Cardiac Performance in Rats with Renal Hypertension

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SUMMARY To evaluate cardiac performance in renal hypertension more precisely we determined cardiac function curves for 12 normotensive rats and 11 other rats with two-kidney Goldblatt hypertension. The hypertensive group (BP = 134 ± 8 mm Hg) showed significant cardiac hypertrophy (44 ± 1% increased ratio of heart weight to body weight, P < 0.01) and markedly increased left ventricular stroke work with a moderate but not significant increase in left ventricular end-diastolic pressure (LVEDP) (5.9 ± 0.8 vs. 4.7 ± 0.4 mm Hg). We evaluated cardiac function by recording left ventricular end-diastolic pressure, stroke volume (SV), and cardiac output (CO) (by electromagnetic flowmeter) during rapid alteration in venous return. Analysis of variations of stroke volume vs. left ventricular end-diastolic pressure showed that renal hypertension is accompanied by a significant decrease in ventricular performance

CARDIAC hypertrophy generally has been considered one of the principal long-term mechanisms of compensation for cardiac stress; the increase in cardiac mass is believed to make the heart as strong a pump as it had been previously. It is known that the increase in contractile strength which follows hypertrophy is due to an increase in muscle mass and that the strength of individual muscle fibers remains unchanged or may even decrease slightly.

The influence of myocardial hypertrophy on the performance of the hypertensive heart is of particular interest because cardiac hypertrophy frequently accompanies arterial hypertension and it has been pointed out that early hypertension, in both man and animals, is associated with an increased cardiac output and signs of a hyperkinetic circulation. The relationship of the increased cardiac output to the development of cardiac hypertrophy has yet to be investigated. Recent studies which show an increased cardiac contractility during the onset of renal hypertension and the early development of cardiac hypertrophy in two forms of hypertension suggest a causal relationship between increased cardiac output and development of cardiac hypertrophy.

With the advent of refinements in microtransducer technology it has become possible to accurately measure cardiac output and arterial and venous pressures in small mammals with and without arterial hypertension and thus evaluate cardiac performance in a precise manner. Further, correlation of hemodynamic alterations with biochemical changes which characterize the type of hypertrophy should open the way for a better understanding of cardiac mechanics. To our knowledge this has not been attempted before in hypertensive heart disease, nor is there direct information on the effects of cardiac hypertrophy on ventricular function curves (see Reference 15 for review). We therefore studied the functional link between the appearance of cardiac hypertrophy and the performance of the heart in rats with chronic renal hypertension.

Methods

We performed experiments on 20 normal Wistar rats and on 14 rats with sustained renal hypertension (average duration, 9 weeks; range, 6–22 weeks). All data presented are expressed as mean ± SE, unless stated otherwise for a specific value.

Hypertension was produced by placing a silver clip with a 0.20-mm gap around the left renal artery; the contralateral kidney was left untouched. The rats were 10 weeks old at the time of constriction and average weight was 244 ± 11 g. All rats were housed in cages (6 × 9 × 18 inches), four to six rats per cage; they received a standard diet (Wayne Lab-Blox) and water ad libitum. Tail cuff pressures were measured twice weekly before and after renal artery constriction by the techneque described by Bunag et al. Rats were considered hypertensive when arterial pressure rose to 170 mm Hg and remained at or above this level for an additional 6–22 weeks. At the time of the experiments the average weight of the hypertensive rats was 357 ± 20 g and that of the unclipped rats was 411 ± 30 g (P > 0.05).

Hemodynamic studies were performed after the rats had been anesthetized with ether and quickly placed on their backs with their legs taped in an extended position. Respiration was maintained with a positive pressure respirator (Harvard Apparatus, model 681) connected to a PE 205 cannula inserted into the trachea; an air-ether mixture
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Figure 1 Drawing illustrates the position of the catheters for measurements of arterial and venous pressures and the recording of cardiac output by means of an electromagnetic flowmeter placed around the ascending aorta. On the right (from top down) are hemodynamic variables we measured: phasic aortic blood flow, left ventricular pressure, mean right atrial pressure, heart rate, stroke volume, maximal blood flow acceleration ($dF/dt$), left ventricular end-diastolic pressure, and left ventricular $dP/dt$.

