Cardiac contractile reserve in spontaneously hypertensive rats

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Summary
1. In response to graded infusions of isoprenaline, adult spontaneously hypertensive rats (20–24 weeks old) showed diminished responses of left ventricular contractile indices, diminished chronotropic responses and impairment of left ventricular relaxation rate as compared with matched Kyoto–Wistar rats.
2. These findings suggest reduced capacity to increase contractility in response to stress.

Key words: contractility, isoprenaline, spontaneous hypertension, ventricular hypertrophy.

Introduction
The effects of hypertrophy on myocardial performance are not uniform; cardiac function has been found to be increased, decreased or unchanged in non-failing, hypertrophied hearts (Ross & Sobel, 1972). The effects of hypertrophy associated with genetic systemic arterial hypertension have been mostly studied in spontaneously hypertensive Okamoto–Aoki strain rats (SH rats); cardiac pumping ability in this model was reported to be increased (Hallback-Nordlander, Noresson & Thoren, 1979), normal (Pfeffer, Pfeffer & Frohlich, 1976) or moderately depressed (Spech, Ferrario & Tarazi, 1980). However, changes in cardiac pumping ability do not necessarily parallel possible changes in velocity of ventricular contraction since the force and velocity characteristics of the myocardium can be altered differently by hypertrophy (Ross & Sobel, 1972; Skelton & Sonnenblick, 1974), although investigations of the ability of the left ventricle in SH rats to increase its velocity of contraction in response to stress (its contractile 'reserve') have not yet been reported. Because that response is largely determined by the adrenergic system, we have assessed the inotropic responses of the intact ventricle of SH rats to isoprenaline using a closed chest preparation. The left ventricular pressure first derivative (dP/dt) and the ratio of left ventricular pressure first derivative and the instantaneously developed pressure (dP/dt/Pi) were used as indices of contractility. Alterations in left ventricular relaxation rate were determined from the peak of the negative phase of left ventricular pressure first derivative (−dP/dt) (Cohn, Liedtke, Serur, Sonnenblick & Urchell, 1972).

Methods

Animals
Seven male SH rats and matched Kyoto-Wistar (WKY) rats, aged 20–24 weeks, were studied under sodium pentobarbital anaesthesia (60 mg/kg intraperitoneally) and subcutaneous atropine sulphate. The left ventricle was punctured through the closed chest, with the use of a micromanipulator (Brinkman Industries, Westbury, New York), and the needle was directly connected to a pressure transducer (Micron MP-15). Ventricular pressures were recorded and electronically differentiated by a preamplifier with a frequency response of 1–100 Hz (-3dB). The whole system, from needle to recorder, had a natural resonant frequency of 166 Hz and a damping coefficient of 0.63.

Protocol
After the needle was finely adjusted for clear and undamped tracings, the preparation was allowed a 15 min period of stabilization, after which control records were obtained. Isoprenaline hydrochloride was then infused through a Harvard pump at sequential steps (5 min for each) of 0·01, 0·02 and 0·04 μg min⁻¹ kg⁻¹. After the last dose, a recovery period of 5 min was allowed.

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Left ventricular pressures at standard (100 mmHg/5 cm) and high amplification (10 mmHg/2.5 cm for left ventricular end diastolic pressure) were recorded together with left ventricular dP/dt at the end of each period for 15 s at a paper speed of 200 mm/s.

Statistical analysis

Paired t-tests and analysis of variance were used to test differences within groups. Unpaired t-tests were used to test differences between groups.

Results

**Heart rate**

Significant dose-related increases in heart rate were observed in the WKY rats, with increasing doses of isoprenaline. In the SH rats group, the first significant increase in heart rate was observed only at 0.04 μg min⁻¹ kg⁻¹. Responses at the maximal dose infused were smaller in the SH than in WKY rats (12.4 ± 5.4 vs 35.4 ± 10.6 beats/min, P < 0.05).

**Contractility**

In the WKY rats, increasing doses of isoprenaline elicited dose-related increases in dP/dt; this index was still elevated at the end of the recovery period. The same pattern of response was also observed in the dP/dt normalized for instantaneously developed pressure (dP/dt/Pi). In the SH group, however, only the first dose (0.01 μg min⁻¹ kg⁻¹) evoked a borderline elevation in left ventricular dP/dt but the subsequent doses failed to further increase this index. None of the isoprenaline doses altered dP/dt/Pi in this group (Table 1).

