Hemodynamic Response to Vascular Expansion Following Immunosympathectomy in Spontaneously Hypertensive Rats

ANTHONY F. CUTILLETTA, M.D., AND SUZANNE OPARIL, M.D.

SUMMARY Spontaneously hypertensive male rats (SHR) or normotensive Kyoto-Wistar (WKY) male rats underwent either sham or nerve growth factor antiserum (NGFAS) treatment during the first week of life. The NGFAS treatment prevented the development of hypertension in SHR but did not prevent the development of left ventricular (LV) hypertrophy. At 48 weeks of age, various parameters of LV function were measured in the four treatment groups in vivo under general anesthesia. After the recording of resting parameters, homologous whole blood was transfused until the rise in cardiac output reached a plateau. At rest, LV systolic pressure of the NGFAS-treated SHR was significantly lower than that of the sham-treated SHR and not statistically different from that of the WKY rat. The LV end diastolic pressures did not differ among the four groups. Both SHR groups had significantly lower cardiac, stroke, and contractility indices than did the WKY groups. Following vascular expansion, LV filling pressure, stroke index, and stroke work index rose in all groups. The response in the SHR was greater than that in WKY groups. Interestingly, the systolic pressure of the NGFAS-treated SHR rose to the same level as in the sham-treated SHR. Heart rate and calculated systemic vascular resistance fell following transfusion. The SHR appears to exhibit an altered response to increased filling pressure and increased afterload. Our findings are consistent with the concept of an alteration in the compliance of the LV in the SHR. (Hypertension 2: 304-310, 1980)

KEY WORDS • cardiac performance • immunosympathectomy • nerve growth factor antiserum • spontaneous hypertension • vascular expansion

P R E V I O U S studies from our laboratories have shown that treatment of spontaneously hypertensive rats (SHR) of the Okamoto strain in the first week of life with nerve growth factor antiserum (NGFAS) prevents the development of hypertension but does not prevent the development of myocardial hypertrophy and left ventricular (LV) dysfunction.1,2 In our study, ejectile parameters of ventricular performance were further depressed in the SHR after peripheral immunosympathectomy,3 suggesting that the increased sympathetic nerve activity found by others in the SHR may serve as a compensatory mechanism.3,4

We interpreted our results as evidence of a myocardial abnormality that could play a role in the pathogenesis of the hypertensive syndrome. The nature and origin of this abnormality are unclear; either predisposing genetic factors or changes in the vascular bed could be involved. In the present study we explored this hypothesis further. We subjected pentobarbital-anesthetized 48-week-old sham- and NGFAS-treated SHR and Kyoto-Wistar (WKY) rats to hemodynamic study under basal conditions and following volume expansion. Our data demonstrated that both sham- and NGFAS-treated SHR exhibited enhanced work and inotropic response to increased blood volume compared with similarly treated normotensive WKY rats.

Methods

The Okamoto strain SHR and normotensive WKY rats were bred in our laboratory from stock originally purchased from Taconic Farms, Inc. Male animals from each strain were injected with either NGFAS or saline beginning at 1 day of age and continuing until 7 days of age, as previously described.5 Four treatment groups of 10 to 12 animals each were established: saline-treated SHR, NGFAS-treated SHR, saline-treated WKY, and NGFAS-treated WKY rats. The animals were kept in group cages of six rats each for 48 weeks. An environmental light cycle of 6 a.m.
"On" to 6 p.m. "Off" was maintained. Unanesthetized tail-cuff systolic blood pressures of the four treatment groups were measured weekly beginning at 40 days of age.5

At 48 weeks of age, the animals were anesthetized with intraperitoneal injections of sodium pentobarbital (Nembutal) 40 mg/kg, ventilated with a Model 680 Harvard respirator via a tracheostomy, and subjected to hemodynamic study in situ. Details of the hemodynamic study have been previously described.6 7 Briefly, catheters were inserted into the abdominal aorta at the bifurcation of the iliacs to measure arterial pressure and into the femoral vein for transfusion of blood. The heart was then exposed through a midline sternotomy, and a square-wave electromagnetic flow probe was placed around the ascending aorta to measure cardiac output. A 22-gauge needle connected directly to a Statham P37 pressure transducer was inserted through the apex of the LV to record LV pressure. All recordings were done with a DR-16 Electronics for Medicine photographic recorder. Peak dP/dt (P 1) was measured from the dP/dt vs pressure loop. Stroke volume and peripheral vascular resistance were calculated from the heart rate, cardiac output, and mean arterial pressure. All flow related parameters were indexed to body weight. Stroke work was calculated as the product of stroke index and the difference between aortic mean and LV end diastolic pressure.

