Left ventricular hypertrophy improves cardiac function in spontaneously hypertensive rats

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Summary

1. The influence of different arterial pressures on the relationship between diastolic filling pressure and stroke volume was studied during pharmacological cardiac nerve blockade in adult, anaesthetized spontaneously hypertensive rats in comparison with matched normotensive Wistar-Kyoto rats.

2. Peak stroke volumes, obtained by rapid blood volume expansion were similar in both types of rat, despite a more than 40% higher mean arterial pressure in the spontaneously hypertensive rats.

3. When peak stroke volumes were compared in the two groups at equal ‘normotensive’ or ‘hypertensive’ arterial pressures, they were always greater in the spontaneously hypertensive rats.

4. Calculation of diastolic wall/lumen ratios indicated that the increase of maximal stroke work in the spontaneously hypertensive rats closely matched the hypertrophic increase in wall/lumen ratio of the left ventricle.

5. These results indicate that left ventricular hypertrophy in established primary hypertension is a physiological adaptation to match left ventricular performance to the raised afterload.

Key words: left ventricular hypertrophy, cardiac function, spontaneously hypertensive rats.

Abbreviations: LVEDP, left ventricular end-diastolic pressure; SH, spontaneously hypertensive; WKY, Wistar–Kyoto strain.

Introduction

It has been suggested that left ventricular hypertrophy in established arterial hypertension represents a ‘physiological’ cardiac adaptation to the raised arterial pressure, just as skeletal muscles respond by hypertrophy to increases in work load [1]. Alternatively, it has been suggested that it is mainly a degenerative phenomenon [2].

The present investigation was undertaken to study further cardiac function in vivo, using anaesthetized SH rats of the Okamoto strain and normotensive WKY rats. We studied, firstly, the relationships between left ventricular end-diastolic filling pressure and stroke volume and, secondly, the extent to which the level of afterload affects the maximal stroke volume. Further, experiments were also performed in vitro to explore how myocardial hypertrophy affects the diastolic volume distensibility of the left ventricle.

Methods

Cardiac performance in vivo

Experiments were performed on 4 months old SH rats of the Okamoto strain and on normotensive WKY rats under pentobarbital anaesthesia. Cardiac autonomic blockade was achieved with propranolol (2.0 mg/kg body weight) and methscopolamine (0.5 mg/kg body weight) given intra-arterially. Measurements were performed of cardiac output (dye-dilution technique in microscale), heart rate, mean arterial pressure and left ventricular end-diastolic pressure (LVEDP, intraventricular catheter inserted via the right carotid artery). Rapid increases of LVEDP were achieved by intravenous infusion of fresh rat blood (38°C) at an initial rate of 3-8 ml/min for 2–3 min and thereafter at a rate of 7 ml/min for 1–2 min, until maximal LVEDP and cardiac output levels were reached. Pure oxygen was supplied through the tracheal tube to keep arterial oxygen saturation between 95 and 80%.

In this way cardiac function curves were
obtained in ten SH rats and nine WKY rats, when starting from their respective mean arterial pressures. In a subgroup of seven SH rats and eight WKY rats cardiac function curves were also obtained at increased mean arterial pressures (achieved by graded constrictions of the abdominal aorta with a snare, implanted 2 days earlier) and in seven SH rats at decreased, 'normotensive' pressures as well (achieved by infusion of hydralazine, 0.3–3.0 mg/kg).

Left ventricular wet weight was determined after the experiment.

Pressure–volume relationship of the isolated left ventricle

Isolated hearts from 11 4 months old male SH rats and ten age-matched WKY rats were used. They were initially perfused via the aorta with an oxygenated Krebs–Henseleit perfusate containing Ca$^{2+}$ (2.5 mmol/l). By changing the perfusate to one without Ca$^{2+}$ the hearts were arrested in diastole. Thereafter repeated pressure–volume curves were obtained (by means of a double-lumen catheter inserted in the left atrium), by stepwise (84 μl) increases of left ventricular volume during simultaneous pressure measurements. In this way pressure increased rapidly (1–2 s) from 0 to 15 mmHg (defined as 'dynamic pressure–volume curves'). In four or five experiments of each group, the left ventricle was also more slowly distended (40 s) from 0 to 15 mmHg, providing 'static pressure–volume curves'. No rigor mortis was observed during the procedure and all hearts started to beat when again perfused with a perfusate containing Ca$^{2+}$ at 2·5 mmol/l.

Results

Cardiac performance in vivo

Mean arterial pressure measured in the awake state was about 45% higher in SH rats (151 ± 3 mmHg) than in WKY rats (104 ± 2 mmHg: $P < 0·001$); left ventricular to body weight ratios differed by a little more than 30% (2·65 ± 0.01 mg/g body wt. in SH rats and 2·01 ± 0·03 mg/g body wt. in WKY rats).

Peak stroke volumes during intravenous blood infusion, obtained at a LVEDP around 20 mmHg in both groups, did not differ significantly between SH rats and WKY rats, despite the fact that SH rats then reached mean arterial pressures more than 40% higher than those of WKY rats (point A in Fig. 1). Further, for equal levels of afterload in the two groups, peak stroke volumes were always substantially larger in SH rats than in WKY rats (also shown in Fig. 1). In both SH and WKY rats peak stroke volume varied inversely as the level of mean arterial pressure, but was at each pressure load always higher in SH rats over the entire range studied ($P < 0·001$).