**Relaxation rate**

Relaxation rate of the left ventricle, as assessed by negative dP/dt was only minimally affected by isoprenaline in WKY rats. In the SH group, however, −dP/dt responded by significant decreases to isoprenaline. Both WKY and SH rats had comparable relaxation rates during the control period, but relaxation rates of the SH rats became significantly smaller at the third dose as compared with WKY rats (Δ−dP/dt = -1998 ± 827 vs Δ−dP/dt = +17 ± 357 mmHg/s, P < 0.01). This difference was still evident throughout the recovery period (Δ−dP/dt = -2598 ± 855 vs Δ−dP/dt = +1005 ± 787 mmHg/s, P < 0.01).

Discussion

Cardiac function in the early stages of hypertrophy induced by systemic hypertension has frequently been estimated by peak cardiac output during volume overload; this index in SH rats was reported to be normal (Pfeffer, Pfeffer, Fletcher & Braunwald, 1979) or moderately depressed (Spech et al., 1980). Studies of pumping ability, however, are not sufficient to fully describe the performance capabilities of a pressure-related ventricular hypertrophy. We have attempted, therefore, to define the left ventricular responsiveness to isoprenaline in SH rats, in order to establish its capacity of facing haemodynamic stresses. Increase of the velocity of contraction is a major compensatory mechanism of the ventricle to face sudden variations in afterload. These increases are largely mediated by adrenergic factors (Braunwald, Ross & Sonnenblick, 1976).

Our results show that SH rats were unable to increase their contractile performance in response to isoprenaline, in striking contrast with the marked response observed in WKY rats. The failure of SH rat hearts to respond by increased contractility to β-adrenoreceptor stimulation suggests a lack of 'contractile reserve' in this type of hypertrophy, in spite of their reportedly normal (Pfeffer et al., 1976; Hallback-Nordlander et al., 1979) or even enhanced haemodynamic pump function.

**Diminished chronotropic and inotropic responses**

Possible causes for this diminished cardiac responsiveness in SH rats could be conceivably related to either decreased β-adrenoreceptor mediation, myocardial metabolic imbalances evoked by isoprenaline, or intrinsic alterations in the hypertrophied myocardial fibres (Alpert, Mulieri & Litten, 1979).

Impaired β-adrenoreceptor mediation has been suggested by decreased chronotropic responsiveness of SH rat atrial muscle (Fujiwara, Kuchii & Shibata, 1972) and of open-chested animals (Pfeffer, Pfeffer & Frohlich, 1974). These results were confirmed in our experiments with atropinized closed-chest preparations (Table 1). Since many studies have suggested the persistence of an increased sympathetic drive in SH rats (Okamoto, Nosaka, Yamori & Matsumoto, 1967; Nosaka, 1973; Yamori, Yanabe, De Jong, Lovenberg & Sjoerdsma, 1972), and since it has been demonstrated in vitro that continued exposure of myocardial tissue to catecholamines can lead to diminished β-adrenoreceptor sensitivity (Lefkowitz, 1978), the marked diminution
Table 1. Effect of graded isoprenaline infusions in heart rate, mean arterial pressure, peak + dP/dt, peak -dP/dt, and dP/dt normalized for instantaneously developed pressure (dP/dt/Pi)