After placement of the catheters and flow probe, the animals were allowed to stabilize for 5 minutes before resting measurements were made. Five minutes after these measurements were completed, a transfusion of whole blood previously obtained from a donor rat was begun at a rate of 1.5 ml/min (table 1). Cardiac output was monitored continuously, and the transfusion continued until a plateau was reached. Hemodynamic measurements were recorded again at this time.

Following the study, the hearts were excised; the atria and great vessels were removed as was the free wall of the right ventricle (RV). The interventricular septum was included with the LV. The RV, septum, and LV were blotted and weighed. The spleens were also removed and quickly frozen in liquid nitrogen for norepinephrine determinations by a modification of the method of Anton and Sayre.8

Results

Systolic blood pressure in the unanesthetized NGFAS-treated SHR was significantly less than that of the sham-treated SHR 40 to 320 days of age (fig. 1). In NGFAS-treated SHR aged 220 to 320 days, however, systolic pressure gradually increased, becoming significantly greater than that of the WKY rats. NGFAS had no effect on systolic blood pressure in the WKY rat.

In the anesthetized rats at rest, a similar pattern of blood pressure was observed (table 2). The LV systolic pressure of the NGFAS-treated SHR was significantly less than that of the sham-treated SHR 40 to 320 days of age (fig. 1). In NGFAS-treated SHR aged 220 to 320 days, however, systolic pressure gradually increased, becoming significantly greater than that of the WKY rats. NGFAS had no effect on systolic blood pressure in the WKY rat.

In the anesthetized rats at rest, a similar pattern of blood pressure was observed (table 2). The LV systolic pressure of the NGFAS-treated SHR was significantly less than that of the sham-treated SHR but slightly, although not significantly, higher than the pressures in the WKY groups. Systolic blood pressures measured under anesthesia were less than those measured by tail cuff in the four groups (WKY

Figure 1. Unanesthetized tail-cuff systolic blood pressures from 40- to 320-day-old sham-treated WKY rats (black circles), NGFAS-treated WKY rats (white circles), sham-treated SHR (black squares), and NGFAS-treated SHR (white squares). Values are means for 10 to 12 animals in each group.

TABLE 1. Amount of Blood Transfused to Reach Peak Cardiac Output

<table>
<thead>
<tr>
<th>Blood</th>
<th>WKY</th>
<th>WKY-NGFAS</th>
<th>SHR</th>
<th>SHR-NGFAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ml</td>
<td>6.5 ± 0.5*</td>
<td>6.1 ± 0.2</td>
<td>7.1 ± 0.5</td>
<td>7.6 ± 0.3†</td>
</tr>
<tr>
<td>ml/kg</td>
<td>15.5 ± 1.1</td>
<td>14.6 ± 0.5</td>
<td>18.0 ± 1.7</td>
<td>19.7 ± 0.8†</td>
</tr>
</tbody>
</table>

*Mean ± SEM. †WKY-NGFAS vs SHR-NGFAS, p < 0.001.
As we reported previously for animals 4 to 24 weeks of age, cardiac index was significantly reduced in both the sham- and NGFAS-treated SHR compared with that of the WKY groups (table 2). This decrease was a manifestation of a diminished stroke volume in the SHR. Stroke index was also slightly decreased in the NGFAS-treated WKY rat. Heart rates of the sham-treated SHR and the NGFAS-treated SHR and WKY groups were all significantly greater than those of the sham-treated WKY rat. Systemic vascular resistance was substantially elevated in the sham-treated SHR, as expected. However, the NGFAS-treated SHR also demonstrated an elevated systemic resistance related to the decreased cardiac output and slight elevation in blood pressure.

