Electrophysiological effects accompanying regression of left ventricular hypertrophy

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Abstract

Objective: The aim of this study was to investigate changes following regression of left ventricular hypertrophy (LVH). Methods: Electrophysiological changes were recorded in isolated guinea-pig myocardial preparations. LVH was induced by constriction of the thoracic aorta and regression was followed after removal of the constriction. Sham-operated animals served as controls. Results: During 42 days constriction, heart/body weight ratio increased (3.19 ± 0.49 vs. 3.85 ± 0.83 g kg⁻¹) and was accompanied by an increase of cell size. Forty-two days after clip removal, values had returned to control values. LVH increased action potential (AP) duration (mean 112% of control) and decreased conduction velocity (60.4 ± 3.3 vs. 45.9 ± 4.6 cm⁻¹). These changes did not return to control after regression of LVH. The changes to condition velocity were attributed solely to increases of intracellular resistivity. The positive staircase response also decreased with LVH, but did recover upon regression. In isolated whole hearts, no changes to subepicardial action potential duration, QRS complex duration or AP refractory period were observed in LVH or its regression. During low-flow ischaemia AP duration shortened reversibly, the rate of shortening was more rapid in hypertrophied hearts but similar to control in regressed hearts. The incidence of ventricular tachyarrhythmias of fibrillation during low-flow ischaemia was similar in control, hypertrophied and regressed hearts. Conclusion: Morphological regression of LVH is not accompanied by reversal of electrophysiological changes measured in isolated preparations, whereas some aspects of contractile function to recover.

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Keywords: Regression; Hypertrophy; Repolarisation; Arrhythmia; Guinea-pig

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1. Introduction

Left ventricular hypertrophy (LVH) is a morphological adaptive increase in left ventricular mass in response to a chronic work overload. LVH remains a significant predictor for cardiovascular mortality and morbidity despite pharma-
and diuretics [12,13]. Despite the fact that most antihypertensive agents regress LVH, there is little evidence that this is accompanied by normalisation of the associated pathophysiology [14]. It has been suggested that vulnerability to ventricular arrhythmias and electrophysiological changes produced by LVH is reversible [15]; nevertheless, the prognosis associated with previous LVH remains poor [16]. Furthermore, it is difficult to separate the effect of drug-induced regression of LVH on the action of the agents themselves or the reversal of the hypertension. Variable normalisation of pathophysiological changes associated with surgical regression of LVH in patients with aortic valve stenosis has been recorded [17]. The aim of this study was to determine whether regression of LVH in a well-validated animal model, induced initially by banding the ascending thoracic aorta, was accompanied by recovery of changes to electrophysiological properties.

2. Methods

2.1. Induction of LVH and regression from LVH

Male Dunkin–Hartley guinea-pigs (600–800 g) were anaesthetised with methohexitone Na (i.p., 30 mg kg$^{-1}$, Brietal, Eli Lilly, Basingstoke, UK); subcutaneous 0.5 mg kg$^{-1}$ sulphadoxine, trimethoprim and lidocaine HCl 7.5% (Borgal, Hoechst, Milton Keynes, UK) was given as an antibiotic. Animals were ventilated with O$_2$ at 100 breaths min$^{-1}$ (Borgal, Hoechst, Milton Keynes, UK) was given as an antibiotic. Animals were ventilated with O$_2$ at 100 breaths min$^{-1}$ (0.4 l min$^{-1}$) with a Harvard ventilator (Edenbridge, Kent, UK). A left-sided thoracotomy at the second intercostal space gave access to the aortic arch. The ascending thoracic aorta was constricted with a high-density plastic clip (int. diam.: 2.0 mm, 1.5 mm thick) to induce LVH. After the procedure, animals were given an analgesic, buprenorphine 0.05 mg kg$^{-1}$ (Temgesic, Reckitt and Coleman, Hull, UK) and allowed to recover. All procedures conformed to The Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised 1996) and UK Guidelines in The Operation of Animals (Scientific Procedures) Act, 1986.

