Left Ventricular Hypertrophy in Rats with Renovascular Hypertension
Alterations in Cardiac Function and Adrenergic Responses
MANOEL A. SARAGOÇA, M.D. AND ROBERT C. TARAZI, M.D.

SUMMARY Performance of the hypertrophied left ventricle was studied by determination of the inotropic response to different stimuli in renal hypertensive rats (two-kidney, one clip Goldblatt, RHR, n = 13) and matched sham-operated controls (NR, n = 11). A model was developed to determine maximal pressure development (transient aortic ligation), maximal pumping ability (rapid transfusion, 2 ml/30 sec), and responses to beta stimulation (isoproterenol, 0.01 to 0.10 μg/kg/min), using dP/dt/P\textsubscript{w} as a load-independent index of contractility. With rapid blood transfusion, RHR developed a higher ventricular systolic pressure (211.5 ± 10.1 mm Hg vs 194.0 ± 9.3 (SE), p < 0.001) but at the expense of higher end-diastolic pressure (LVEDP) (12.2 ± 1.1 mm Hg vs 7.7 ± 1.0, p < 0.02). The maximal response of dP/dt/P\textsubscript{w} to isoproterenol was diminished in RHR (29.5 ± 3.2 sec\textsuperscript{-1} vs 49.6 ± 5.2, p < 0.01) whereas the maximal developed pressure (MDP) was greater in RHR than in NR (239.2 ± 7.5 mm Hg vs 197.0 ± 3.9, p < 0.001). A positive correlation was found between MDP and ventricular weight (r = 0.846, p < 0.001) in contrast with the negative correlation found between ventricular weight and maximal dP/dt/P\textsubscript{w} response to isoproterenol (r = 0.677, p < 0.001). Thus, cardiac hypertrophy in RHR allowed higher developed ventricular pressures but at the expense of higher LVEDP; at the same time, however, the ability to increase contractility in response to beta adrenergic stimulation was decreased. The contrast in results obtained using different tests of cardiac function indicates the need for a multifactorial approach. It also suggests a subtle transformation in this hypertrophy of the pattern of cardiac adaptation to the increased load. (Hypertension 3 (suppl II): II-171-II-176, 1981)

KEY WORDS • cardiac contractility • volume load • isoproterenol • pressure overload • isovolumic beats • contractile reserve

THE oft-reported heterogeneity in functional consequences of cardiac hypertrophy\cite{1,2} precludes simple extrapolations from one type of hypertrophy to another; thus, conclusions regarding the impact of hypertension on the heart cannot be deduced, without direct confirmation, from the large body of knowledge developed from other types of cardiac hypertrophy.\cite{3} However, in contrast to the many studies of systemic hemodynamics, investigations regarding cardiac contractility in hypertension have been relatively few;\cite{4,5} most have dealt with cardiac pumping ability as determined from cardiac output curves obtained during rapid volume overload.\cite{5,6} Cardiac function cannot, however, be fully assessed from the heart's response to increased ventricular filling. Similarly, although earlier studies did suggest that inotropic responses to beta stimulation were reduced in hypertensive rats,\cite{7,8} the results again concerned only one aspect of ventricular function. A better understanding of the spectrum of cardiac alterations with hypertension requires a simultaneous study of responses to different types of stress because ventricular response to pressure overload or to beta-adrenergic stimulation might not necessarily mirror the results obtained from volume overload.

In this study, we have determined in rats with experimental renovascular hypertension (two-kidney, one clip Goldblatt) ventricular responses to three types of stress: transient aortic occlusion, rapid volume overload, and graded isoproterenol infusions. Comparison of the responses to these different stimuli helped define a spectrum of cardiac adaptation in this model of hypertension, marked by increased dependence on the Frank-Starling mechanism and reduced responsiveness to adrenergic stimulation.
Material and Methods

