Sympathetic Contribution to the Cardiac Response to Stress in Hypertension

CARLO ALICANDRI, M.D., FETNAT M. FOUAD, M.D., ROBERT C. TARAZI, M.D., EMMANUEL L. BRAVO, M.D., AND RICHARD L. GREENSTREET, PH.D.

SUMMARY Studies of cardiac performance in hypertension have often been restricted to cardiac output determinations, although the latter alone are inadequate for that purpose. To define the range of cardiac performance in hypertension, the response of left ventricular filling pressure to increased workload (static exercise) was determined in 39 subjects — eight normotensive (NT) volunteers, seven patients with borderline hypertension (BLH), and 24 essential hypertensives (EH), of age-matched groups. A rise of mean pulmonary wedge pressure (PWP) by 5 mm Hg or more during maximum handgrip (HG) was considered "abnormal" for a workload (SBP x HR x 10^{-3}) increase of ≥ 25%.

All NT subjects and all patients with BLH as well as 16 of the 24 EH (EH-I) showed normal cardiac performance by this definition. In contrast, PWP increased ≥ 5 mm Hg during HG in eight patients with EH (EH-II). The calculated increase in cardiac workload was not significantly different among the four groups (+5, 5.8, 5.4 and 5.5 respectively). Beta blockade (propranolol, 10 mg i.v.) slowed heart rate in all subjects and reduced SBP x HR product in all groups both at rest and during HG. Responses of PWP to HG were widely divergent in the different patients. However, as a group those patients with "impaired cardiac performance" before propranolol (EH-II) had a greater reduction in performance following propranolol than EH-I or NT. This study suggests that adrenergic support of cardiac performance might be important in some hypertensive patients with no evidence of heart failure. (Hypertension 5: 147-154, 1983)

KEY WORDS • exercise • cardiac output • left ventricular filling • workload • pulmonary wedge pressure • beta blockade • handgrip • propranolol • adrenergic agents

SYSTEMIC arterial hypertension has been shown to be the most common cause of left ventricular hypertrophy1 and of congestive heart failure at present.2 Of the factors helping the heart adapt to the increased workload of hypertension, adrenergic influences play a major role.3,4 In fact, induction or aggravation of heart failure was observed in hypertensive subjects treated with antiadrenergic agents5,9 as it was in patients with valvular or coronary arterial lesions.10 The frequent use of such agents in antihypertensive therapy requires, therefore, more precise definition of sympathetic contribution to cardiac performance in hypertension; this would help identify the stage of evolution of the disease and plan more adequate and safer therapy.

The relationship of cardiac work to left ventricular filling pressure, particularly under the stress of an increased cardiac load, has been considered a reliable test of cardiac performance.11,12 A particularly useful and safe way to impose a transient acute increase of pressure work on the heart is by static exercise.12-14 The response to that stress was shown to be useful for the assessment of left ventricular function in patients with coronary arterial disease14 and untreated systemic hypertension.15 Although the circulatory responses to static exercise involve sympathetic stimulation to the heart and peripheral vessels,16 it has been established that the reflex rise in systemic pressure was not abolished by acute beta-adrenergic blockade.17,18 Since intravenous propranolol interferes with adrenergic support of the heart without significant reduction of the acute pressure overload, static exercise performed before and after beta-adrenergic blockade could be used to assess the contribution of adrenergic influences to cardiac performance. Our experience with this method uncovered a wide spectrum of findings among hypertensive patients that could not be predicted by consideration of the more usual indices used in clinical evaluation.
Material and Methods

Patient Population
The study included 39 subjects: eight normotensive (NT) volunteers (aged 35 years ± 5.3 se), seven patients with borderline hypertension (BLH) (aged 35.3 years ± 5.2 se), and 24 essential hypertensives (EH) (aged 44.2 years ± 4.2 se). BLH was defined by the standard criteria of a blood pressure elevation to > 150/90 mm Hg on at least one of the three separate clinic examinations. In all patients, a secondary cause for hypertension was excluded on the basis of thorough clinical, laboratory, and radiographic examinations including renal arteriography and all special tests for primary aldosteronism or pheochromocytoma when warranted. None gave a history, or presented clinical or radiologic evidence, of cardiac decompensation. In all, antihypertensive therapy had been discontinued at least 2 weeks prior to the study. In none was there any definite evidence of left ventricular hypertrophy by EKG; the only electrocardiographic abnormalities detected in the hypertensive groups included congenital left bundle branch block in one patient, signs of old myocardial infarction in two patients, and nonspecific ST-T changes in three. Echocardiography was not used for further classification in this group of patients. The criteria used to define hypertension and left ventricular hypertrophy were described in detail previously. Details of the procedure and its investigative objective, as well as of the drug used, were explained to all the patients and NT volunteers. All gave their informed consent to the study which had been reviewed and approved beforehand by the Institutional Review Committee of the Cleveland Clinic Foundation.