Figure 2 Hemodynamic changes during acute alterations in circulating blood volume. Bleeding and reinfusion are associated with parallel changes in left ventricular end-diastolic pressure, aortic blood flow, stroke volume, blood flow acceleration ($dF/dt$), and left ventricular $dP/dt$. The cardiac function study lasted no more than 150 seconds.

(Phipps and Bird, Haley ether chamber) was connected to the intake port for maintenance of anesthesia.

Catheters were placed in the right atrium (PE 50) through a jugular vein and in the left ventricle (PE 10) through the right carotid artery. Each catheter was connected to a pair of strain gauge transducers matched for frequency response (Micron MP-15). Another catheter (PE 50) was advanced into the inferior vena cava through a femoral vein and connected to a Harvard 941 infusion pump to permit rapid withdrawal and reinfusion of blood.
TABLE 1  Hemodynamic Changes Due to Renal Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Normal rats (n = 20)</th>
<th>Renal hypertensive rats (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt (kg)</td>
<td>0.411 ± 0.030</td>
<td>0.357 ± 0.020</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>84 ± 4</td>
<td>134 ± 8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>380 ± 14</td>
<td>379 ± 10</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>100 ± 5</td>
<td>95 ± 7</td>
</tr>
<tr>
<td>Peripheral resistance [(mm Hg/ml per min) x 100]/kg</td>
<td>247 ± 16</td>
<td>423 ± 36</td>
</tr>
</tbody>
</table>

Values are means ± 1 SE of hemodynamic measurements in 20 normal rats and 14 rats with renal hypertension sustained for an average of 9 weeks (n.s. = not significant).

Cardiac output was measured with a Statham electromagnetic flow probe which was implanted around the ascending aorta by a surgical approach described previously. Zero blood flow was assumed to be the flat portion of the flow waveform; this was confirmed for each rat by arresting the heart at the termination of the experiment. Probes were calibrated with blood as previously described. The output signal from the blood flowmeter was led into an integrating circuit to compute stroke volume as a voltage step which was proportional to the area under the systolic portion of the aortic flow wave. The voltage steps were accumulated and automatically recycled every 4 seconds to compute cardiac output during this interval. Heart rate was obtained on a beat-to-beat basis by a track and hold circuit (Gould Instruments) that computes the $1/t$ period ($t$ = time interval between two consecutive beats) and converts it to rate using the pulse obtained from the first derivative of aortic blood flow. The circuitry for these analog computations, as they are used in our laboratory, has been described in detail elsewhere.

We obtained blood flow acceleration ($dF/dt$) by electronic differentiation of the aortic flow wave, using a differential amplifier with a flat frequency response to 100 Hz, as recommended by Noble. A similar differentiator was used to determine the maximum rate of rise of left ventricular pressure ($LV\ dP/dt$). This information was recorded on a rectilinear, direct-writing oscillograph (Fig. 1) with adequate frequency response (linear from 0 to 75 Hz). Peripheral resistance [(mm Hg/ml per min) per kg] was calculated arithmetically as mean arterial pressure (mm Hg) times 100 divided by cardiac output (ml/min); this quotient was corrected for body weight. Left ventricular stroke work (g·cm) was calculated from the product of stroke volume (ml) and systolic pressure (mm Hg) multiplied by 1.36 g·cm/mm Hg·cm$^3$. Right atrial pressure, aortic pressure, and aortic blood flow were measured for 30 minutes after the completion of surgery; the arterial catheter was then advanced into the left ventricle and the function curve was determined.

These studies were performed on 12 of 20 undipped rats and on 11 of 14 rats with renal artery constriction. Blood was withdrawn at a rate of 6 ml/min into a reservoir containing 4 ml of heparinized blood; the total volume was then infused at the same rate. The blood contained in the reservoir was obtained from a donor Wistar rat. Withdrawal and reinfusion lasted no more than 150 seconds (Fig. 2).