Male Sprague-Dawley rats (Hilltop Laboratories, Scottsdale, New Jersey) aged 40–45 days, weighing 150–175 g, were operated on: 13 had left renal artery clipping (silver clip, 0.2 mm internal width) and 11 had a sham operation. All rats had their blood pressure (BP) determined biweekly by the tail-cuff method. The clipped rats were studied after 8 weeks of sustained hypertension; sham-operated controls were studied under the same conditions after an equal period of time. Anesthesia was pentobarbital (Abbott Laboratories) 50 mg/kg by intraperitoneal injection; atropine sulfate 0.1 mg/kg (s.c.) was given prior to tracheostomy. Details of vascular cannulation and left ventricular puncture through the closed chest were described in detail previously. The needle-transducer system used for ventricular recordings had a natural resonant frequency of 166 Hz and a damping coefficient of 0.63. The first derivative of intraventricular pressure was obtained electronically using a differentiator preamplifier with a flat frequency response from 1–100 Hz (−3dB).

The contractility index, dP/dt/P criticised, was obtained as follows: from data stored on tape in a Honeywell 5600-C recorder, plots of left ventricular pressure (y-axis) and their corresponding electronically derived dP/dt (y-axis) were drawn mechanically on a flat frequency response from 1–100 Hz (−3dB).

The completeness of aortic occlusion was controlled by observing the abolition of the carotid pulse. None of the rats had any significant bleeding during the procedure.

Left Ventricle Pressure—Volume Relationship

The pressure-volume relationship of the left ventricle was studied in a separate group of rats, submitted to left renal artery clipping (n = 7) or sham operation (n = 5). These rats were handled and followed exactly as for the animals used for the volume and pressure overload experiments. Under the same anesthesia as used before, thoracotomy and pericardectomy were performed rapidly while the animals were ventilated mechanically. After the heart was arrested with 0.5 ml i.v. KCl (19.1%), a double lumen catheter was advanced into the LV through a small opening in the root of the aorta. The LV and atria were then tied around the catheter by a thread placed along the atriocoronary groove, leading to complete occlusion of the LV chamber. The right ventricle was sutured open, and after careful emptying of the LV and careful calibration and zero adjustments, saline was infused into the LV at a rate of 0.206 ml/min. Left ventricular pressure was recorded continuously during the infusion. Accurate timing of the experiment allowed exact determination of the intraventricular volume corresponding to LV pressures of 5, 10, 20, 30, and 40 mm Hg.

At the end of the procedure, the heart was excised and carefully trimmed, as described previously; the ventricles were washed of blood, blotted dry, and weighed on a Mettler precision balance.

Statistical Analysis

The changes produced by the graded infusion of isoproterenol were evaluated by an analysis of variance. Student's t test was used to compare results between groups; regression analysis, correlation coefficients, and evaluation of statistical significance were performed by standard methods. Results are expressed as average ± one standard error of the mean.

Results

Development of Hypertension and Cardiac Hypertrophy

Hypertension was induced in rats with left renal artery clipping (RHR) but not in the sham-operated animals (NR), as demonstrated by both indirect tail cuff and direct intraarterial pressure (184.5 ± 12.3

Acute Pressure Overload

Six hypertensive and six normotensive rats then had a thoracotomy, and the aortic arch was carefully exposed. After a 10-minute rest period to insure stability of the preparation, the aortic arch was acutely occluded while the LVESP and LVEDP were registered continuously. The completeness of aortic occlusion was controlled by observing the abolition of the carotid pulse. None of the rats had any significant bleeding during the procedure.
mm Hg vs 142.3 ± 7.5, p < 0.001). Cardiac hypertrophy was evident in RHR as shown by both the absolute ventricular weight (RHR = 1.259 ± 0.039 g vs NR = 1.030 ± 0.010 g, p < 0.001) and its ratio to body weight (RHR = 3.345 ± 0.118 vs NR = 2.591 ± 0.041 mg/g, p < 0.001). An equivalent degree of ventricular hypertrophy was also found in the rats (7 RHR and 5 sham) prepared for the study of LV pressure volume relationship; both absolute ventricular weight and the ratio of ventricular to body weight were significantly increased (RHR = 1.193 ± 0.036 vs NR = 0.934 ± 0.027 g, p < 0.001 and 3.110 ± 0.076 vs 2.473 ± 0.067 mg/g, p < 0.001). The degree of hypertrophy obtained in this group was not statistically different from the hypertrophy obtained in the larger group studied by aortic occlusion and volume overload.