However, at low LVEDP stroke volume was lower in SH rats than in WKY rats when both were exposed to their ordinary afterloads. Thus at LVEDP of 4 mmHg stroke volume was 62 ± 2 μl/100 g body wt. in SH rats and 75 ± 3 μl/100 g in WKY rats ($P < 0·01$) at mean arterial pressures of 164 ± 4 mmHg and 108 ± 6 mmHg ($P < 0·001$) respectively. Also in this situation stroke volume was inversely related to mean arterial pressure and, when afterload was lowered in the SH rats to normotensive levels (109 ± 6 mmHg) by hydralazine, stroke volume increased to 79 ± 4 μl/100 g body wt., which was not different from that of WKY rats.

Pressure–volume relationship of the isolated left ventricle

Also in this group left ventricular weight was substantially higher in SH rats (2.92 mg/g body
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wt.) than in WKY rats (2.06 ± 0.05 mg/g; 
P < 0.001). Diastolic 'dynamic distensibility' (defined as percentage left ventricular volume increase per mmHg, when rapidly increasing intraventricular pressure from 2.5 to 12.5 mmHg) was 11.4 ± 0.8% in SH rats and 10.4 ± 0.8% in WKY rats. Thus, with respect to left ventricular lumen distension, there was no difference between SH rats and WKY rats, despite the thicker left ventricular wall in SH rats, where the calculated wall/lumen ratio was 15–20% higher than in WKY rats.

Discussion

Maximal stroke volume during rapid blood volume expansion was similar in SH rats and WKY rats, despite a 40–50% higher mean arterial pressure in the former. When peak stroke volumes were instead compared at similar arterial pressures for both (either at 'normotensive' or 'hypertensive' levels) they were always significantly greater in SH rats and almost in proportion to their higher left ventricular weight. The increase in cardiac performance in SH rats was if anything actually greater than the hypertrophic increase in diastolic wall/lumen ratio of the left ventricle deduced from the diastolic volume expansions and the left ventricular weight. The increase in cardiac performance in SH rats was if anything actually greater than the hypertrophic increase in diastolic wall/lumen ratio of the left ventricle deduced from the diastolic volume expansions and the left ventricular weight. The increase in cardiac performance in SH rats was if anything actually greater than the hypertrophic increase in diastolic wall/lumen ratio of the left ventricle deduced from the diastolic volume expansions and the left ventricular weight. The increase in cardiac performance in SH rats was if anything actually greater than the hypertrophic increase in diastolic wall/lumen ratio of the left ventricle deduced from the diastolic volume expansions and the left ventricular weight. The increase in cardiac performance in SH rats was if anything actually greater than the hypertrophic increase in diastolic wall/lumen ratio of the left ventricle deduced from the diastolic volume expansions and the left ventricular weight. The increase in cardiac performance in SH rats was if anything actually greater than the hypertrophic increase in diastolic wall/lumen ratio of the left ventricle deduced from the diastolic volume expansions and the left ventricular weight. The increase in cardiac performance in SH rats was if anything actually greater than the hypertrophic increase in diastolic wall/lumen ratio of the left ventricle deduced from the diastolic volume expansions and the left ventricular weight. The increase in cardiac performance in SH rats was if anything actually greater than the hypertrophic increase in diastolic wall/lumen ratio of the left ventricle deduced from the diastolic volume expansions and the left ventricular weight. The increase in cardiac performance in SH rats was if anything actually greater than the hypertrophic increase in diastolic wall/lumen ratio of the left ventricle deduced from the diastolic volume expansions and the left ventricular weight. The increase in cardiac performance in SH rats was if anything actually greater than the hypertrophic increase in diastolic wall/lumen ratio of the left ventricle deduced from the diastolic volume expansions and the left ventricular weight.

Earlier studies by Pfeffer et al., [3] have also indicated well-maintained cardiac function in SH rats with established hypertension. In contrast, Spech et al. [2] reported considerably depressed cardiac function in 17–29 week old SH rats. However, in these studies the influence of the afterload level, in terms of the inotropic effects of 'homeometric autoregulation' (Anrep effect), was not considered. The marked effect of afterload on stroke volume illustrated in the present study could be one of the explanations why so widely different results have been obtained in earlier studies of cardiac function [2, 3].

At low levels of preload a rightward shift of the Frank–Starling relationship was observed in the SH rats compared with WKY rats at their respective afterloads in vivo. This can mainly be explained by the impact of the increased afterload against which SH rat hearts are working. This rightward shift has earlier been observed also in isolated beating hearts from SH rats [1]. This might be interpreted as a relatively depressed myocardial function in SH rats at low levels of prestretch. However, in a thicker myocardial wall the outer wall layers will be slightly less extended. To this is added the possibility that the inner wall layers of the hypertrophied left ventricle might be relatively more slackened and therefore they might not fully participate either in passive resistance to stretch or in active tension generation upon systolic contraction until they are exposed to still greater luminal expansion.

Because of the altered geometry of the hypertrophied heart, cardiac performance should be evaluated at optimal preload and at appropriate afterload, When these prerequisites are met with there is no evidence of any contractile deficiency in SH rat hearts but the present results strongly suggest that left ventricular hypertrophy in established primary hypertension represents a beneficial physiological adaptation, well matching contractile performance to the raised afterload.

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References