On completion of the experiment, the heart was excised and cleaned as described previously. The atria were removed and the major vessels were cut flush with the heart; the ventricles were washed, blotted dry, and weighed. The left ventricle, including the interventricular septum, was weighed after the right ventricular wall had been removed. Biochemical studies were performed on a weighed apical section of the left ventricle. The remaining section was dried to constant weight for the determination of the ratio of wet to dry weight.

Deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and hydroxyproline were measured by the techniques described by Ceriotti, Fleck and Munro, and Bergman and Loxley, respectively.

The technique employed to fit the nonlinear data from ventricular function curves are described below (see Appendix).
CARDIAC PERFORMANCE IN HYPERTENSION

showed a significant decrease [20.46 ± 5.97% (P < 0.05)] in the maximum acceleration of blood from the left ventricle (Fig. 3). Average maximum left ventricular dP/dt was essentially the same for both normotensive and renal hypertensive rats. Left ventricular dP/dt ranged from 4.8 to 17.2 mm Hg/sec² x 10⁴ for normal rats; similar values (range, 5.4-17.6 mm Hg/sec² x 10⁴) were found for rats with renal hypertension (Fig. 3). End-diastolic pressure averaged 5.9 ± 0.8 mm Hg for renal hypertensives in comparison to 4.7 ± 0.4 for normals (P > 0.05), while stroke work rose to 69.9 ± 6.9 g·cm for the hypertensives in comparison to 49.1 ± 3.2 g·cm (P < 0.005).

CARDIAC PERFORMANCE IN RENAL HYPERTENSIVE RATS

Pressure-flow curves were obtained for 12 of the 20 normal rats and 11 of the 14 rats with renal hypertension by

Results

HEMODYNAMIC CHARACTERISTICS OF LONG-TERM RENAL HYPERTENSION IN RATS

Arterial pressure and cardiac output were measured 30 minutes after thoracotomy and placement of the flow probe in 20 normal rats and in 14 rats with sustained renal hypertension [BP = 206 ± 5 (mean ± se) mm Hg] of an average duration of 9 weeks. Stroke volume, heart rate, and cardiac output of the hypertensive rats were similar to those of unclipped rats (Table 1). After the chest had been opened, mean arterial pressure in rats with renal hypertension averaged 134 ± 8 mm Hg (P < 0.001) and calculated average peripheral resistance was 423 ± 36 [(mm Hg/ml per min) per kg] (P < 0.001). In normal rats, arterial pressure averaged 84 ± 4 mm Hg and peripheral resistance was 247 ± 16 [(mm Hg/ml per min) per kg] (Table 1).

In comparison to normotensive rats, hypertensive rats

FIGURE 4 Computer plots of data points for stroke volume vs. left ventricular end-diastolic pressure (LVEDP) in 12 normotensive rats (top panel) and 11 rats with sustained renal hypertension. Plot for hypertensive rats (bottom) shows a greater scatter of data points distributed along the nonlinear regression line; coefficients and F value are documented in Table 2.

FIGURE 5 Relationship of cardiac output as a function of left ventricular end-diastolic pressure (LVEDP). When compared to normotensive rats, renal hypertensive rats exhibit: (1) a decrease in cardiac output for the same values of end-diastolic pressure, and (2) an inability to either maintain or increase cardiac output at end-diastolic pressures higher than about 12 mm Hg. Coefficients for the cubic polynomial are documented in Table 2.
plotting the instantaneous changes in stroke volume, cardiac output, and stroke work as a function of left ventricular end-diastolic pressure; we and others have chosen this as an estimate of mean cardiac filling pressure. Data, as illustrated in Figures 4, 5, and 6, were determined at 10-second intervals throughout each study; none lasted more than 150 seconds. These scattergrams showed an initial steep rise at low filling pressures and then flattened off to a plateau with little or no decline at the higher end-diastolic pressures in normal rats but not in rats with renal hypertension. The shape of the curves precluded the use of linear regression to characterize this physiological relationship. Thus, the significance of the regression coefficients describing the best fit of the data and the statistical differences between normal and hypertensive rats are based on a polynomial of third order as denoted in Table 2. The statistical bases for this analysis are detailed in the Appendix.