**Chronotropic and Contractile Responses to Isoproterenol**

Chronotropic responses to the graded infusion of isoproterenol were parallel in NR and RHR; the maximal increase in heart rate (at 0.10 μg/kg/min infusion rate) was not statistically different between the two groups (+60.0 ± 9.1 vs 58.4 ± 6.9 bpm, not significant). In contrast, there was a significant difference in inotropic responses; isoproterenol produced a sharp, dose-dependent increase of dP/dt/Pₚ in the normotensive but not the hypertensive rats. In the latter, there was a tendency for the responses to plateau after the second level of infusion; the difference in ∆dP/dt/Pₚ between NR and RHR was significant at both the third and fourth infusion levels (fig. 1). Furthermore, a significant inverse correlation (r = -0.677, p < 0.001) was observed between ventricular weight and the maximal contractile response to isoproterenol (fig. 2).

**Acute Volume Overload**

With acute blood transfusion (2 ml/30 sec), quantitatively similar increases were observed in systolic pressure, which rose from 135.6 ± 6.2 to 154.2 ± 5.7 mm Hg in normotensive rats and from 192.0 ± 9.3 to 211.5 ± 10.1 mm Hg in RHR (table 1). Left ventricular end-diastolic pressure was higher to start with in RHR compared to normotensive rats (4.5 ± 0.6 mm Hg vs 2.7 ± 0.5, p < 0.05), and it increased to higher levels with transfusion (12.2 ± 1.1 vs 7.7 ± 1.0 g in NR, p < 0.02); the magnitude of this increase was larger in the hypertensive rats (+7.7 vs +5.0 mm Hg, p < 0.05).

**Acute Pressure Overload**

During transient aortic occlusion, both groups developed equivalent increases in left ventricular systolic pressure (LVSP) (+115.5 ± 10.6 vs 122.1 ± 17.2 mm Hg, not significant (tables 2 and 3) but the concomitant increase in LVEDP was significantly greater in RHR (+18.8 ± 1.8 vs 9.0 ± 2.2 mm Hg, p < 0.01). The maximal pressure developed (LVSP – LVEDP) by the left ventricle in the RHR was greater than in controls (239.2 ± 7.5 vs 197.0 ± 3.9 mm Hg, p < 0.001); furthermore, there was a significant positive correlation between the maximal LV developed pressure and ventricular weight, whether expressed as a ratio of body weight (r = 0.846, p < 0.001) (fig. 3) or in absolute value (r = 0.834, p < 0.001).

**Left Ventricular Pressure-Volume Relationships**

No significant difference was found between hypertensive and normotensive rats as regards the pressure volume curve of the arrested left ventricle (fig. 4). These curves were used to convert the LV end-diastolic pressure data obtained from the overload ex-
TABLE 1. Changes in Intraventricular Pressure and Volume with Acute Volume Overload

<table>
<thead>
<tr>
<th></th>
<th>NR (n = 11)</th>
<th>RHR (n = 13)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>LVSP (mm Hg)*</td>
<td>135.6 ± 6.2</td>
<td>154.2 ± 5.2</td>
</tr>
<tr>
<td>LVEDP (mm Hg)!</td>
<td>2.7 ± 0.5</td>
<td>7.7 ± 1.0</td>
</tr>
<tr>
<td>DevP (mm Hg)*</td>
<td>133.2 ± 6.1</td>
<td>146.4 ± 3.2</td>
</tr>
<tr>
<td>LVEDV (ml)!</td>
<td>0.12 ± 0.02</td>
<td>0.27 ± 0.02</td>
</tr>
</tbody>
</table>

LVSP = left ventricular systolic pressure; LVEDP = left ventricular end diastolic pressure; DevP = developed left ventricular pressure calculated as LVSP - LVEDP; LVEDV = left ventricular end-diastolic volume calculated from pressure-volume curves (fig. 1).