Animals underwent one of two procedures: the first was a single operation to place a clip around the thoracic aorta for 42 ± 3 days, or a sham operation to expose the aorta but not insert a clip (sham-operated controls). The second was a double operation 42 ± 3 days by a right-sided thoracotomy after the original procedure. This produced three further groups: (i) the clip was removed (regressed group), (ii) the clip left in place (an age-matched LVH group) and (iii) a second sham-operation (an age-matched group to the LVH animals). Animals were studied after a further 42 ± 3 days. Fig. 1 shows the time-lines for the five groups.

2.2. Isolated preparations

Animals were weighed, killed by cervical dislocation and the hearts rapidly removed. Left ventricular papillary muscles (≤ 1 mm diameter, 3–5 mm long) were isolated, secured at one end to a fixed hook in a horizontal bath and superfused at 4 ml min$^{-1}$ with Tyrode’s solution (mM): NaCl 118, KCl 4.0, NaHCO$_3$ 24, NaH$_2$PO$_4$ 0.4, MgCl$_2$ 1.0, CaCl$_2$ 1.8, glucose 6.1 and Na pyruvate 5.0, gassed at 37 °C with 95% O$_2$/5% CO$_2$. The other end was tied to an isometric tension transducer and electrically stimulated 1.5-times threshold with 0.2 μs pulses at 1 Hz by Ag–AgCl electrodes placed on one end of the preparation.

APs were recorded with 3 M KCl-filled microelectrodes at known distances (d) from the stimulating electrodes. Conduction latency (t, Fig. 2A) was recorded as the interval between the start of the stimulus artefact and the maximum AP upstroke velocity (dV/dt$^{max}$). Conduction velocity (θ) was calculated from the ratio of d to t for AP’s recorded at distances greater than 1 mm from the stimulating source. Intracellular resistivity ($R_i$) was calculated from Eq. (1): $a$ is cell radius and $C_m$ specific membrane capacitance (1.0 μF cm$^{-2}$ [18]).

$$R_i = \frac{a}{2\theta^2 C_m \tau_{ap}} \quad (1)$$

The time constant of the subthreshold region (foot) of the conducted action potential foot ($\tau_{ap}$, Fig. 2B) was calculated by Eq. (2): $A$, $B$, $t_0$ constants; V is the voltage at time t [19].

$$V = A + B \times \exp\left(\frac{t - t_0}{\tau_{ap}}\right) \quad (2)$$

The force-frequency relationship was recorded by measuring peak tension (normalised to muscle cross-section area) at 1.6 Hz stimulation frequency as a ratio of that at 0.8 Hz ($T_{1.6/0.8}$).

2.3. Whole heart experiments

Isolated hearts were mounted in a modified Langendorff system and perfused retrogradely with a solution (mM: NaCl 118, KCl 4.8, NaHCO$_3$ 25, Mg$_2$SO$_4$ 1.2, CaCl$_2$ 2.6, glucose 7.9, Na pyruvate 1.9) equilibrated with 95% O$_2$/5% CO$_2$, pH 7.4, 32 °C [20,21]. Hearts were paced (5 ms pulses, 3.3 Hz) at twice diastolic threshold. Perfusion pressure was monitored at the side-arm of the perfusion cannula. Electrocardiograms were recorded with three Ag electrodes fixed securely in the organ bath. APs were recorded from the subepicardium of the left ventricle apex with 3 M KCl-filled floating microelectrodes [20]. A fine stainless steel hook through the
apex of the heart, attached to a force transducer provided a diastolic resting tension of 19 mN. Refractory periods were determined by delivering extra pulses in the basic train after every eighth pulse at increasing intervals of 10 ms until an additional AP was elicited. APs and ECGs were captured via an A–D converter and analysed using the Po-Ne-Mah data acquisition system (Gould Instrument Systems; sampling rate 1 kHz). AP duration at 95% repolarisation (APD95), QRS duration, mean perfusion pressure and tension were monitored.