The effects of altering cardiac inflow on the volume of blood ejected by the hearts of normal and renal hypertensive rats are illustrated in Figures 4 and 5. When compared to hearts of normal rats, the hearts of hypertensive rats (1) exhibited an ascending limb with a greater scatter of points relating stroke volume and cardiac output to end-diastolic pressures, and (2) at pressures greater than about 10 mm Hg, appeared unable to eject a volume of blood as great as that ejected by hearts of normotensive rats. These two factors were responsible for both a significant shift of the curve for hypertensive rats along the left ventricular pressure axis and a decrease in the plateau values obtained during loading with blood (P < 0.001, Table 2).

This effect of hypertension on cardiac performance is more easily understood when values for cardiac output are plotted at increments of 4 mm Hg in left ventricular end-diastolic pressure (Fig. 7) for the pooled data from the two groups. Treatment of the data in this manner shows that as left ventricular end-diastolic pressure rises from 2.0 to about 10.0 mm Hg, significantly lesser (P < 0.001) quantities of blood are delivered into the systemic circulation by the hypertrophied heart. In addition, plateau values for cardiac output are below those measured in normotensive rats at matched left ventricular end-diastolic pressures. At end-diastolic pressures greater than 16.0 mm Hg, cardiac output falls sharply in a manner reminiscent of a descending limb and suggestive of the development of acute ventricular dilation and cardiac failure. A descending limb could not be obtained at these higher rates of venous inflow in normotensive rats, despite loading with equal amounts of blood. Although cardiac function curves were not determined for rats under various constant pressure loads, the lack of significant differences between groups in left ventricular systolic pressures (Table 3) and stroke work as a function of left ventricular end-diastolic pressure (Fig. 6 and Table 2) further supports the existence of a stage of depressed myocardial performance in hypertension of long duration.

Finally, the reduction in cardiac output during both the ascending and plateau portions of the curve in rats with renal hypertension seems not to be dependent on differences in cardiac rate and autonomic drive. Normal and hypertensive rats responded to the variations in venous return with comparable changes in both pressures and heart rate (Table 3).

**BIOCHEMICAL CHARACTERIZATION OF MYOCARDIAL HYPTERTROPHY DUE TO RENAL HYPERTENSION**

In the hypertensive group the ratio of heart weight to body weight was significantly above values for rats without renal artery constriction; the former averaged 3.70 ± 0.10 mg/g compared to 2.57 ± 0.06 mg/g for the latter (P < 0.001) (Fig. 8). In rats with renal hypertension the ratio of dry weight to wet weight averaged 0.260 ± 0.020; in normal rats it averaged 0.300 ± 0.010 (0.05 > P > 0.025). Thus, the larger myocardial mass probably reflects a proportionally greater increase in contractile material than does tissue water.

In hypertrophied hearts DNA concentration fell and RNA content rose (Table 4). A 2-fold increase in myocardial hydroxyproline content also was found, indicating the presence of increased collagen and elastin. Since the pre-
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TABLE 2  Nonlinear Regression Analysis of Left Ventricular Function in Normal Compared to Hypertensive Rats

<table>
<thead>
<tr>
<th></th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.0430 ± 0.0470</td>
<td>0.0190 ± 0.0540</td>
</tr>
<tr>
<td>Linear term</td>
<td>0.0644 ± 0.0063</td>
<td>0.0509 ± 0.0059</td>
</tr>
<tr>
<td>Quadratic term</td>
<td>-0.0040 ± 0.0009</td>
<td>-0.0025 ± 0.0006</td>
</tr>
<tr>
<td>Cubic term</td>
<td>0.0001 ± 0.0001</td>
<td>0.0001 ± 0.0001</td>
</tr>
<tr>
<td>r</td>
<td>0.89</td>
<td>0.85</td>
</tr>
<tr>
<td>F</td>
<td>30.43</td>
<td>21.43</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± 1 SE of coefficients describing the relationship between stroke volume (SV), cardiac output (CO), and stroke work (SW) as a function of left ventricular end-diastolic pressure (LVEDP) in 12 normotensive and 11 rats with renal hypertension. When compared to normotensive rats, hypertension results in a significant depression of cardiac performance for the relationships of both stroke volume and cardiac output to end-diastolic pressure. There are no significant differences in the polynomial function of stroke work to ventricular filling pressure (r = correlation coefficient; n.s. = not significant).

dominant source of hydroxyproline is collagen, we calculated the 2% of the increase in heart weight could be accounted for by increased connective tissue.