**TABLE 2. Resting Hemodynamic Parameters in Sham- and NGFAS-treated WKY and SHR**

<table>
<thead>
<tr>
<th>Rat group</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>HR (b/min)</th>
<th>CI (ml/min/kg)</th>
<th>SI (ml/kg)</th>
<th>RI (mm Hg-min/kg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>107 ± 4.9*</td>
<td>2.7 ± 0.5</td>
<td>390 ± 10</td>
<td>167 ± 8.7</td>
<td>0.46 ± 0.03</td>
<td>0.57 ± 0.04</td>
</tr>
<tr>
<td>WKY-NGFAS</td>
<td>116 ± 5.0</td>
<td>2.5 ± 0.4</td>
<td>398 ± 8</td>
<td>159 ± 7.9</td>
<td>0.40 ± 0.02</td>
<td>0.66 ± 0.03</td>
</tr>
<tr>
<td>SHR</td>
<td>168 ± 8.8</td>
<td>3.0 ± 0.06</td>
<td>412 ± 9</td>
<td>128 ± 5.9</td>
<td>0.32 ± 0.01</td>
<td>1.01 ± 0.05</td>
</tr>
<tr>
<td>SHR-NGFAS</td>
<td>132 ± 5.0</td>
<td>3.9 ± 0.06</td>
<td>411 ± 10</td>
<td>127 ± 9.2</td>
<td>0.32 ± 0.02</td>
<td>0.01 ± 0.05</td>
</tr>
</tbody>
</table>

**p values:**
- WKY vs SHR: < 0.001 (NS)
- WKY-NGFAS vs SHR-NGFAS: NS (NS)
- WKY vs WKY-NGFAS: < 0.001 (NS)
- SHR vs SHR-NGFAS: < 0.001 (NS)

*Mean ± SEM, n = 10-12 for each group.
LVSP = left ventricular systolic pressure; LVEDP = left ventricular end diastolic pressure; HR = heart rate; CI = cardiac index; SI = stroke index; RI = resistance index.
EFFECT OF VASCULAR EXPANSION IN SHR/Cutilella and Oparil

The LV pressure, cardiac index, stroke index, heart rate, and systemic resistance in both sham- and NGFAS-treated WKY rats were altered by the transfusion of whole blood, as shown in table 3. The LV systolic pressure rose by 25.2% and 22.6%, and end diastolic pressure by 100% and 92% for sham- and NGFAS-treated WKY rats respectively. Since cardiac index increased by 58.1% and 56% in sham- and NGFAS-treated WKY rats, systemic resistance decreased by 17.5% and 18.2% respectively, despite the increase in systolic pressure. The increase in cardiac index was due to a substantial increase in stroke index, since the heart rate decreased after vascular expansion.

The response of both SHR groups to transfusion tended to be more dramatic than that of the WKY rats. There were, however, also differences between sham- and NGFAS-treated SHR groups. In the sham-treated SHR, LV systolic pressure increased by 24.4%, similar to the increase found in the WKY animals. The NGFAS-treated SHR, however, demonstrated a 54.8% increase in systolic pressure. The increases in LV end diastolic pressures were similar to those of the WKY rats. Both sham- and NGFAS-treated SHR had a greater response in cardiac index than did either WKY group. Once again, the increase in cardiac index in the NGFAS-treated SHR (90.6%) was greater than that of the sham-treated SHR (79.7%). Stroke index also increased to a greater extent in both SHR groups, 95.0% and 117.4% for sham- and NGFAS-treated SHR respectively.

As a result of the differences in response to increased blood volume, the relationships of the various parameters among the four treatment groups were altered compared with resting values (table 4). Systolic pressures in the SHR groups were now identical regardless of NGFAS treatment. Cardiac index and stroke index remained depressed in the sham-treated SHR; however, both parameters rose in the NGFAS-treated SHR to the level of the NGFAS-treated WKY rat. The relationships of LV end diastolic pressure, heart rate, and systemic resistance among the four groups remained similar to those measured at rest.

