Cardiac Pumping Ability Following Reversal of Hypertrophy and Hypertension in Spontaneously Hypertensive Rats

MICHELLE M. SPECH, B.S., CARLOS M. FERRARIO, M.D., AND ROBERT C. TARAZI, M.D.

SUMMARY Direct measurements of arterial pressure, stroke volume (SV), and cardiac output (CO) were obtained in ether-anesthetized rats with established spontaneous hypertension (SHR) treated with \( \alpha \)-methyldopa and compared to both untreated hypertensive and normotensive Wistar-Kyoto (WKY) rats. Left ventricular pumping ability was determined by the maximum levels of SV and CO reached during rapid intravenous volume loading with blood. Treatment with methyldopa reduced the SHR arterial blood pressure (average 57 mm Hg) and reversed the cardiac hypertrophy toward normal. In comparison to untreated SHR, therapy increased heart rate and CO and decreased peripheral resistance. During volume-loading, the levels of SV and CO at matched left ventricular end-diastolic pressures were significantly higher in treated vs untreated SHR. To evaluate the role of blood pressure in the improved peak pumping ability observed in treated rats, a phenylephrine infusion was used to equalize pressures while repeating cardiac function studies. In normotensive WKY and untreated SHR, left ventricular pump function was not greatly affected. A pronounced depression in peak SV and peak CO was observed only in treated SHR. The data indicate that treatment with methyldopa is associated with improved ventricular function in part related to the reduction in arterial pressure.

(Hypertension 2: 75-82, 1980)

KEY WORDS arterial pressure • cardiac output • genetic hypertension • methyldopa • cardiac hypertrophy • reversal of cardiac hypertrophy • left ventricular function

The development of concentric cardiac hypertrophy in arterial hypertension is believed to represent a physiological adaptation of the heart whereby normal cardiac output (CO) is maintained in the presence of an increased pressure load. However, a number of reports have failed to demonstrate a stable stage of ventricular function following the development of hypertension and cardiac hypertrophy. Pfeffer et al. observed a rough association between duration of hypertension and decreased pump performance in rats with spontaneous hypertension (SHR). Averill et al. showed the presence of left ventricular dysfunction in Wistar rats with renovascular hypertension of 9 to 22 weeks' duration.

Before the development of antihypertensive agents, cardiac dilatation and failure were primary complications of untreated hypertension. This suggests a progressive encroachment on cardiac function by hypertension. Depressed contractility ensues as the Frank-Starling mechanism, the development of cardiac hypertrophy and dilatation, and endogenous adrenergic stimulation are all maximally utilized. Therefore, it was considered important to determine whether medical control of the hypertensive process (i.e., reduction of blood pressure and reversal of cardiac hypertrophy) alters the ultimate deterioration of myocardial function in the rat with genetic hypertension. For this purpose, the ability of the left ventricle to pump blood was assessed in SHR after hypertension was controlled by \( \alpha \)-methyldopa treatment. This drug was selected since it is the only one reported to date that both reverses cardiac hypertrophy and lowers blood pressure.

Methods

Studies were performed on 49 male SHR of Okamoto-Aoki strain (Charles Rivers, NJ) ranging in age from 17 to 29 weeks after they had been given \( \alpha \)-methyldopa for either 3 weeks (Group 1: 17 rats) or 6 weeks (Group 2: 32 rats). For hypertensive and normotensive controls, 23 untreated age-matched SHR and 17 Wistar-Kyoto (WKY) rats (Taconic Farms, NJ) were used. All animals were housed two or three in a cage, handled in exactly the same way, and fed a standard pellet diet (Teklad Rat Chow).

Therapeutic Regime

For at least 2 weeks preceding onset of treatment with methyldopa, and throughout the duration of therapy, the systolic blood pressure of SHR was measured twice weekly by a tail-cuff method as

From the Research Division, Cleveland Clinic Foundation, Cleveland, Ohio.