Hemodynamic Investigation
All studies were performed in the morning after an overnight fast and at least 30 minutes supine rest, as previously described. No premedication was used. An arterial catheter was introduced percutaneously (Seldinger technique) into the brachial artery and advanced to the root of the aorta. A Swan-Ganz catheter was similarly introduced in an arm vein and advanced to the main pulmonary or right pulmonary artery. Cardiac output was determined in triplicate using either dye dilution (indocyanine green) or thermodilution as previously described. Values obtained by the two methods in our laboratory correlated closely (thermodilution output – y = 1.0x – 0.143, r = 0.92, p < 0.001). Following the output determination, the balloon was inflated and the tip of the venous catheter advanced and properly wedged to determine pulmonary capillary pressure.

The subject was then re instructed in the technique of handgrip (HG) and repeatedly told to use only the forearm and hand muscles, to avoid straining or increasing muscle tension in the rest of the body. The subject was then asked to develop the maximum pressure possible by voluntary HG and sustain it as long as possible without straining or intermittent pumping. That maximum effort could be maintained for 50 to 60 seconds before the patient relaxed. During the whole test, simultaneous EKG (lead 2), intraarterial pressure, and pulmonary wedge pressure (PWP) were continuously recorded beginning at least 1 minute before the grip, continuing all through the static exercise, and then for at least 2 minutes after the patient relaxed. Following determination of hemodynamic indices at rest and during exercise, four of the NT subjects and 14 of the patients with fixed essential hypertension (EH) were given propranolol (10 mg intravenously) while the electrocardiogram, intraarterial pressure, and mean PWP were continuously monitored. Fifteen minutes later, the response to maximum HG was determined in exactly the same way. This part of the study was performed only with those volunteer subjects and patients who agreed to the longer test; no other selection criteria were involved.

Calculations
Control values for cardiac output were derived from the average of at least three consecutive curves that did not differ by more than 10%. Left ventricular function could be characterized by the relationship between its filling pressure and external work; the mean PWP was taken as an index of left ventricular filling pressure in the absence of mitral valve lesion. External cardiac work is usually calculated as the product of stroke volume by heart rate and systolic blood pressure. However, stroke volume was repeatedly shown to remain unchanged during static exercise; this has also been our experience in 26 hypertensive patients studied previously; their stroke index averaged 40.5 ± 8.1 ml at rest and 38.6 ± 8.1 during HG (p > 0.10). In nine patients, the stroke index was measured at rest and during static exercise both before and after intravenous propranolol; it averaged 41.4 ± 3.6 (rest) and 39.6 ± 3.3 (exercise) before and 42.0 ± 3.5 (rest) and 41.8 ± 5.1 (exercise) after beta-blockade. None of the differences was statistically significant. Therefore, it was possible to simplify the calculation of cardiac work for the particular purpose of estimating the load imposed by sustained HG; only systolic blood pressure and heart rate values were used as an index of the cardiac load. This approach offered many advantages; the response to static exercise could be determined at maximum effort maintained for only 1 minute, without the patient getting unduly tired or beginning to strain, and with the tip of the venous catheter maintained in the same wedge position all through the resting and effort periods. If cardiac output had to be measured at different times, manipulation of the catheter to allow injection of dye or of cold solution, would have resulted in possible changes in wedge position and required a longer period of stress with attending disadvantages.