2.3.1. Ischaemic protocol
Hearts were initially perfused for 20 min at a constant flow rate to achieve a perfusion pressure of 50 mmHg [21]. They were then rendered ischaemic for 30 min by a 90% reduction of flow, and subsequently reperfused for 15 min at the control flow rate. Electrophysiological parameters were measured continuously throughout. The incidence and recovery of reperfusion-induced ventricular tachyarrhythmias (VT) and ventricular fibrillation (VF) were recorded as described by the Lambeth convention [22].

2.4. Cell size measurements
After electrophysiological studies with perfused hearts, representatives from each experimental group were perfusion-fixed with 10% formol saline, immersion fixed for 24 h, dehydrated, wax embedded and 5 μm sections cut and stained with haemotoxylin and eosin. Morphometric analysis of the sections was carried out using an image analysis system (Seescan Solitaire Plus, Cambridge, UK). The cross-sectional areas of myocytes with clear, distinct nuclei [23] from the left ventricular free wall were measured. The cell radius (a) was calculated from the mean cross sectional area for each group, assuming a circular cross-section profile.

2.5. Statistical analyses
Data values are mean ± S.D. Effects between groups used ANOVA followed by post-hoc Bonferroni multiple comparisons (Prism, Graphpad Software, v3.00, San Diego, USA). Fisher’s exact test compared the percentage incidence of arrhythmias between groups. A χ²-test was used to test for significance in the number of hearts demonstrating arrhythmias in different groups. The null hypothesis was rejected if p < 0.05.

3. Results
3.1. Development of cardiac hypertrophy and regression from hypertrophy
Table 1 shows that heart-to-body weight ratio (HBR) was raised after 42 and 84 days constriction, compared to age-matched controls. This growth was mirrored in cellular hypertrophy (cell cross-sectional area, CSA). Larger HBR values were matched by increases of heart weight, but there was also a small loss of body weight in the 42-day con-

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Table 1
Morphological changes associated with constriction of the thoracic aorta, and removal of the constriction after 42 days (de-constricted)

<table>
<thead>
<tr>
<th></th>
<th>42 days</th>
<th>84 days</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Constricted</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>1082 ± 59 (18)</td>
<td>1031 ± 67 (17)*</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>3.47 ± 0.57 (18)</td>
<td>3.96 ± 0.82 (17)*</td>
</tr>
<tr>
<td>HBR (g kg⁻¹)</td>
<td>3.19 ± 0.49 (18)</td>
<td>3.85 ± 0.83 (17)*</td>
</tr>
<tr>
<td>CSA (μm²)</td>
<td>316 ± 17 (5)</td>
<td>451 ± 31 (3)*</td>
</tr>
</tbody>
</table>

The numbers of animals are in parenthesis. The first row refers to the number of days when the heart was studied after the initial procedure.

* Indicates constriction vs. age-matched control.
‡ De-constriction vs. constriction, p < 0.05.
Table 2
Electromechanical properties of isolated preparations from guinea-pigs with sham-operations (controls), thoracic aortic constriction or deconstriction