This work was supported by a grant from the Whitaker Foundation and Grant HL-15837 from the National Heart, Lung, and Blood Institute.

Address for reprints: Carlos M. Ferrario, M.D., Research Division, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106.

Received January 19, 1979; revision accepted August 9, 1979.
described by Williams et al. Powdered α-methyldopa (Aldomet, Merck Sharpe & Dohme, Rahway, NJ) was dissolved in deionized water and given in lieu of normal drinking water for either the 3- or 6-week period of treatment. Although the initial concentration was about 2.5 g/liter, it was necessary to raise the dosage to between 3.0 and 5.0 g/liter to overcome drug tolerance. The sole criterion for the increase in drug concentration during treatment periods was maintenance of systolic blood pressure at or near normotensive levels.

Hemodynamic Studies

On the day of the experiment, rats were anesthetized with ether, and direct hemodynamic measurements were obtained using techniques we have described previously. Briefly, animals were mechanically respirated with a rodent respirator (model 681, Harvard Apparatus, Millis, MA) via a cannula (PE-205, Clay Adams, NJ) inserted into the trachea. Positive end-expiratory pressure was maintained by submerging the outflow line of the respirator under 2-3 cm of water. Arterial, left ventricular, and right atrial pressures were obtained by way of catheters placed via the right carotid artery (PE-10) and jugular vein (PE-50) respectively. Catheters were connected to solid-state micro strain gauge transducers (MP-15 and MP-17, Micron Inc., Los Angeles, CA) matched for frequency response. The fluid-filled catheter transducer system has a natural resonant frequency of 83 Hz and a damping coefficient of 0.57. An additional catheter (PE-50) was advanced from a femoral vein into the inferior vena cava for blood infusions. Aortic blood flow was measured with an electromagnetic flow transducer placed around the ascending aorta (SP-2202 Gould, Inc., Statham Division, Oxnard, CA). Zero aortic blood flow was defined as the flat portion of the flow curve at the end of the diastolic period; its accuracy was confirmed after cessation of cardiac activity at the end of the experiment. The electrical signal from the flowmeter was fed into an analog integrator (model 4307-05, Gould Inc., Cleveland, OH) to obtain beat-by-beat values of stroke volume, and into a tachometer (model 4307-13, Gould Inc., Cleveland, OH) to obtain a beat-by-beat display of heart rate. The electronic circuitry employed in the experiments has been described previously. Peripheral vascular resistance was calculated as the ratio of mean arterial pressure (mm Hg) to cardiac output (ml/min) times 100.

Baseline hemodynamic values were recorded for a minimum of 10 minutes following completion of all surgical manipulations and after the animals were judged to be in a steady-state level of anesthesia. The aortic catheter was then advanced into the left ventricle to record left ventricular systolic and end-diastolic pressures.

Preload Stress

Acute increases in venous return were produced by infusion of heparinized blood, obtained from a donor WKY rat, at a rate of 10 ml/min for 60 seconds. Corresponding changes in pressure, stroke volume (SV), and CO were continuously recorded throughout the infusion period (fig. 1). The time course of the changes in these hemodynamic variables during blood volume expansion were analyzed by dividing the period of infusion into 20 intervals of 3-second duration and averaging the values from five consecutive beats at the start of each interval. Changes in SV and

FIGURE 1. Tracings illustrating hemodynamic changes in aortic blood flow, left ventricular and right atrial pressures, heart rate, left ventricular end-diastolic pressure and stroke volume produced by a 1-minute infusion of blood in an untreated spontaneously hypertensive rat.
CO were then plotted along the entire range of end-diastolic pressures to ascertain both the rate of change and peak values.

