<td>2.6(2.3)</td>
<td>-5.0(2.2)</td>
<td>-7.1(2.5)*</td>
</tr>
<tr>
<td></td>
<td>[-8 to +10]</td>
<td>[-15 to +3]</td>
<td>[-15 to +2]</td>
</tr>
<tr>
<td>Posterior LV</td>
<td>1.2(2.2)</td>
<td>-9.6(3.2)*</td>
<td>-5.4(1.7)*</td>
</tr>
<tr>
<td></td>
<td>[-8 to +9]</td>
<td>[-15 to -3]</td>
<td>[-14 to -1]</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ant. LV</td>
<td>-0.9(2.3)</td>
<td>-4.4(1.7)*</td>
<td>-6.4(2.8)*</td>
</tr>
<tr>
<td></td>
<td>[-13 to +9]</td>
<td>[-15 to +3]</td>
<td>[-12 to -1]</td>
</tr>
<tr>
<td>Apical LV</td>
<td>2.8(2.5)</td>
<td>-2.8(1.6)</td>
<td>-11.0(2.2)*</td>
</tr>
<tr>
<td></td>
<td>[-1.5 to +17]</td>
<td>[-10 to +5]</td>
<td>[-23 to -2]</td>
</tr>
<tr>
<td>Posterior LV</td>
<td>1.9(2.3)</td>
<td>-2.5(1.4)</td>
<td>-6.3(1.4)*</td>
</tr>
<tr>
<td></td>
<td>[-5 to +17]</td>
<td>[-13 to -3]</td>
<td>[-15 to -1]</td>
</tr>
</tbody>
</table>

ΔAPD = change in action potential duration from baseline working heart; ΔERP = change in effective refractory period from baseline working heart.

* p < 0.05, †p < 0.01, ‡p < 0.005, §p < 0.001 vs baseline working heart mode. None of the comparisons between control and hypertrophy groups at any site was significant.
Contraction-excitation feedback in left ventricular hypertrophy

Figure 2: Histograms illustrating dispersion of repolarisation (A) and refractoriness (B). In each case the white bars correspond to the values for the control group and the hatched bars to the hypertrophy group. The loading conditions are given as Langendorff (Lang), baseline working heart (BLWH), increased afterload (+A), increased preload (+P), and increased afterload and preload (+A and +P). Error bars = SEM.

A combined increase of both the preload and the afterload resulted in no significant change in action potential duration. The effect of increasing both the preload and the afterload together on the effective refractory period was to result in significant shortening at both the anterior and the apical left ventricular sites in the hypertrophied hearts, with significant shortening also occurring at the anterior and posterior left ventricular sites in the control hearts. All these changes resulting from alterations in myocardial loading were reversible.

Dispersion of repolarisation did not differ between the two groups under any of the loading conditions (fig 2). The values for hypertrophied and control hearts in Langendorff perfusion were 11.8(1.8) and 10.3(2.4) ms respectively. The corresponding values under baseline working heart conditions were 12.7(1.4) and 10.6(2.9) ms, for increased afterload 15.1(2.5) and 13.0(2.8) ms, for increased preload 17.4(2.5) and 11.3(3.0) ms, and for both increased afterload and preload 15.9(1.2) and 14.8(2.6) ms. Similarly, dispersion of refractoriness did not differ between the two groups under any of the loading conditions (fig 2). The values for hypertrophied and control hearts in Langendorff perfusion were 20.4(2.3) and 17.6(2.5) ms respectively, the corresponding values under baseline working heart conditions being 16.8(2.8) and 17.1(3.6) ms, for increased afterload 23.2(3.3) and 15.1(2.8) ms, for increased preload 20.7(2.1) and 19.2(5.0) ms, and for both increased afterload and preload 22.1(3.1) and 18.0(3.4) ms.