Standard statistical methods were used to calculate unpaired and paired t-tests as well as correlation coefficients and to determine their statistical significance. Values are expressed as means ± 1 se of the mean.
Results

Patients were subdivided into two groups according to the PWP response to the increased load induced by HG; if in response to the increase in load (at least +25%), mean PWP decreased, did not change, or increased by less than 4 mm Hg, cardiac performance was considered “normal.” A rise of mean PWP by 5 mm Hg or more during maximum HG was considered “abnormal” and cardiac performance was labelled “impaired.”

All NT subjects and all patients with BLH showed a normal cardiac performance by this definition. Also, having normal cardiac performance were 16 of the 24 EH patients designated as EH-I. In contrast, mean PWP increased by 5 mm Hg or more during HG in eight EH patients, designated EH-II. The values obtained at rest and during maximum static exercise in the four groups investigated are summarized in table 1.

Heart rate and systolic blood pressure increased significantly in all four groups. In absolute numbers, the increase in heart rate was higher in BLH, and somewhat lower among EH-I and EH-II; the increase in systolic blood pressure was also more marked in BLH but was not different from normal in both EH groups. The calculated increase in cardiac load (SBP x HR x 10^-3) was not significantly different among the four groups whether expressed in absolute numbers (5.0, 6.8, 5.4 and 5.5 respectively) or in percentage change from control (58.7%, 67.6%, 39.3% and 47.4% respectively). The most significant difference among the groups was in the response of the PWP to static exercise; it decreased slightly in the NTs but increased in all hypertensive patients. The increase averaged 42.6% in BLH, 27.4% in EH-I, and 114.8% in EH-II; all of which were significantly different (p < 0.01) from the NT response.

Baseline Hemodynamic Characteristics

Patients with BLH happened to have a normal blood pressure at the time of the study; they also had a slight increase in heart rate which was not, however, significantly different from normal (table 2). The more impressive characteristic of these patients was a significantly lower stroke volume (34.8 ml/m²). Total peripheral resistance and cardiac output were not different from normal. Patients with EH had a marked increase in total peripheral resistance; stroke volume was again reduced significantly from normal in both EH-I and EH-II, while cardiac index was lower than normal in EH-II only. There was no significant difference in any of the indices determined between the two subgroups EH-I and EH-II. Although mean PWP tended to be slightly higher in EH-II, the difference from either NT subjects or EH-I patients was not significant.

Changes Following Beta-Adrenergic Blockade

Immediately after the first study was completed, propranolol was infused (10 mg intravenously, at a rate of 1 mg/min) in four of the NT volunteers and 14 of the patients with essential hypertension (eight of EH-I and six of EH-II). Propranolol slowed heart rate in all sub-

### Table 1. Response of Hypertensive Patients to Static Exercise

<table>
<thead>
<tr>
<th></th>
<th>Normotensives (n = 8)</th>
<th>BLH (n = 7)</th>
<th>EH-I (n = 16)</th>
<th>EH-II (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (HR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>76.9 ± 3.6</td>
<td>84.9 ± 7.1</td>
<td>80.5 ± 2.8</td>
<td>69.8 ± 2.0</td>
</tr>
<tr>
<td>Handgrip</td>
<td>96.0 ± 3.5</td>
<td>107.7 ± 8.6</td>
<td>94.6 ± 4.1</td>
<td>84.8 ± 5.6</td>
</tr>
<tr>
<td>% Δ</td>
<td>26.3 ± 5.7</td>
<td>27.7 ± 4.2</td>
<td>17.3 ± 2.7</td>
<td>20.8 ± 5.2</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>119.3 ± 5.0</td>
<td>126.3 ± 3.8</td>
<td>170.8 ± 4.8</td>
<td>173.5 ± 8.4</td>
</tr>
<tr>
<td>Handgrip</td>
<td>146.3 ± 5.3</td>
<td>172.1 ± 8.6</td>
<td>200.9 ± 5.3</td>
<td>209.8 ± 7.6</td>
</tr>
<tr>
<td>% Δ</td>
<td>22.7 ± 3.8</td>
<td>36.3 ± 5.7</td>
<td>18.0 ± 2.5</td>
<td>21.3 ± 3.0</td>
</tr>
<tr>
<td>SBP x HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>9.2 ± 0.7</td>
<td>10.7 ± 1.0</td>
<td>13.8 ± 0.7</td>
<td>12.1 ± 0.7</td>
</tr>
<tr>
<td>Handgrip</td>
<td>14.2 ± 0.8</td>
<td>17.5 ± 1.1</td>
<td>19.0 ± 1.2</td>
<td>17.8 ± 1.5</td>
</tr>
<tr>
<td>% Δ</td>
<td>58.7 ± 12.5</td>
<td>67.6 ± 11.6</td>
<td>36.5 ± 5.8</td>
<td>47.4 ± 7.3</td>
</tr>
<tr>
<td>Mean pulmonary wedge pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>6.3 ± 0.7</td>
<td>5.6 ± 0.4</td>
<td>6.5 ± 0.7</td>
<td>9.0 ± 1.4</td>
</tr>
<tr>
<td>Handgrip</td>
<td>5.3 ± 0.7</td>
<td>7.9 ± 0.7</td>
<td>8.1 ± 0.8</td>
<td>17.5 ± 1.8</td>
</tr>
<tr>
<td>% Δ</td>
<td>−12.9 ± 10.7</td>
<td>42.6 ± 9.9</td>
<td>27.4 ± 5.1</td>
<td>114.8 ± 22.8</td>
</tr>
</tbody>
</table>