Pressure-Load Stress

In 13 of the 32 rats of Group 2 (6 weeks of treatment), in 8 of 23 untreated SHR, and in 7 of 17 WKY rats, cardiac function studies were obtained after their arterial pressures were further elevated by a continuous intravenous infusion of phenylephrine hydrochloride (40 μg/ml, Neo-Synephrine, Winthrop Laboratories, NY). Infusion rates were adjusted (range: 0.07–0.10 ml/min) to raise and maintain left ventricular systolic blood pressures between 145 and 165 mm Hg throughout the cardiac function study. Preliminary experiments aided in determining a final concentration and rate that kept the volume infused at a minimum.

Determination of Heart Weight and Statistical Significance

At the completion of all experiments, the heart was carefully removed and cleaned. All major vessels were cut flush with the surface, and the total heart wet weight was determined. The atria were then cut free to obtain total ventricular weight. Left ventricular weight was also determined after removal of the free right ventricular wall, leaving the interventricular septum intact.

The Student's t test for either paired or unpaired data was used in the statistical evaluation. Differences at the 95% level were considered statistically significant.

Results

Figure 2 illustrates the effect of methyldopa on the elevated blood pressure in SHR. Prior to commencing treatment, systolic tail-cuff blood pressures were at a hypertensive level of 172 ± 13 (SD) and 184 ± 12 mm Hg in Group 1 (3 weeks) and Group 2 (6 weeks) respectively. The hypotensive response following methyldopa treatment was relatively immediate and not enhanced by extending the treatment period. The pooled values of tail-cuff blood pressures averaged throughout were virtually the same, being 157 ± 4 (se) and 153 ± 4 mm Hg for both Groups 1 and 2 respectively. In 23 untreated hypertensive rats, systolic blood pressure continued to rise from 168 ± 3 to 204 ± 2 mm Hg during the 6-week period of observation. In comparison, final tail-cuff pressures in the treated groups averaged 147 ± 4 and 146 ± 3 mm Hg by 3 and 6 weeks. These differences were statistically significant (p < 0.001) from control levels.

Following induction of anesthesia and insertion of catheters, but before thoracotomy, untreated SHR had a direct mean arterial pressure of 128 ± 7 mm Hg, while treated animals in Groups 1 and 2 averaged 85 ± 5 and 78 ± 2 mm Hg respectively. In WKY normotensive controls, mean arterial pressure averaged 76 ± 6 mm Hg.

Post-thoracotomy baseline hemodynamic levels in treated and untreated SHR, and WKY controls are detailed in table 1. The hypotensive effect of methyldopa was associated with a significant fall in peripheral resistance of about the same magnitude whether therapy was carried out for 3 or 6 weeks; however, peripheral resistance remained significantly increased when compared to the values recorded in WKY normotensive controls. Treated animals displayed mild tachycardia and a slight, but statistically significant, increase in cardiac output from the subnormal values measured in untreated SHR. When compared to normotensive WKY rats, treatment with methyldopa at a dose sufficient to normalize arterial
blood pressure caused only partial improvement of their basal hemodynamics in terms of cardiac output and total peripheral resistance (table 1). Prolonged control of blood pressure with methyldopa was accompanied by decreases of cardiac weight/body weight values. Table 2 shows these decreases. Methyldopa treatment produced a 9% (3 weeks) to 11% (6 weeks) decrease in the left ventricular weight/body weight ratio. While these decreases in left ventricular weight were statistically significant, there remained a statistically significant difference. Right ventricular weight was substantially decreased (table 2).

### Table 1. Effect of Methyldopa on the Hemodynamics of SHR

<table>
<thead>
<tr>
<th></th>
<th>SHR</th>
<th>Group 1</th>
<th>Group 2</th>
<th>WKY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic (mm Hg)</td>
<td>140</td>
<td>106</td>
<td>105</td>
<td>107</td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>= 2.3</td>
<td>= 1.8</td>
<td>= 2.9</td>
<td>= 3.2</td>
</tr>
<tr>
<td>Heart rate (b/min)</td>
<td>= 357</td>
<td>= 447</td>
<td>= 423</td>
<td>= 396</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>= 0.15</td>
<td>= 0.15</td>
<td>= 0.15</td>
<td>= 0.30</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>= 54</td>
<td>= 66</td>
<td>= 65</td>
<td>= 117</td>
</tr>
<tr>
<td>Peripheral resistance (units/kg)</td>
<td>= 145</td>
<td>= 99</td>
<td>= 96</td>
<td>= 52</td>
</tr>
</tbody>
</table>