Arrhythmia induction

In the unloaded Langendorff setting ventricular tachycardia could not be induced in any heart. In baseline working heart mode one of the hypertrophied hearts became inducible, whereas all the control hearts remained non-inducible. In each of the settings of increased afterload, increased preload, and increase of both afterload and preload, ventricular tachycardia could be induced in two of the hypertrophied hearts while all the control hearts remained non-inducible. Different hypertrophied hearts became inducible under different loading conditions, with a total of four hypertrophied hearts (44%) showing ventricular tachycardia inducibility overall. The ventricular fibrillation threshold currents under the different loading conditions are displayed in fig 3. A tendency is apparent for lower current requirements to induce ventricular fibrillation in the hypertrophied than in control hearts under the different loading conditions, thereby suggesting an increased susceptibility to ventricular fibrillation. This difference attains statistical significance in the setting of increased preload where the hypertrophied group shows increased vulnerability to ventricular fibrillation (p < 0.05).

Discussion

This study was designed to investigate the possible role of contraction-excitation feedback in arrhythmogenesis in hearts with left ventricular hypertrophy. We have shown that hypertrophied hearts tend to show a prolongation in action potential duration and effective refractory period when the myocardium is either loaded or unloaded and that these hearts show a greater susceptibility to arrhythmias as loading is increased when compared to normal hearts. It has also been shown that both normal and hypertrophied hearts show contraction-excitation feedback, as manifest as a decrease in action potential duration and effective refractory period under various loading conditions. However, it was not possible to demonstrate any differential responses between the two groups that could be considered as at least one potential mechanism for the increased susceptibility to arrhythmias that was observed.

The most dramatic loading change, switching from the unloaded Langendorff to the loaded baseline working heart mode, produced the most marked electrophysiological changes, namely a parallel shortening in both action potential duration and effective refractory period at all three left ventricular sites. A further increase of left ventricular loading in the form of an increased preload resulted in consistent shortening of action potential duration. The response of effective refractory period to increased preload was a shortening at the apical and posterior sites in the hypertrophied hearts but in the controls only the apical sites showed this significant shortening. The responses of action potential duration and effective refractory period to increased afterload were variable and not significant with the exception of a minor shortening of effective refractory period in the anterior left ventricle of hypertrophied hearts. The response to a combined increase in afterload and preload were intermediate between the effects of isolated increases in preload and afterload. Hypertrophied hearts responded by shortening effective refractory period at the anterior and apical sites, while in the controls effective refractory period shortened at the anterior and posterior sites. No significant changes in action potential duration were noted. The apparent differential effects of changing preload and afterload on action potential duration and effective refractory period is not unexpected and has been shown previously in isolated guinea pig hearts. Alterations in preload and afterload would be expected to exert different effects on end diastolic pressure and thus initial myocardial fibre length.
prior to the contraction. Our data are consistent with end diastolic wall stress being the best correlate of refractoriness in isolated ejecting rabbit hearts.\(^3\) There is marked variability in the responses to changes in the loading conditions at the different recording sites. This could be the result of a combination of the complex geometry and fibre orientation of the heart and the limited number of recording sites used in this study, superimposed on biological variability.

This study showed that there was an increased susceptibility of hypertrophied hearts to arrhythmias under conditions of increased loading, that is, a mechanically induced increase in susceptibility to arrhythmias, which was more pronounced in the hypertrophied hearts. We could not find any convincing evidence of a differential sensitivity in contraction excitation feedback as expressed by changes in action potential duration and effective refractory period under any of the loading conditions examined which could contribute to the greater susceptibility to arrhythmias in the hypertrophied hearts. One possible explanation for this unexpected negative result could be that there were smaller changes in wall stress in the hypertrophied group. According to Laplace's law, a greater wall thickness in the hypertrophied group would reduce the relative stress imposed by the same changes in pressure and therefore could mask differences that could be present if the changes in wall stress were comparable.