<table>
<thead>
<tr>
<th></th>
<th>42 days</th>
<th></th>
<th>84 days</th>
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<th>42 days de-constricted</th>
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<tr>
<td></td>
<td>Control</td>
<td>Constricted</td>
<td>Control</td>
<td>Constricted</td>
<td>Control</td>
</tr>
<tr>
<td>APD&lt;sub&gt;95&lt;/sub&gt; (ms)</td>
<td>195 ± 7 (8)</td>
<td>219 ± 6 (8)*</td>
<td>176 ± 10 (8)</td>
<td>197 ± 16 (8)*</td>
<td>192 ± 9 (6)*</td>
</tr>
<tr>
<td>Conduction velocity, θ (cm s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>60.4 ± 3.3 (7)</td>
<td>45.9 ± 4.6 (9)*</td>
<td>56.1 ± 4.3 (8)</td>
<td>47.1 ± 4.9 (8)*</td>
<td>49.2 ± 6.1 (6)*</td>
</tr>
<tr>
<td>dV/dt&lt;sub&gt;max&lt;/sub&gt; (V s&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>160 ± 15 (8)</td>
<td>148 ± 20 (8)</td>
<td>135 ± 13 (8)</td>
<td>110 ± 22 (8)</td>
<td>114 ± 17 (6)</td>
</tr>
<tr>
<td>τ&lt;sub&gt;ap&lt;/sub&gt; (ms)</td>
<td>0.30 ± 0.03 (8)</td>
<td>0.39 ± 0.01 (5)*</td>
<td>0.30 ± 0.02 (7)</td>
<td>0.31 ± 0.04 (7)</td>
<td>0.34 ± 0.03 (5)</td>
</tr>
<tr>
<td>Intracellular resistivity, R&lt;sub&gt;i&lt;/sub&gt; (Ω cm)</td>
<td>259 ± 36 (7)</td>
<td>384 ± 71 (9)*</td>
<td>322 ± 69 (8)</td>
<td>585 ± 300 (8)*</td>
<td>412 ± 100 (6)*</td>
</tr>
<tr>
<td>T&lt;sub&gt;1.6/0.8&lt;/sub&gt;</td>
<td>1.23 ± 0.04 (7)</td>
<td>1.01 ± 0.10 (6)*</td>
<td>1.13 ± 0.03 (7)</td>
<td>1.03 ± 0.05 (7)*</td>
<td>1.12 ± 0.07 (5)</td>
</tr>
</tbody>
</table>

Intracellular resistivity, R<sub>i</sub>, was calculated from Eq. (2) (Section 2). The first row refers to the number of days after the initial procedure when the heart was studied.

*Indicates p<0.05 vs. age-matched control.

3.2. Isolated preparations—electromechanical changes during hypertrophy and regression

Action potentials were recorded during continuous 1 Hz stimulation. Action potential duration (APD<sub>95</sub>) was increased significantly in hearts hypertrophied after 42 and 84 days constriction, and by a similar proportion at both times (Table 2). Moreover, prolongation persisted when the aortic constriction was removed and was not different from the 84-day constricted group.

In a similar pattern, Table 2 also shows that unidirectional action potential conduction velocity, θ, was significantly reduced in the 42- and 84-day LVH groups, again by similar proportions. Furthermore, the decline of conduction velocity did not reverse 42 days after removal of the constriction, the value was not significantly different from the age-matched LVH group.

To examine possible causes for changes to conduction velocity the maximum upstroke rate of the action potential, dV/dt<sub>max</sub>, and the time course of the action potential foot (τ<sub>ap</sub>, Eqs. (1) and (2); Section 2) were measured. Fig. 2 illustrates a sample action potential and its first derivative. Table 2 shows that dV/dt<sub>max</sub> was not altered in the hypertrophied groups, compared to their respective controls, and was also unchanged in the deconstricted group.

Fig. 2B shows the region of the conducted action potential used to calculate τ<sub>ap</sub> and Table 2 shows the values of τ<sub>ap</sub> and calculated values of R<sub>i</sub> for the five groups, using Eq. (1). LVH at 42 and 84 days was associated with an increase of R<sub>i</sub> (Table 2). Furthermore, the value of R<sub>i</sub> remained elevated after 42 days of deconstriction and remained not significantly different from the age-matched LVH group.

Table 2 also shows that in control groups the ratio of contraction strength at 0.8–1.6 Hz, T<sub>1.6/0.8</sub>, was >1, i.e. there was a positive staircase effect. Following 42 or 84 days of constriction the ratio was significantly reduced to values not different from unity, but had recovered in the deconstricted group to control values.