Values are mean ± se for untreated SHR, SHR treated for 3 weeks (Group 1) and 6 weeks (Group 2), and WKY controls. The p values denote statistical difference from untreated SHR. Symbols denote difference from WKY controls (*, t, t) and between Groups 1 and 2 (§); p values are as follows: * = p < 0.001; t = p < 0.01; § = p < 0.05. n.s. = not significant.

### Table 2. Cardiac Weights After Reversal of Hypertrophy

<table>
<thead>
<tr>
<th></th>
<th>Untreated SHR (n = 23)</th>
<th>Treated SHR Group 1 (n = 17)</th>
<th>Treated SHR Group 2 (n = 32)</th>
<th>Wistar-Kyoto (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart weight (g)</td>
<td>1.27 ± 0.03</td>
<td>0.96 ± 0.02†</td>
<td>0.99 ± 0.01†</td>
<td>1.05 ± 0.02</td>
</tr>
<tr>
<td>Heart wt/body wt (g)</td>
<td>3.64 ± 0.04</td>
<td>3.39 ± 0.06</td>
<td>3.29 ± 0.03</td>
<td>3.20 ± 0.07</td>
</tr>
<tr>
<td>Ventr weight (g)</td>
<td>1.17 ± 0.03</td>
<td>0.88 ± 0.02</td>
<td>0.91 ± 0.01</td>
<td>0.95 ± 0.02</td>
</tr>
<tr>
<td>Ventr wt/body wt (mg/g)</td>
<td>3.38 ± 0.03</td>
<td>3.11 ± 0.05‡</td>
<td>3.02 ± 0.02‡</td>
<td>2.91 ± 0.06</td>
</tr>
<tr>
<td>Lt ventr wt (g)</td>
<td>0.92 ± 0.02</td>
<td>0.68 ± 0.02</td>
<td>0.71 ± 0.01</td>
<td>0.73 ± 0.02</td>
</tr>
<tr>
<td>Lt ventr wt/body wt (mg/g)</td>
<td>2.64 ± 0.03</td>
<td>2.41 ± 0.05†</td>
<td>2.34 ± 0.02†</td>
<td>2.23 ± 0.05</td>
</tr>
<tr>
<td>Rt ventr wt (g)</td>
<td>0.26 ± 0.01</td>
<td>0.20 ± 0.01</td>
<td>0.20 ± 0.01</td>
<td>0.22 ± 0.01</td>
</tr>
<tr>
<td>Rt ventr wt/body wt (mg/g)</td>
<td>0.74 ± 0.02</td>
<td>0.68 ± 0.01</td>
<td>0.67 ± 0.01</td>
<td>0.67 ± 0.02</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>347 ± 8</td>
<td>283 ± 5*</td>
<td>301 ± 3*§</td>
<td>327 ± 6</td>
</tr>
</tbody>
</table>

Values are mean ± se heart weights of spontaneously hypertensive rats, both untreated and methyldopa-treated for 3 weeks (Group 1) and 6 weeks (Group 2), and WKY controls. The p values denote statistical difference from untreated SHR. Symbols denote difference from WKY controls (*, †, §) and between treated groups [§]. * = p < 0.001; † = p < 0.01; ‡ = p < 0.05; § = p < 0.005.
both 3 and 6 weeks of methyldopa treatment as indicated by the upward shift of the function curves. Since changes in pump performance were essentially the same for 3 or 6 weeks, the data for both groups are combined. Individual results are shown in table 3. At an end-diastolic pressure of about 15 ± 0.1 mm Hg the maximum SV and CO of treated rats exceeded the values obtained in untreated SHR controls by 17% and 38% respectively. During the preload stress, normotensive WKY rats reached a slightly higher level of SV (p < 0.02) and CO than treated SHR (table 3). Although the peak CO between control WKY and treated SHR was not statistically different at 3 weeks, at 6 weeks it was, probably because of the smaller size of the standard error and larger degree of freedom.