<table>
<thead>
<tr>
<th>Isoprenaline (µg min⁻¹ kg⁻¹)</th>
<th>Control</th>
<th>0.01</th>
<th>0.02</th>
<th>0.04</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wistar-Kyoto rats</td>
<td></td>
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<td></td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>392.4 ± 19.8</td>
<td>401.0 ± 20.2*</td>
<td>418.3 ± 20.2*</td>
<td>427.8 ± 23.1*</td>
<td>395.5 ± 19.8</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>116.3 ± 9.5</td>
<td>108.7 ± 9.2*</td>
<td>103.8 ± 8.1*</td>
<td>97.8 ± 7.8*</td>
<td>125.8 ± 8.7</td>
</tr>
<tr>
<td>+dP/dt (mmHg/s)</td>
<td>11437 ± 942</td>
<td>12077 ± 1071*</td>
<td>14219 ± 1006*</td>
<td>16120 ± 650*</td>
<td>13310 ± 722*</td>
</tr>
<tr>
<td>-dP/dt (mmHg/s)</td>
<td>8650 ± 390</td>
<td>7534 ± 283*</td>
<td>8328 ± 227</td>
<td>8668 ± 236</td>
<td>8993 ± 636</td>
</tr>
<tr>
<td>dP/dt(Pi) (Hz)</td>
<td>105.9 ± 5.3</td>
<td>130.4 ± 5.9*</td>
<td>152.5 ± 6.9*</td>
<td>184.6 ± 5.6*</td>
<td>126.8 ± 7.7*</td>
</tr>
<tr>
<td>Spontaneously hypertensive rats</td>
<td></td>
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</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>389.9 ± 21.4</td>
<td>385.4 ± 19.9</td>
<td>397.8 ± 19.3</td>
<td>401.7 ± 22.8*</td>
<td>365.0 ± 18.3</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>151.1 ± 13.5</td>
<td>144.6 ± 15.3*</td>
<td>142.8 ± 16.6*</td>
<td>140.0 ± 16*</td>
<td>151.6 ± 17.4</td>
</tr>
<tr>
<td>+dP/dt (mmHg/s)</td>
<td>14400 ± 810</td>
<td>12444 ± 706</td>
<td>13643 ± 1060</td>
<td>13281 ± 835</td>
<td>1134 ± 813</td>
</tr>
<tr>
<td>-dP/dt (mmHg/s)</td>
<td>8850 ± 1065</td>
<td>7640 ± 810*</td>
<td>7294 ± 808*</td>
<td>6710 ± 699*</td>
<td>6186 ± 650*</td>
</tr>
<tr>
<td>dP/dt(Pi) (Hz)</td>
<td>120.4 ± 14.1</td>
<td>123.6 ± 12.6</td>
<td>129.9 ± 9.6</td>
<td>124.3 ± 7.0</td>
<td>120.2 ± 11.1</td>
</tr>
</tbody>
</table>

* Significant differences from control (P < 0.05 or less) with isoprenaline. Changes in mean arterial pressure are not statistically different in the two groups.

of cardiac chronotropic and of inotropic responses in our experiments could be attributed to diminished sensitivity or decreased number of cardiac β-adrenoreceptors in this model of hypertension.

Another possible factor that can be invoked to explain the reduced inotropic responses in SH rats is that induction of a relative myocardial cardiac P-adrenoreceptors in this model of cardiac chronotropic and of inotropic responses in our experiments could be attributed to imbalance between increased demand and actual needs by this catecholamine might lead to an imbalance between increased demand and actual oxygen supply in the hypertrophied heart. This view is supported by reports of reduced myocardial capillary reserve in cardiac hypertrophy because of increased intercapillary distances (Honig & Bordeau-Martini, 1974; Marcus, Mueller, Gascho & Kerber, 1979).

**Relationship to ventricular relaxation rate**

Although catecholamines were shown to exert a relaxing effect on cardiac muscle in vitro (Morad & Rolett, 1972), this effect was not easily demonstrable in whole heart preparations. In fact Cohn et al. (1972) reported a paradoxical effect of catecholamines on the relaxation rate of the left ventricle of dogs as measured by negative dP/dt. Our results are in agreement with their observation. There was an actual slight decrease in left ventricular relaxation rate in both normal and hypertrophied ventricles with the first dose of isoprenaline. With increased dosage, however, a significant difference emerged; although -dP/dt tended to return towards control levels in WKY rats, a marked continued diminution in this index was observed in the SH rats, with increasing isoprenaline doses. Since it has been shown that ischaemia of the myocardium can lead to diminution in relaxation rates (McLaurin, Rolett & Grossman, 1973), this observation might support the suggestion of an imbalance evoked by isoprenaline in hypertrophied hearts between oxygen demands and supply. Further, to the extent that an impaired relaxation can influence contractility in the subsequent cardiac cycle, impairment of relaxation rate might in turn lead to the reduced inotropic response that we observed in response to isoprenaline.

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**References**