Discussion

These experiments demonstrate the feasibility of investigating the performance of the left ventricle in small mammals, such as the rat, by the use of a time-honored technique that describes the ability of the heart to perform as a pump. This simple analysis of ventricular function was proposed by Patterson and Starling in 1914; the applicability and limitation of the method have been documented extensively.

The advent of miniaturized transducers for the reliable measurement of blood flow and pressures enabled us now to apply this technique to compare cardiac performance in situ in rats with and without renal hypertension. It is pertinent to recognize the benefits and limitations of this technique: the effect of opening the thoracic cavity imposes certain restrictions; these were not considered to unduly influence interpretation of the results. Pfeffer and Frohlich have shown that ether anesthesia exerts less of a depressant effect on cardiovascular function than other commonly employed anesthetic agents. To avoid gross hemodilution during cardiac loading, blood was used instead of plasma expanders or saline. Aside from physiological considerations, accurate measurements of blood flow with an electromagnetic flowmeter are precluded by variations in the viscosity of blood and in the hematocrit.

Left ventricular function commonly has been determined in mammals by one of two different procedures: in one, aortic pressure is allowed to change without constraint; in the other, a Starling resistor fixes the afterload at a constant value. In our preparation no attempt was made to keep the afterload constant, since we were interested in evaluating cardiac performance in a system which closely mimics the intact circulation. Although marked variations in cardiac function can occur in response to different conditions of afterload, recent evidence suggests that the left ventricle is able to maintain stroke volume during increased afterload up to a left ventricular end-diastolic pressure of about 40 mm Hg; the implication of these findings have been reviewed by Ross and Sobel. Further, Guyton et al. indicated that cardiac function curves obtained for the entire

Figure 7  Cardiac output and left ventricular end-diastolic pressure (LVEDP) were averaged at increments of 4 mm Hg in end-diastolic pressure. Hypertensive rats exhibited a decreased slope in the ascending limb of the cardiac function curve and the appearance of a descending limb at higher end-diastolic pressures, suggesting a decrease in ventricular compliance.
heart-lung compartment are very insensitive to changes in afterload. We believe that after proper consideration of the limitations imposed by the method, the technique allowed reasonable description and comparison of cardiac function in hypertension.

Our experiments indicate that renal hypertension which is sustained for an average of 9 weeks is associated with a significant decrease in cardiac performance. The ascending limb of the function curve for cardiac output in hypertensive rats suggested this conclusion; it was further confirmed by the more elaborate and definitive comparison of cardiac function curves by use of nonlinear polynomials. Significant differences in cardiac function were demonstrated for stroke volume and cardiac output as a function of the independent variable, left ventricular end-diastolic pressure. There were, however, no significant differences in stroke work between normotensive rats and rats with renal hypertension. Even at matched end-diastolic pressures the increase in left ventricular mass of the hypertensive rats was not accompanied by a greater stroke work. Further, stroke volume and cardiac output of hypertensive rats actually fell with loading. The reduction in output at high end-diastolic pressures did not occur in any of the normotensive rats. Thus, overloading could demonstrate a depression of cardiac performance when differences in resting hemodynamics suggested only a slight impairment and no evidence of decompensation.

These results are in agreement with observations on hypertensive patients. For example, cardiac output is increased in young spontaneously hypertensive rats during the onset of experimental renal hypertension, and in patients with borderline essential hypertension. With more prolonged hypertension cardiac output appears to return to normal; the elevation in pressure is associated with an augmented peripheral resistance. Thus, it is possible to suggest that the decrease in cardiac output which occurs as hypertension becomes sustained may be related to an inability of the ventricle to maintain a stroke volume even in the presence of an elevated end-diastolic pressure. Thus, depression of cardiac performance is particularly important because it might become the limiting factor in the cardiovascular adjustment to sustained hypertension. This alternative has not received consideration previously.