Ventricular function curves were constructed relating either stroke index or stroke work index to LV end diastolic pressure (fig. 2). In figure 2 left, stroke index in both SHR groups was significantly less than that in the WKY animals at similar LV filling pressures. Following transfusion, stroke index and LV end diastolic pressure increased proportionally in all groups except the NGFAS-treated SHR. In this

### Table 3. Percent Changes in Hemodynamic Parameters Following Whole Blood Transfusion in Sham- and NGFAS-treated SHR and WKY Rats

<table>
<thead>
<tr>
<th>Rat group</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>HR (b/min)</th>
<th>CI (ml/min/kg)</th>
<th>SI (ml/kg)</th>
<th>RI (mm Hg-min-kg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>25.2</td>
<td>100.0</td>
<td>-8.4</td>
<td>58.1</td>
<td>66.7</td>
<td>-17.5</td>
</tr>
<tr>
<td>WKY-NGFAS</td>
<td>22.6</td>
<td>92.0</td>
<td>-8.8</td>
<td>56.0</td>
<td>67.2</td>
<td>-18.2</td>
</tr>
<tr>
<td>SHR</td>
<td>24.4</td>
<td>86.7</td>
<td>-9.2</td>
<td>79.7</td>
<td>95.0</td>
<td>-30.7</td>
</tr>
<tr>
<td>SHR-NGFAS</td>
<td>54.8</td>
<td>89.7</td>
<td>-10.0</td>
<td>90.6</td>
<td>117.4</td>
<td>-22.0</td>
</tr>
</tbody>
</table>

LVSP = left ventricular systolic pressure; LVEDP = left ventricular end diastolic pressure; HR = heart rate; CI = cardiac index; SI = stroke index; RI = resistance index.

### Table 4. Hemodynamic Parameters Following Whole Blood Transfusion in Sham- and NGFAS-treated SHR and WKY Rats

<table>
<thead>
<tr>
<th>Rat group</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>HR (b/min)</th>
<th>CI (ml/min/kg)</th>
<th>SI (ml/kg)</th>
<th>RI (mm Hg-min-kg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>134 ± 4.5</td>
<td>5.4 ± 0.4</td>
<td>334 ± 8</td>
<td>264 ± 8.2</td>
<td>0.77 ± 0.04</td>
<td>0.47 ± 0.03</td>
</tr>
<tr>
<td>WKY-NGFAS</td>
<td>141 ± 3.0</td>
<td>4.8 ± 0.6</td>
<td>383 ± 8</td>
<td>248 ± 10.8</td>
<td>0.67 ± 0.04</td>
<td>0.54 ± 0.03</td>
</tr>
<tr>
<td>SHR</td>
<td>209 ± 7.9</td>
<td>5.6 ± 0.8</td>
<td>375 ± 10</td>
<td>230 ± 9.9</td>
<td>0.62 ± 0.05</td>
<td>0.70 ± 0.07</td>
</tr>
<tr>
<td>SHR-NGFAS</td>
<td>209 ± 4.2</td>
<td>5.5 ± 0.8</td>
<td>370 ± 9</td>
<td>242 ± 9.2</td>
<td>0.69 ± 0.02</td>
<td>0.71 ± 0.03</td>
</tr>
</tbody>
</table>

p values:

- WKY vs SHR: < 0.001 NS < 0.01 < 0.05 < 0.025 < 0.005
- WKY-NGFAS vs SHR-NGFAS: < 0.001 NS NS NS NS < 0.001
- WKY vs WKY-NGFAS: NS NS < 0.01 NS NS NS
- SHR vs SHR-NGFAS: NS NS NS NS NS NS

*Mean ± SEM; n = 10–12 for each group.
LVSP = LV systolic pressure; LVEDP = LV end diastolic pressure; HR = heart rate; CI = cardiac index; SI = stroke index; RI = resistance index.
group the slope is steeper, thus normalizing stroke index. At low LV filling pressures before transfusion, there are no significant differences in stroke work index among the four groups (fig. 2 right). At higher but similar filling pressures after transfusion, however, stroke work index is significantly greater in both SHR groups than in the WKY animals.

A similar response was seen when peak dP/dt (P') was measured as an index of myocardial contractility. This parameter was significantly depressed in both sham- and NGFAS-treated SHR compared to the WKY groups before transfusion (fig. 3). After transfusion, peak dP/dt (P') rose slightly, but insignificantly, in the WKY rats. In the SHR, however, we found 26.3% and 51.4% increases in peak dP/dt (P') for sham- and NGFAS-treated SHR respectively. Because of these increases, posttransfusion values for this index did not differ among the four treatment groups.