Pressure Load Stress

The finding of increased cardiac pumping ability under circumstances of reduced arterial pressure and reversal of cardiac hypertrophy led us to examine the effect of acute increases in arterial pressure on pump performance. The findings are illustrated in figure 4 where for each group studied the average peak CO at the plateau of the function curve is plotted as a function of left ventricular systolic pressure. The arrows point to the direction of the change in performance as a result of increasing arterial pressure with phentylephrine. In normotensive WKY, peak cardiac pumping ability averaged about 155 ± 4 ml/min at a systolic pressure of about 120 ± 2 mm Hg. When the preload stress was obtained with systolic pressure held at 149 ± 3 instead of 120 mm Hg, peak cardiac pumping ability fell by an average of 12% (p < 0.025). A much more pronounced depression in ventricular performance, amounting to 26% (p < 0.001), was noted following elevation of the pressure load from 135 ± 3 to 148 ± 3 mm Hg in treated SHR. When these small ventricles were forced to pump at hypertensive levels, their peak CO was not different from the depressed performance recorded in untreated SHR. In contrast, no further depression (p > 0.05) in pumping ability occurred as a result of increasing arterial pressure in untreated SHR from 153 ± 7 to 165 ± 4 mm Hg.

| Table 3. Differences in Left Ventricular Performance at Plateau Levels |
|--------------------------|---------------------|-----------------|-----------------|
| Systolic blood pressure | Untreated SHR       | Treated SHR     | Wistar-Kyoto   |
| (mm Hg)                 | 151 ± 4             | 145 ± 2*         | 116 ± 3         |
| Heart rate              | 295 ± 4             | 361 ± 5*         | 323 ± 10        |
| (b/min)                 | p < 0.001           | p < 0.001        | p < 0.001       |
| Stroke volume           | 0.35 ± 0.01         | 0.40 ± 0.01*     | 0.46 ± 0.01     |
| (ml)                    | p < 0.005           | p < 0.001        | p < 0.001       |
| Stroke index            | 0.91 ± 0.08         | 1.29 ± 0.06      | 1.40 ± 0.03     |
| (ml/kg)                 | p < 0.001           | p < 0.001        | p < 0.001       |
| Cardiac output          | 104 ± 2             | 143 ± 5          | 155 ± 1         |
| (ml/min)                | p < 0.001           | p < 0.001        | p < 0.001       |
| Cardiac index           | 294 ± 19            | 473 ± 27         | 472 ± 13        |
| (ml/min/kg)             | p < 0.001           | p < 0.001        | p < 0.001       |

Values are the mean ± SE of peak hemodynamic levels at a matched end-diastolic pressure of 15 mm Hg. p values denote statistical significance from untreated SHR. Symbols denote difference from WKY controls [*1,2] and between Groups 1 and 2[3]; p values are as follows: * = p < 0.001; † = p < 0.02; § = p < 0.001.
This very striking effect of arterial pressure on cardiac pumping ability is expressed differently in figure 5, which is a composite of the average left ventricular function curves obtained from the different groups of animals studied. Between both extremes of cardiac performance observed in normotensive-normal (WKY) and hypertensive-hypertrophied (untreated SHR) hearts, we see that maximum cardiac pumping ability is greatly influenced by the level of arterial blood pressure. While cardiac hypertrophy was equally reversed in all SHR treated with α-methyldopa, the beneficial effect of therapy in terms of improved ventricular performance was present only when these ventricles were pumping at reduced arterial pressure. Subjecting the normalized hearts of treated SHR to an acute hypertensive stimulus (phenylephrine) brought the curve down to the reduced levels present during the chronic phase of spontaneous hypertension, as illustrated by the curves that were obtained after the infusion of phenylephrine.