Cardiac output and the maximum value to which cardiac output could be raised by a 5-minute infusion of polyvinylpyrrolidone (PVP) was studied by Beznak in rats with aortic coarctation of 1 to 21 days' duration. She concluded that cardiac hypertrophy was accompanied by a significant increase in cardiac reserve. However, the long duration of the infusion and the use of a plasma expander probably were inappropriate; the changes in peripheral resistance and vasomotor activity that could result from altered hematocrit can greatly influence the maximum value to which cardiac output is raised. On the other hand, Geha et al. found no appreciable difference in maximal right ventricular work in conscious dogs with and without pulmonary artery stenosis. Unfortunately the use of sympathomimetic amines as the stimuli to assess ventricular performance did not take into consideration possible changes in sensitivity of the hypertrophied myocardium to adrenergic agents. In contrast with the foregoing studies, Spann et al. concluded that myocardial contractility is depressed when cardiac hypertrophy is present; this finding is in accord with the results of our present experiments and the data reviewed by Ross and Sobel.

Although the precise cause of this diminished cardiac function is unclear, it appears that it could be due to structural changes in the myocardium, such as increased wall thickness, as well as functional changes, such as altered myofibrillar arrangement and decreased myofibrillar cross-bridge activity. Additionally, changes in the extracellular matrix, such as increased collagen deposition, may contribute to the reduced contractility.

The data presented in this study suggest that renal hypertension is associated with a significant decrease in cardiac performance. Further research is needed to determine the specific mechanisms responsible for this decrease and to develop strategies to prevent or reverse the associated cardiovascular dysfunction.
The studies of Meerson et al. 40 show a decrease in the number of muscle nuclei per unit of myocardial area; this led them to conclude that there were insufficient amounts of DNA for adequate protein renewal. This also may imply that insufficient amounts of DNA for adequate renewal of cellular protein leads to a depression in contractile force. Although further clarification of the anatomical changes. The studies of Meerson et al. 40 show a decrease in the number of muscle nuclei per unit of myocardial area; this led them to conclude that there were insufficient amounts of DNA for adequate protein renewal. This may imply that the increased volume of myocardial cells is a result of increased RNA synthesis and increased protein synthesis, and in particular the heavy and light chains of myosin.

Associated with changes in DNA and RNA there was a 2-fold increase in total myocardial hydroxyproline content, a change indicative of increased collagen synthesis. Grove et al. 44 reached a similar conclusion; rats with supravalvular aortic stenosis exhibited an increase in the total amount and concentration of hydroxyproline that was coincident with proliferation of connective tissue cells during the development of cardiac hypertrophy. In rats with aortic coarctation, Meerson et al. 46 showed that a significant increment in connective tissue cells kept pace with the associated enlargement of myocardial cells. This increase in noncontractile fibrous tissue may be a potent factor in altering cardiac structure that leads to a decrease in ventricular compliance and depression of cardiac performance. The finding that there is an increase in end-diastolic pressure of hypertensive hearts needed to provide the same stroke volume as in normal rats suggests that ventricular compliance is indeed decreased. Also in accord with this interpretation are the findings of Grossman et al. 48 who recently have shown that in patients with chronic pressure overload there is an increased intrinsic stiffness of the left ventricular chamber.

Exact determination of myocardial contractility is notoriously difficult. It probably would be unwise to interpret the diminished overall cardiac performance found in rats with renovascular hypertension as incontrovertible evidence of diminished cardiac contractility. However, our combined biochemical and hemodynamic approach allows a better understanding of the alteration in cardiac performance which is associated with hypertrophy. Further studies in animals with total autonomic blockade should aid in evaluating more precisely the role of adrenergic influences in causing the observed differences in cardiac function curves between normotensive rats and those with renovascular hypertension.

Appendix

The nonlinear data depicted on the scattergrams of Figures 4, 5, and 6 can be characterized by the use of either an exponential 27 or polynomial equation. Both techniques have been applied to the analysis of function curves relating cardiac output to end-diastolic pressure. In the present experiments we chose to express those data as a linear combination of powers of the independent variable, left ventricular end-diastolic pressure, because it allowed for (1) the unbiased estimation of the functions, and (2) the direct statistical comparison of two or more populations. 44 Fit of the data from either normotensive or hypertensive populations to successively higher power polynomials indicated that terms beyond the third power ($X^3$) did not contribute significantly to the estimate. Thus, in all calculations depicted in Table 2 a cubic polynomial was used.