As we reported previously in younger SHR, LV hypertrophy developed in the NGFAS-treated SHR despite attenuation of the hypertension (table 5). The NGFAS treatment had no effect on LV/body weight ratios in either SHR or WKY rats. The RV/body weight ratios did not differ among the four groups. Splenic norepinephrine levels were profoundly decreased in NGFAS-treated SHR and WKY rats (table 5), signifying nearly complete sympathetic denervation of these organs.

**Discussion**

In this study we transfused rat whole blood into 48-week-old sham-treated and NGFAS-treated SHR and WKY rats, and measured cardiac performance before and after the transfusion. The findings at rest were similar to those reported in our previous studies on sham- and NGFAS-treated SHR and WKY rats at ages 4 to 24 weeks. We found a decrease in cardiac index, due mainly to a low stroke index, in both sham- and NGFAS-treated SHR compared with WKY rats. In the latter SHR group, this reduction in cardiac index occurred despite the attenuation of hypertension by treatment with NGFAS. Myocardial contractility was also markedly depressed in both SHR groups as measured by peak isovolumic dP/dt (P'). The heart rates of sham- and NGFAS-treated SHR and the NGFAS-treated WKY rat were significantly elevated compared to the sham-treated WKY rat. An elevation in heart rate seen in SHR has been attributed to increased sympathetic nerve activity. Since we have shown that catecholamine stores are depleted in the heart and spleen after NGFAS treatment, pathways other than direct sympathetic innervation, such as adrenal medullary function, may be responsible for the increased heart rate in the three treatment groups.

In our hemodynamic studies of the SHR we have consistently found that stroke index is reduced and myocardial hypertrophy develops even in the absence of hypertension. All of our parameters except tail-cuff blood pressures were measured under pentobarbital anesthesia. The validity of hemodynamic studies performed in the open chest preparation under barbiturate anesthesia has been questioned. Sodium pen-

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**Table 5. Heart and Body Weights and Splenic Norepinephrine Levels in Sham- and NGFAS-treated SHR and WKY Rats**

<table>
<thead>
<tr>
<th>Rat group</th>
<th>BW (g)</th>
<th>LVW (mg)</th>
<th>LV/BW (mg/g)</th>
<th>Norepinephrine (µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>437 ± 10*</td>
<td>902 ± 3</td>
<td>2.06 ± 0.03</td>
<td>0.338 ± 0.065</td>
</tr>
<tr>
<td>WKY-NGFAS</td>
<td>419 ± 7</td>
<td>827 ± 18</td>
<td>1.97 ± 0.03</td>
<td>0.058 ± 0.005</td>
</tr>
<tr>
<td>SHR</td>
<td>397 ± 9</td>
<td>994 ± 30</td>
<td>2.54 ± 0.10</td>
<td>0.43 ± 0.05</td>
</tr>
<tr>
<td>SHR-NGFAS</td>
<td>384 ± 6</td>
<td>925 ± 18</td>
<td>2.43 ± 0.06</td>
<td>0.025 ± 0.004</td>
</tr>
</tbody>
</table>

**p values:**

- WKY vs SHR  < 0.01  < 0.02  < 0.001  NS
- WKY-NGFAS vs SHR-NGFAS  < 0.005  < 0.01  < 0.001  < 0.001
- WKY vs WKY-NGFAS  NS  < 0.05  NS  NS
- SHR vs SHR-NGFAS  NS  NS  NS  < 0.001

*Mean ± SEM; n = 12 for each group.
BW = body weight; LV = left ventricular weight; LV/BW = left ventricular/body weight ratio.
EFFECT OF VASCULAR EXPANSION IN SHR/Cutilletta and Oparil