Discussion

The established phase of arterial hypertension in SHR is accompanied by cardiac hypertrophy, subnormal CO, and an elevated total peripheral resistance. Moreover, left ventricular performance estimated from the plateau of ventricular function curves was markedly reduced in a manner reminiscent of that observed in rats with chronic two-kidney one clip hypertension. Therapy with methyldopa for a time sufficient to normalize the elevated blood pressure of SHR was associated with a significant reversal of cardiac hypertrophy toward normal. The hemodynamic effects of methyldopa were chiefly accounted for by a reduction in peripheral resistance of essentially the same magnitude whether treatment was prolonged for either 3 or 6 weeks. Vasodilatation was accompanied by a moderate increase in CO due to tachycardia. With the exception of the increased heart rate, the hemodynamic changes associated with methyldopa treatment are similar to those reported previously in both man and experimental animals. Several investigators have used a preload stress to assess the mechanical performance of the heart and estimate cardiac reserve. The term "pumping ability" was popularized by Bishop and Stone, who also showed that in the dog the ventricular output curve is a reproducible index of performance not greatly influenced by arterial pressure. The validity and limitations of this procedure to assess pump performance in the rat have been detailed by Pfeffer et al. and Averill et al. In their studies, ventricular performance has been evaluated in terms of peak SV, CO, and stroke work. Based on the convincing
CARDIAC PERFORMANCE AFTER REVERSAL OF HYPERTROPHY/Specch et al.

arguments presented recently by Noble, we have refrained from using peak stroke work as an index of pump performance.

It was not the purpose of these experiments to evaluate the pharmacological actions of a-methyldopa in normal and spontaneously hypertensive rats. Rather, we wanted to determine what changes in mechanical ventricular performance arose as a result of reversing the course of spontaneous hypertension. A control group of normotensive WKY rats provided necessary point of reference to assess the degree of myocardial dysfunction present in the hypertensive untreated controls. In addition, the data from WKY rats enabled us to quantitate the extent of improved performance in treated SHR and the response of a normal ventricle to an increase in arterial pressure.

Mature SHR had significant hemodynamic abnormalities suggestive of depressed ventricular function despite presence of cardiac hypertrophy. These findings are compatible with the suggestion of Spann et al. and the data reported by Averill et al. in renal hypertensive rats. They indicated that pressure-induced cardiac hypertrophy does not significantly alter a downhill course of myocardial depression leading to overt heart failure. Other investigators have reached a different conclusion. In an inbred colony of SHR, Pfeffer et al. found that the stable phase of hypertension was associated with a peak CO no different from that of age-matched WKY controls. In rats with hypertension of longer duration, however, peak CO fell markedly despite further increases in cardiac weight. In comparison to their data, our findings showed that untreated SHR had a significantly reduced level of resting CO even after allowing for variations in body weight. However, there was little difference in hemodynamics between their WKY controls and ours. While there is no definitive explanation for this discrepancy, several factors may account for it. There may be some differences in the evolution of hypertension in various SHR colonies. In this respect, selective inbreeding may be desirable over commercially available sources. Thus, age alone may not be a valid criterion when comparing data among laboratories. This is of importance since Meerson has indicated that depressed cardiac performance may be a function of both duration and severity of hypertension.