Values expressed as average ± SEM. BLH = borderline hypertensives; EH-I = essential hypertensives Group 1; EH-II = essential hypertensives Group 2. Statistical significance: The increase in (SBP x HR x 10^-3) was not significantly different among the four groups (p > 0.05) whether expressed in absolute numbers or in Δ%. In contrast, the response of pulmonary wedge pressure was significantly different in normotensive vs hypertensive groups; the reduction by −12.9% in normotensives was significantly different from the increases by 42.6% in BLH (p < 0.01), by 27.4% in EH-I (p < 0.001), and by 114.8% in EH-II (p < 0.001).
TABLE 2. Baseline Hemodynamic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normotensives (n = 8)</th>
<th>BLH (n = 7)</th>
<th>EH-I (n = 16)</th>
<th>EH-II (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>76.9 ± 3.6</td>
<td>84.9 ± 7.1</td>
<td>80.5 ± 2.8</td>
<td>69.8 ± 2.0</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>89.8 ± 3.7</td>
<td>96.4 ± 2.6</td>
<td>125.6 ± 2.7</td>
<td>121.6 ± 5.5</td>
</tr>
<tr>
<td>CI (L/m²)</td>
<td>3.3 ± 0.1</td>
<td>2.9 ± 0.3</td>
<td>2.9 ± 0.1</td>
<td>2.6 ± 0.1</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>43.8 ± 2.6</td>
<td>34.8 ± 3.2</td>
<td>36.6 ± 1.6</td>
<td>36.4 ± 2.9</td>
</tr>
<tr>
<td>TPR (units)</td>
<td>27.7 ± 1.7</td>
<td>35.1 ± 4.0</td>
<td>44.0 ± 1.8</td>
<td>48.3 ± 4.0</td>
</tr>
<tr>
<td>mPWP (mm Hg)</td>
<td>6.3 ± 0.7</td>
<td>5.6 ± 0.4</td>
<td>6.5 ± 0.7</td>
<td>9.0 ± 1.4</td>
</tr>
</tbody>
</table>

Values expressed as average ± SEM.

BLH = borderline hypertensives; EH-I = essential hypertensives Group 1; EH-II = essential hypertensives Group 2;
HR = heart rate; MAP = mean arterial pressure; CI = cardiac index; SI = stroke index; TPR = total peripheral resistance; and mPWP = mean pulmonary wedge pressure.

Statistical Significance:
HR = Differences from normotensives = ns; EH-II vs BLH and EH-I = p < 0.05.
MAP = EH-II vs EH-I, ns; BLH vs N, ns; EH-II and EH-I vs BLH = p < 0.01.
CI = EH-II vs N; p < 0.01; others = ns.
SI = p < 0.05 for all hypertensive groups vs N.
TPR = BLH vs N, ns; EH-I and EH-II vs N = p < 0.001.
mPWP = only significant difference (p < 0.05) is EH-II vs BLH.

jects but did not alter the systolic blood pressure in any of the groups; consequently, the systolic blood pressure \times heart rate product at rest (expressed as 1 \times 10^3) was decreased from 14.4 ± 0.9 to 11.5 ± 0.7 (p < 0.01) in EH-I patients and from 12.4 ± 0.8 to 10.7 ± 0.9 (p < 0.05) in EH-II patients (table 3). Concomitant with that decrease, mean PWP increased in most hypertensive subjects whereas it was essentially unchanged by propranolol in NT volunteers (6.5 ± 0.3 mm Hg vs 6.3 ± 0.7 mm Hg control). Among EHs, PWP increased from 6.5 ± 0.7 mm Hg to 7.6 ± 0.8 mm Hg in EH-I (p > 0.05) whereas it increased significantly in EH-II from 9 to 10.5 mm Hg (p < 0.05).