To barbital is said to alter myocardial function and opening of the chest has been shown to lower cardiac output, so absolute values for indices of cardiac performance might be expected to be depressed in our preparation. In our study, SHR and WKY rats that received NGFAS treatment were evaluated in comparison with control groups of sham-treated animals of the same age subjected to exactly the same anesthetic agent and surgical procedure. In comparing the fall in systolic pressure under anesthesia to the tail cuff pressures obtained in the conscious animals, we found changes of -4% to -21%. The greatest fall occurred in the sham-treated WKY rat and the least in the sham-treated SHR. The fall in blood pressures in the two NGFAS-treated groups was between 11% and 15%. There did not appear to be any pattern in the decrease in blood pressure related to treatment. The slightly greater fall, 14.8% vs 11.5%, in the NGFAS-treated SHR compared with the NGFAS-treated WKY rat accounted for the difference in LV systolic pressure measured under anesthesia no longer attaining statistical significance. We feel that the use of control groups permits us to interpret the contributions of immunosympathectomy and of strain differences to myocardial and hemodynamic function in these animals.

The findings in the present study are consistent with the experiments of Hallback et al.,16 which showed that, at similar filling pressure, stroke volume was diminished in the isolated LV of the SHR. We found nearly identical LV filling pressures among the four treatment groups. Stroke indices in the hypertensive sham-treated SHR and in the normotensive NGFAS-treated SHR were lower than in the sham-treated WKY rat. In the conscious SHR, however, it has recently been shown that left atrial pressure is increased compared with that of the WKY rat.13 This increase in filling pressure in the SHR would tend to augment stroke volume and thus improve cardiac pumping performance.

To study further the relationship of LV filling and cardiac performance in the SHR, we assessed the hemodynamic response to volume expansion. After transfusion with whole blood to attain peak cardiac output, there was an increase in preload, manifested as a rise in LV end diastolic pressure and an increase in afterload, since systolic pressure and stroke work increased. Because heart rate fell, the increase in cardiac index was a result of a rise in stroke index. Systemic resistance also fell, probably in response to baroreceptor stimulation. There were no differences between the responses of the sham- and NGFAS-treated WKY rats. The response to transfusion of the SHR was more marked than that of the WKY rats. Differences were also found between sham- and NGFAS-treated SHR. An increase in LV filling pressure similar to that in the WKY rats evoked a marked increase in systolic pressure in the NGFAS-treated SHR such that systolic pressures in the SHR treatment groups were equalized. Stroke work index and myocardial contractility increased to a greater extent in the SHR than in the WKY groups. These changes demonstrate a greater sensitivity to changes in preload and enhanced cardiac performance with increased afterload in the SHR.

Our findings could be explained by a structural abnormality in the heart, resulting in an altered relationship of end diastolic pressure and wall tension. Displacement of the Frank-Starling curve to the right has been found in SHR in vitro.19 This displacement appeared related to the degree of wall hypertrophy. At higher filling pressures, stroke work and stroke volume were greater in the SHR than WKY hearts. Although the LV filling pressures measured in our study were less than those measured in vitro,13 we found similar changes with volume expansion.

The LV hypertrophy in the SHR is usually considered to be a compensatory response to increased pressure work. We have repeatedly found LV hypertrophy in the absence of elevated blood pressure in the NGFAS-treated SHR and in the newborn rat.18 Previously, we attributed this to a myocardial abnormality of unknown etiology. Another possible mechanism could involve changes in the arterial vessel wall, such as an increase in the stiffness of the wall of the systemic resistance vessels, which could increase inertia to forward flow by decreasing elastic recoil. A ventricle ejecting into this circulation would perform increased total work. This work, however, would not be detectable as external work by the product of pressure and flow in the absence of elevated pressure. An abnormality of this nature could also explain the marked increase in systemic pressure in the NGFAS-treated SHR in response to vascular expansion. Folkow et al.19 postulated that a structural adaptation in response to repeated pressure load may be genetically determined in hypertensive subjects. It is possible that alterations in vessel wall stiffness may even precede elevated blood pressure.

In conclusion, we have found an enhanced response to vascular expansion in the sham- and NGFAS-treated SHR in terms of stroke work and contractility. We also demonstrated a reduction in stroke volume in the SHR at filling pressures similar to those of the WKY and the presence of LV hypertrophy in the absence of measurable elevations in blood pressure. These findings could be explained by a structural abnormality in the myocardium resulting in decreased LV compliance. Structural changes in the resistance vessel wall could have a role in the development of LV changes.

References
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