Linear regression analysis on cubic polynomials describing either stroke volume (SV), cardiac output (CO), or stroke work (SW) in terms of left ventricular end-diastolic pressure (LVEDP) were calculated for the normotensive, hypertensive, and the combination of these two populations.

The analysis gave three equations of the form:

\[ Y = a_0 + a_1 \cdot LVEDP + a_2 \cdot LVEDP^2 + a_3 \cdot LVEDP^3 \]

where $Y$ is either SV, CO, or SW and $n$ = normotensive rats, $h$ = hypertensive rats, and $c$ = the combination of both. Implicit in Equation 1 is a restriction of the independent variable (LVEDP) to its range within the respective sample populations.

The demonstration that there are significant differences between the normotensive and hypertensive groups is based on preliminary assumption of identity of these groups. Under this assumption the three regression curves should be

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
 & Myocardial DNA & & Myocardial RNA & & Myocardial hydroxyproline \\
 & Content (mg) & Concentration (mg/g) & Content (mg) & Concentration (mg/g) & Content (mg) & Concentration (mg/g) \\
\hline
Normotensives ($n = 11$) & 1.97 $\pm$ 0.07 & 2.21 $\pm$ 0.10 & 2.73 $\pm$ 0.10 & 3.05 $\pm$ 0.09 & 0.65 $\pm$ 0.04 & 0.72 $\pm$ 0.03 \\
Hypertensives ($n = 14$) & 2.47 $\pm$ 0.11 & 1.86 $\pm$ 0.05 & 4.36 $\pm$ 0.23 & 3.27 $\pm$ 0.12 & 1.30 $\pm$ 0.20 & 0.93 $\pm$ 0.09 \\
$P$ & $<0.005$ & $<0.005$ & $<0.005$ & (<n.s.) & $<0.01$ & $<0.05$ \\
\hline
\end{tabular}
\caption{Differences in the Biochemical Correlates of Cardiac Hypertrophy in Wistar Rats}
\end{table}

Myocardial DNA, RNA, and hydroxyproline content and concentration determined from an apical section of the left ventricle in rats with and without renal hypertension. Content is expressed as total amount (milligrams) as measured in the apical section and extrapolated to the whole heart. Concentration is expressed as amount per gram of myocardial tissue.
roughly coincident; thus, the error sum of squares (SSEC) about the common regression should not be significantly different from the sum of error sums of squares (SSSEI) about the individual regressions.

Where:

\[
SSEC = \sum (\hat{Y} - Y)^2
\]

\[
\hat{Y} = \text{predicted values of dependent variable}
\]

\[
Y = \text{observed values of dependent variable}
\]

\[
c = \text{denotes common regression}
\]

and:

\[
SSSEI = \sum (\hat{Y}_n - Y_{in})^2 + \sum (\hat{Y}_h - Y_{ih})^2
\]

If the normotensive and hypertensive populations were distinct, it would then be expected that the individual curves would be displaced somewhat from the common regression which would lie between them. As a result of the large error, terms arising from one regression attempting to approximate two distinct populations SSEC will be relatively inflated. On the other hand, SSSEI will be relatively small, since the individual regression curves need fit only their respective populations. Thus, the quantity SSEC minus SSSEI is an index of the dissimilarity of the populations.

According to Smillie, if the error variances of the regressions on the individual population are similar, the statistic

\[
F = \frac{(SSC - SSSEI)(N - 4)}{SSSEI(N - 8)}
\]

\[N = \text{sum of points in individual populations.}\]

has an F distribution with 4 and \(N - 8\) degrees of freedom. This statistic is used to test the hypothesis of identity of the normotensive and hypertensive groups. The large value for \(F\) shown in Table 2 demonstrated significant differences between the hypertensive and normotensive populations.

References


13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45.
Cardiac performance in rats with renal hypertension.
D B Averill, C M Ferrario, R C Tarazi, S Sen and R Bajbus

doi: 10.1161/01.RES.38.4.280

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

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