We also failed to show any statistical differences in dispersion of either repolarisation or refractoriness, which are thought to be an important determinants of vulnerability to arrhythmias.\(^3\)\(^4\) Dispersion of repolarisation and refractoriness was only assessed from three left ventricular sites and perhaps a difference would have been detected if sampling from a much larger number of left ventricular sites had been possible. Alternatively, a similar argument to that given to explain the lack of differential effects of action potential duration and effective refractory period could equally apply to the absence of differences in the dispersion of repolarisation and refractoriness. Although dispersion of repolarisation is a function of both conduction time and action potential duration using our definition, the maximum variation in action potential duration between the groups under the different loading conditions was also compared and failed to uncover any significant differences (data not shown).

The presence of differences in one manifestation of contraction-excitation feedback, namely the susceptibility to arrhythmias, without expression of differences in action potential duration, effective refractory period, and dispersion, may also reflect the choice of loading conditions studied. In vivo the hypertrophied hearts would have been subjected to increased preload and afterload. It is possible that an alternative comparison between effects of increasing loads from baseline levels which mimic those seen in vivo may have uncovered differences which were masked by unloading the hypertrophied hearts.

There are alternative explanations for the increased susceptibility to arrhythmia formation in the presence of increased preload in the hypertrophied heart. We and previous investigators\(^6\)\(^-\)\(^8\) have shown an increase in action potential duration in hypertrophied hearts. In the spontaneously hypertensive rat heart, this is associated with an increase in the amplitude of the intracellular calcium transient which was shown to be due to enhanced calcium loading of the sarcoplasmic reticulum.\(^9\) It has also been shown that changes in the length of isolated multicellular preparations and single cells affect intracellular calcium transients during contraction\(^10\)\(^-\)\(^12\) and it is therefore possible that increases in preload may enhance a tendency to calcium

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**Figure 3** Ventricular fibrillation threshold currents for the two groups of hearts under the different loading conditions. Those on the left refer to the control hearts and those on the right to the hypertrophied hearts. NI = non-inducible; VFT = ventricular fibrillation threshold. From top downwards, each pair refers to the thresholds under Langendorff, baseline working heart, increased afterload, increased preload, and increased afterload and preload.
overload, which may provoke arrhythmogenic inward currents and delayed afterdepolarisations.

Myocardial ischaemia is a powerful factor in arrhythmogenesis; accordingly absence of myocardial ischaemia is important in a study such as this. There has previously been some concern regarding the adequacy of oxygen delivery to hearts perfused by crystalloid perfusate in vitro. However Coulshed and Cowan have shown that there is no ischaemia in a crystalloid perfused small animal heart preparation. The hearts in this study maintained their cardiac output and electrophysiology for the duration of the protocol, changes in cardiac output and in electrophysiological indices consequent on alterations in loading were reversible throughout, and we have no evidence of ischaemia under the different loading conditions which could have affected the results.

In hypertension, particularly with the effect of antihypertensive medication or possible decompensation into left ventricular failure, neurohumoral factors and heart rate may well be altered. Our study excludes any possible influence of neurohumoral factors on susceptibility to arrhythmias which could further complicate studies carried out in vivo. In addition, by controlling heart rate by right atrial pacing we abolished any potential influence of heart rate variation in our study.

In the setting of increased loading, hypertrophied hearts showed an increase in arrhythmias which is consistent with the observed increase in arrhythmias and sudden death in patients with left ventricular hypertrophy. Rather than attempting to reduce mortality with pharmacological antiarrhythmic therapy, which has proved disappointing in the past, a different therapeutic possibility would be to manipulate the loading conditions of the heart, which could provide a mechanism for reducing arrhythmias and perhaps mortality. Increased myocardial loading has been shown to increase the frequency of ventricular arrhythmias, while a reduction in myocardial loading has the opposite effect. The use of angiotensin converting enzyme inhibitors, which are thought not to possess an intrinsic antiarrhythmic effect, has been shown to reduce ventricular arrhythmias and mortality in patients with heart failure. Perhaps a potential exists for reducing arrhythmias and sudden death in subjects with left ventricular hypertrophy by selective reduction of ventricular preload.

Key terms: hypertrophy; arrhythmias; electrophysiology; contraction-excitation feedback.

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