Technical factors also appear to be involved. Pfeffer et al. appear to have kept their rats under light ether anesthesia and, following thoracotomy, to have applied positive end-expiratory pressure intermittently rather than throughout the study. They determined CO from a capacitance-coupled averaging circuit, a method that may overestimate CO, particularly at rapid heart rates. In addition, the averaging capacitance circuit does not take into consideration any drifts in the zero flow baseline, which would influence readings. Thus, we and others have employed an analog integrator to obtain the area under each forward aortic flow waveform and to first determine SV on a beat-by-beat basis, and then derive CO as the product of SV times heart rate. It is also known that the electromagnetic flowmeter is sensitive to decreases in the normal hematocrit. Therefore, the use of whole blood rather than Tyrode's solution during the preload stress is an added precaution in our experiments, ensuring valid and reproducible results. Use of a plasma expander may account for the fall in arterial pressure reported by Pfeffer et al. at the plateau of the function curve. In our experiments, arterial pressure either did not change or even rose moderately during the preload stress.

With regard to the mechanism(s) responsible for improved performance after antihypertensive therapy, hemodynamic factors appear to be important. This is suggested by the drastic fall in peak SV and CO observed in treated SHR when their systolic blood pressure was raised acutely to a level equivalent to that of anesthetized untreated SHR. In normotensive WKY controls, peak cardiac pumping ability fell by about 12% when systolic pressure was raised to the same level. The comparably greater depression of pump performance in treated SHR suggests a key influence of arterial pressure on pumping ability following reversal of cardiac hypertrophy.

Cohn and Franciosa have illustrated well the relationship between pump function and outflow resistance or impedance in normal and dysfunctioning hearts. Drugs such as phenylephrine decrease the compliance of the large arteries and constrict the arteriolar resistance vessels. When the left ventricle is normal, moderate increases in arterial impedance have been shown not to affect pump function greatly. This was confirmed in our WKY controls. Likewise, in untreated SHR a further, albeit small, increase in arterial pressure did not alter pump function. This indicates that the hypertrophied heart can withstand an abrupt but moderate increase in blood pressure without further debilitation of performance.

On the other hand, the marked ventricular decompensation that followed an acute rise in pressure in treated SHR poses a question regarding the state of pump performance and/or contractile properties of the myocardium after reversal of cardiac hypertrophy with methyldopa. The decline in myocardial function may be related to either one or a combination of several factors. Methyldopa may affect myocardial contractility either directly or as a result of decreasing the adrenergic drive to the heart. Alternatively, the structural influence associated with reduced pump performance may not be corrected by treatment with methyldopa. This is an attractive possibility considering that Sen et al. have shown that reversal of cardiac hypertrophy with methyldopa caused the hydroxyproline concentration present in the hypertrophied heart to increase significantly during treatment.

An increase in fibrous tissue during development of cardiac hypertrophy was considered by Averill et al. to account for the reduced ventricular performance in experimental renal hypertension. It could, therefore, be assumed that the smaller and presumably more fibrous heart of treated SHR is unable to cope with acute stresses that call for an increase in ventricular
tension to overcome an increase in impedance to left ventricular ejection. From theoretical consideration, Skelton and Sonnenblick inferred that alterations in cardiac collagen might not interfere with cardiac performance but would probably influence myocardial compliance. It is therefore possible that in our experiments ventricular compliance remained reduced following treatment with methyldopa. More direct determinations of pressure-volume curves in treated animals are needed for firm conclusions regarding the influence of increased hydroxyproline concentration in hearts with reversed hypertrophy.

In conclusion, the data indicate that the reduced global mechanical performance present during the established phase of spontaneous hypertension is improved significantly by treatment with methyldopa. This effect appears to depend, at least in part, on the less demanding job of ejecting CO at a lower arterial pressure. There remains the possibility that reversal of cardiac hypertrophy by methyldopa does not modify the structural influences responsible for decreased pump function in rats with established genetic hypertension.

References

Cardiac pumping ability following reversal of hypertrophy and hypertension in spontaneously hypertensive rats.
M M Spech, C M Ferrario and R C Tarazi

_Hypertension_. 1980;2:75-82
doi: 10.1161/01.HYP.2.1.75
_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/2/1/75

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/