*p = not significant. Refers to statistical significance of difference in responses (Δ) between hypertensive rats (RHR) and normotensive controls (NR).

†p = < 0.05

TABLE 2. Changes in Intraventricular Pressure and Volume with Aortic Occlusion

<table>
<thead>
<tr>
<th></th>
<th>NR (n = 6)</th>
<th>RHR (n = 6)</th>
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<tr>
<td></td>
<td>Before</td>
<td>After</td>
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<tr>
<td>LVSP (mm Hg)*</td>
<td>93.0 ± 10.3</td>
<td>208.3 ± 3.3</td>
</tr>
<tr>
<td>LVEDP (mm Hg)!</td>
<td>2.5 ± 0.4</td>
<td>11.5 ± 2.2</td>
</tr>
<tr>
<td>DevP (mm Hg)*</td>
<td>90.5 ± 7.6</td>
<td>197.0 ± 3.9</td>
</tr>
<tr>
<td>LVEDV (ml)!</td>
<td>0.11 ± 0.02</td>
<td>0.30 ± 0.04</td>
</tr>
</tbody>
</table>

Abbreviations as in table 1.

*p = not significant

†p = < 0.01

TABLE 3. Response of Intraventricular Pressure and Volume to Acute Volume Overload and Acute Aortic Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Acute volume overload</th>
<th>Acute pressure overload</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>NR</td>
<td>RHR</td>
<td></td>
</tr>
<tr>
<td>LVSP (mm Hg)*</td>
<td>18.5 ± 3.6</td>
<td>19.5 ± 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDP (mm Hg)!</td>
<td>5.0 ± 0.7</td>
<td>7.6 ± 0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DevP (mm Hg)*</td>
<td>13.1 ± 4.1</td>
<td>13.5 ± 5.5</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDV (ml)!</td>
<td>0.15 ± 0.01</td>
<td>0.19 ± 0.02</td>
<td>&lt;0.05</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Acute volume overload</th>
<th>Acute pressure overload</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NR</td>
<td>RHR</td>
<td></td>
</tr>
<tr>
<td>LVSP (mm Hg)*</td>
<td>115.5 ± 10.6</td>
<td>122.1 ± 17.2</td>
<td></td>
</tr>
<tr>
<td>LVEDP (mm Hg)!</td>
<td>9.0 ± 2.2</td>
<td>18.9 ± 1.8</td>
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</tr>
<tr>
<td>DevP (mm Hg)*</td>
<td>106.5 ± 12.3</td>
<td>103.5 ± 18.2</td>
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<tr>
<td>LVEDV (ml)!</td>
<td>0.23 ± 0.04</td>
<td>0.36 ± 0.01</td>
<td></td>
</tr>
</tbody>
</table>

Values are changed from control (Δ). Abbreviations as in table 1

*p = not significant

†p = < 0.01

![Figure 3](http://hyper.ahajournals.org/)

**Figure 3.** Maximal pressure developed by the left ventricle (Mx Dw P) in response to transient aortic occlusion was calculated after 3 seconds of occlusion as (LVSP - LVEDP); it correlated significantly with ventricular weight expressed either in relation to body weight (graph) or in absolute numbers (r = 0.834, p < 0.001).

![Figure 4](http://hyper.ahajournals.org/)

**Figure 4** Pressure-volume curves of the left ventricle obtained in arrested hearts showed no difference between the renovascular hypertensive rats (RHR) and sham-operated normotensive controls, over a pressure range from 0-40 mm Hg.
periments into an estimate of changes in ventricular volume. Under these conditions, it appeared that the LV end-diastolic volume tended to increase more in RHR than in NR, in response to either pressure or volume overload (tables 1 and 2).