3.3. Whole heart electrophysiology during hypertrophy and regression—base-line values

Flow rates required to maintain a constant perfusion pressure of 50 ± 5 mm Hg were similar in hearts from all experimental groups when normalised to unit heart weight. Subepicardial APD (APD<sub>95</sub>) at 3.3 Hz stimulation was similar after 42 days constriction but reduced significantly after 84 days. In the deconstricted group, APD<sub>95</sub> was similar to the sham-operated group. A similar pattern was observed for QRS durations. Refractory periods were similar in all groups and all values are also shown in Table 3.

Table 3
Base-line flow rates and electrophysiological properties of isolated guinea-pigs hearts with sham-operations (controls), thoracic aortic constriction or deconstriction

<table>
<thead>
<tr>
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<th>42 days</th>
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<th>84 days</th>
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<th>42 days de-constricted</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Constricted</td>
<td>Control</td>
<td>Constricted</td>
<td>Control</td>
</tr>
<tr>
<td>Perfusion flow rate (ml min&lt;sup&gt;-1&lt;/sup&gt; g&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>4.9 ± 2.6 (10)</td>
<td>4.9 ± 1.9 (7)</td>
<td>4.9 ± 2.6 (9)</td>
<td>4.9 ± 2.1 (7)</td>
<td>4.4 ± 5.8 (8)</td>
</tr>
<tr>
<td>Epicardial APD&lt;sub&gt;95&lt;/sub&gt; (ms)</td>
<td>165 ± 6 (10)</td>
<td>161 ± 11 (7)</td>
<td>181 ± 21 (9)</td>
<td>155 ± 16 (7)*</td>
<td>167 ± 4 (7)§</td>
</tr>
<tr>
<td>QRS interval (ms)</td>
<td>34 ± 7 (5)</td>
<td>31 ± 8 (7)</td>
<td>39 ± 4 (8)</td>
<td>34 ± 9 (6)*</td>
<td>38 ± 2 (6)§</td>
</tr>
<tr>
<td>Refractory period (ms)</td>
<td>148 ± 12 (10)</td>
<td>143 ± 7 (7)</td>
<td>142 ± 11 (9)</td>
<td>144 ± 19 (7)</td>
<td>150 ± 16 (8)</td>
</tr>
</tbody>
</table>

The first row refers to the number of days after the initial procedure when the heart was studied.

*Indicates p<0.05 vs. age-matched control.

§ Deconstriction vs. constriction.
3.3.1. Effects of ischaemia

APD$_{95}$ was measured during the ischaemic protocol and Fig. 3A shows data as a percentage of values during normal flow. Absolute values in the two sham-operated groups were identical and have been combined for clarity; the same was true for the two hypertrophied groups. Several hearts (see below) developed arrhythmias after 12 ($\pm$ 3) min but in those that did not APD$_{95}$ and other electrophysiological variables were measured throughout the ischaemic period. Several features are noteworthy: (i) the magnitude of APD$_{95}$ reduction at 30 min was similar in the control, hypertrophied and regressed groups; (ii) recovery was complete in all groups 15 min after restoration of flow; (iii) during the first 2 min of ischaemia APD$_{95}$ was shortened significantly more in the hypertrophied hearts, compared to the control or deconstricted hearts. Indeed, in control hearts, there was a small but significant prolongation of APD$_{95}$ at this time (102 $\pm$ 2% of control), after which APD$_{95}$ shortened.

QRS duration increased significantly, but by a small amount ($<5\%$), during low-flow ischaemia in all groups and returned to control on restoration of normal flow. There were no differences between the various groups of the extent of prolongation. Refractory periods increased to a greater extent during low-flow ischaemia, reached a new level after 2 min, remained constant thereafter for the 30-min intervention and recovered fully on restoration of normal flow. Values during normal flow are shown in Table 3. Fig. 3B shows the percentage increase of refractory period after 5 min low-flow ischaemia. There were no differences in the magnitude of prolongation between the experimental groups.