Discussion

The results obtained outline a wide spectrum of functional alterations associated with cardiac hypertrophy in renovascular hypertension — on the one hand, an increased power to develop pressure correlated with increased ventricular weight (fig. 3), and on the other hand, a reduced inotropic response to beta adrenergic stimulation. This multifaceted alteration with hypertrophy must be judged in relation to the major mechanisms enabling the heart to cope with increased pressure. The ability to increase cardiac contractility helps maintain adequate pump function against the continuously changing working loads imposed on the heart by the evolution of hypertension. A second mechanism that can also help face these demands is an increase in ventricular end-diastolic volume, as exemplified by the Frank-Starling curve. Both mechanisms may be active simultaneously; dilations of the ventricular chamber involved in the latter mechanism are constantly corrected by increases in the contractile state of the heart in response to beta stimulation.

However, responsiveness of the hypertrophied heart to beta-adrenergic stimulation appears to be limited in both SHR and the renovascular hypertensive rat. This finding was confirmed in the present study (fig. 1), which also showed that this impairment of contractile response was inversely correlated with the degree of cardiac hypertrophy (fig. 2). This limitation could not be explained only by diminished beta-adrenoceptor function since chronotropic response to isoproterenol were unchanged. It is conceivable that metabolic imbalances during beta stimulation, possibly related to the diminished coronary reserve of hypertensive hypertrophy, might be involved in this limitation.

At the same time and in the same animals, the pressure and volume overload experiments revealed a greater rise of LV end-diastolic pressure in hypertensive rats in response to stress. Transient aortic occlusion was used to impose a maximal pressure load on the LV. The responses obtained by this maneuver have been used as indices of maximal force development by the nonejecting ventricle. Not only did the renovascular hypertensive rats develop a greater maximal pressure but there was also a found positive correlation between the LV pressure developed during aortic occlusion and ventricular weight (fig. 3). However, this enhanced power of hypertensive hearts to generate pressure was associated with a significant increase in LVEDP (table 3). Essentially similar results were observed with acute volume overload; the RHR showed a greater increase in LVEDP for the same degree of increase of intraventricular systolic pressure at the end of blood transfusion (table 3). The significance of these results depends in great part on the accuracy of estimates of concomitant alterations in LV volume.

The greater increase in LVEDP in RHR might reflect their greater dependence on the Starling mechanism during stress or it might alternatively reflect only a reduced LV compliance induced by hypertension. The lack of difference in pressure volume curves between normotensive rats and RHR would favor the first conclusion. These pressure-volume curves were obtained in the arrested hearts of a separate group of rats with the same model of hypertension and a comparable degree of hypertrophy. They showed a remarkable similarity in passive distensibility between normal and hypertensive ventricles (fig. 4), suggesting that the increased LVEDP in RHR was indeed related to a higher end-diastolic volume. The lack of significant change in ventricular compliance in RHR appears to differ from the general impression of an elevated ventricular muscle stiffness in other types of pressure induced hypertrophy. This discrepancy may be related to many factors including the duration and extent of hypertension as well as possible differences among the different experimental models of hypertension. Further, pressure-volume curves in arrested hearts might not fully describe the stiffness of the intact beating heart because of possible changes due to such factors as cardiac activity and influence of the pericardium or right ventricle on the LV. However, despite these limitations, the diastolic pressure-volume relationship described from these curves has been used as a valid index of volume changes associated with different levels of LV end-diastolic pressure; this was recently validated by Jewell and Blinks. On this basis, our data suggest that the greater rise of LVEDP in RHR under pressure or volume-loading stress was related to a larger increase in end-diastolic volume.

In summary, the simultaneous determination of cardiac response to different types of stress allowed a better understanding of the functional consequences of ventricular hypertrophy than could be derived from the study of any one stimulus alone. Taken all together, our results suggest a subtle alteration in cardiac function as LV hypertrophy develops secondary to renovascular hypertension; maximal pressure development was well maintained or even significantly increased, but this was associated with greater dependence on the Frank-Starling mechanism while inotropic responsiveness to beta-adrenergic stimulation was reduced.

References

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