Several hearts developed VT or VF during the low-flow intervention, some of which exhibited spontaneous recovery. Fig. 3C shows the number of hearts in each experimental group that developed VT alone (grey area) or VF (preceded or not by VT, black area) during the ischaemic period. The number in the back box indicates those that recovered in the low-flow period. There were no significant differences in the number of hearts developing arrhythmias or showing recovery, in the constricted or deconstricted groups, when compared to sham-operated controls for either age-matched group ($\chi^2$-test).

4. Discussion

4.1. Morphological changes with aortic banding

Placement of a tight ring around the thoracic aorta produced gross cardiac and cellular left ventricular hypertrophy, evident after 42 days and confirms previous findings [7,21,24]. Thus, 42 days constriction was a well-characterised time point to refer electrophysiological changes associated with regression after surgical unloading. Myocyte growth was progressive between 42 and 84 days constriction, but was not mirrored in an equivalent progression of cardiac growth. Whether this represents a significant loss of myocyte number remains to be determined. Both cardiac and myocyte growth were reversible on removal of the constriction, to values approaching those of the age-matched control group. Regression of ventricular hypertrophy, induced by pharmacological or surgical interventions, has
been reported in other studies [4,25,26] and is a consistent observation.

4.2. Electrophysiological changes and LVH regression—isolated preparations

The reversibility of changes to cardiac morphology after removal of the additional afterload was not mirrored in the electrophysiological properties of isolated subendocardial ventricular preparations. LVH was accompanied by action potential (AP) prolongation and slowing of AP conduction, as reported in other studies [6,27]. Both changes can contribute to the generation of arrhythmias in the intact heart [28]. Slowing of conduction could in principle result from: (i) a smaller cell radius; (ii) reduction of local circuit currents, exemplified by reduced AP dV/dtmax; (iii) an increase of the intracellular resistivity, Ri, through which such currents flow. The first two options are not causal in these experiments: compared to control, cell radius was larger in hypertrophied hearts and dV/dtmax was unchanged. The final option was examined by calculating Ri using Eq. (2) and experimentally derived parameters (Section 2). Calculations showed that reduced conduction velocity in hypertrophied hearts could be attributed to an increase of Ri. Previous studies [7] have shown that the increase of Ri in LVH is due to a raised gap-junction resistance between adjacent cells.

Of significance was that these electrophysiological changes were not reversed during morphological regression of hypertrophy after deconstriction of the thoracic aorta. Thus, the gross morphological changes are not mirrored in the cellular changes that determine AP shape and conduction velocity, including intracellular resistivity This implies that, if these cellular changes predispose the hypertrophied heart to arrhythmias, this risk is not reduced during regression of LVH, at least during the time period of this study. Whether these changes reverse later in the course of regression remains to be determined.

The decreased force-frequency relationship in hypertrophied hearts has been proposed to contribute to impaired cardiac function during tachycardia [29]. Other studies have also shown slowed relaxation of the twitch in hypertrophied cardiac myocytes [30]. Changes to the contractile properties of myocardium from hypertrophied and deconstricted hearts did not follow the pattern of electrophysiological alterations, but the morphological properties. The attenuation of the positive staircase response in myocardium from hypertrophied and failed hearts [31,32] has been attributed to an increase of the intracellular [Na⁺], [Na⁺], [31]. It remains to be shown if [Na⁺], makes a similar recovery to the contractile response during regression of LVH. However, these data show that alteration to the cellular properties of myocardium during hypertrophy and its regression do not all follow a similar pattern.

Raised [Na⁺], will increase [Ca²⁺], and reduce pH, [33], and in turn increase gap junction resistance slowing AP conduction. However, because electrophysiological and contractile events followed different courses after regression of hypertrophy, a change to the intracellular environment is not solely responsible for the conduction changes. Several important experimental objectives follow: to measure precisely changes to the intracellular ionic environment during regression of LVH; and to determine the other factors that slow conduction in hypertrophied and regressed myocardium, e.g. re-modelling of gap junctions, or changes to the number and sub-type of connexin proteins that comprise the gap junction.

4.3. Electrophysiological changes and LVH regression—whole hearts

Measurements in whole hearts extended these measurements and examined the influence of ischaemic interventions. It is important to emphasise that there were several experimental differences between whole hearts and isolated strips. Experiments were carried out at 32 °C with a pacing frequency of 3.3 Hz, and were chosen after previous studies [20,21,26] showed they are optimal to maintain normal functional and metabolic activities and also achieve adequate pacing. Thus any change to the experimental variables as a result of LVH or its regression would be readily demonstrable. Action potentials were also recorded from subepicardial myocytes, but, in intact perfused hearts, there is little regional variation in action potential duration [34].

In contrast to the isolated preparations, APD₉⁵ recorded from whole hearts was not prolonged after 42 days constriction nor after deconstriction, and a small reduction was measured after 84 days constriction. This difference might result from the more rapid stimulation frequency, as APD₉⁵ prolongation observed in subendocardial myocardium from constricted hearts is absent at high frequencies, compared to the standard rate of 1 Hz (CH Fry unpublished data). Refractory period was unchanged in the constricted and deconstricted hearts and of interest is dissociation between this constancy and the reduction of APD₉⁵ in the 84-day constricted hearts. Na⁺ channel mutations can lead to changes of inactivation characteristics and may account for such a dissociation [35], although it is not known if this occurs in hypertrophied myocardium.

A previous study in cat hearts [15] showed that regression of wall thickness after aortic banding was associated with reversal of several electrophysiological changes that occurred with hypertrophy, including a raised incidence of inducible VT, lowered threshold for VF and prolonged APD. Our study showed that regression did not lead to reversal of APD prolongation or conduction properties in isolated preparations. However, it did show that during low-flow ischaemia, constricted hearts were more susceptible to a significant reduction of APD₉⁵ within the first 2 min of ischaemia and this tendency was absent in decon-
stricted hearts. If AP shortening is an important determinant of increased arrhythmias during ischaemia [36], this phenomenon may exacerbate the incidence of arrhythmogenesis in hypertrophied hearts exposed to brief ischaemic periods and regression may reverse this tendency. However, most arrhythmias in our study occurred later in the ischaemic period when AP duration was similar in all groups. Thus, similar shortening of the AP after 30 min low flow for hypertrophied and regressed hearts correlated with a similar incidence of ventricular arrhythmias during ischaemia. Increased dispersion of refactoriness has been reported to resolve with regression of hypertrophy [15], but this was not examined in the present study.

QRS duration did not correlate with the changes to conduction velocity observed in the isolated preparations. Although AP conduction will contribute to overall QRS duration, other factors such as path length and heart size mean that any quantitative comparison is not possible. It may be concluded that there are no gross deficiencies in cardiac conduction in any group and variation in AP conduction velocity is most effectively studied in isolated preparations.

Further work is needed to clarify whether our observations are applicable to human LVH and whether the electrophysiological changes associated with hypertrophy may be reversible over a longer time scale. There is good evidence that regression of LV mass following treatment for hypertension improves prognosis [37]. However, lack of reversal of electrophysiological abnormalities in patients with LVH correlates with a poor prognosis [16]. Further work is also needed to clarify whether and to what extent, persistence of electrophysiological abnormalities, despite regression of LV mass may contribute to a residual risk in treated hypertensive patients.

In conclusion, morphological regression of LVH is not accompanied by in vitro reversal of electrophysiological changes, whereas some aspects of contractile function do recover. This suggests that hypertension is associated with a number of cellular alterations that exhibit different rates of plasticity. The lack of reversal of electrophysiological changes may correlate with the poor prognosis associated with previous LVH [16]. Such changes were not associated with an altered incidence of arrhythmias, during normal or low coronary flow using the same animal model. It remains to be determined if: (i) more severe ischaemic models will demonstrate differences between hypertrophied and regressed hearts; (ii) antihypertensive treatment added to regression might confer additional benefits.

Acknowledgements

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