During the maximum HG performed after intravenous propranolol, systolic blood pressure increased equally in both groups of hypertensive patients. Heart rate also

TABLE 3. Response to Static Exercise after \(\beta\)-Adrenergic Blockade

<table>
<thead>
<tr>
<th></th>
<th>Normotensives (n = 4)</th>
<th>EH-I (n = 8)</th>
<th>EH-II (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (HR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>72.5 ± 2.5</td>
<td>65.9 ± 2.3</td>
<td>63.7 ± 2.3</td>
</tr>
<tr>
<td>Handgrip</td>
<td>85.0 ± 5.4</td>
<td>75.5 ± 3.5†</td>
<td>72.5 ± 3.1†</td>
</tr>
<tr>
<td>%Δ</td>
<td>17.5 ± 7.6</td>
<td>14.5 ± 3.0</td>
<td>14.0 ± 3.1</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>129 ± 3.1</td>
<td>174 ± 8.2*</td>
<td>167.7 ± 12*</td>
</tr>
<tr>
<td>Handgrip</td>
<td>157 ± 11.0†</td>
<td>192.2 ± 9.6‡</td>
<td>193.3 ± 10.2*‡</td>
</tr>
<tr>
<td>%Δ</td>
<td>21.2 ± 6</td>
<td>14.5 ± 2.1</td>
<td>16.2 ± 2.6</td>
</tr>
<tr>
<td>SBP \times HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>9.4 ± 0.4</td>
<td>11.5 ± 2.8</td>
<td>10.7 ± 0.9</td>
</tr>
<tr>
<td>Handgrip</td>
<td>13.5 ± 1.7†</td>
<td>15.1 ± 1.1‡</td>
<td>14.1 ± 1.2‡</td>
</tr>
<tr>
<td>%Δ</td>
<td>44 ± 16.1</td>
<td>31.9 ± 4.1</td>
<td>32 ± 2.9</td>
</tr>
<tr>
<td>Mean pulmonary wedge pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>6.5 ± 0.3</td>
<td>7.6 ± 0.8</td>
<td>10.5 ± 1.6*</td>
</tr>
<tr>
<td>Handgrip</td>
<td>9.2 ± 0.5†</td>
<td>11.6 ± 1.3‡</td>
<td>19.0 ± 1.9§</td>
</tr>
<tr>
<td>%Δ</td>
<td>43.0 ± 8.5</td>
<td>55.0 ± 12.6</td>
<td>92.5 ± 20.0</td>
</tr>
</tbody>
</table>

* p < 0.05 compared to normotensives.
† p < 0.01 between resting and handgrip.
‡ p < 0.001 between resting and handgrip.
§ p < 0.05 compared to normotensives or EH-I.
increased but did not, however, attain levels equivalent to those observed before propranolol; in EH-I, heart rate reached 75.5 ± 3.5 vs 91.8 ± 3.3 before beta-blockade \( (p < 0.01) \); in EH-II, it increased to 72.5 ± 3.1 as compared to 91 ± 5.2 before beta-blockade \( (p < 0.01) \). Consequently, the level of the \( (SBP \times HR) \) product during HG after propranolol was significantly lower than before propranolol in both EH-I \( (15.1 \pm 1.1 \text{ vs } 18.4 \pm 1.1, p < 0.001) \) and in EH-II \( (14.1 \pm 1.2 \text{ vs } 19.1 \pm 1.6, p < 0.01) \). Although these differences were statistically significant when expressed in absolute values, they did not attain statistical significance when values were expressed in percent changes from control (table 3).

The response of mean PWP to static exercise during beta-blockade did, however, show significant \( (p < 0.001) \) differences from preblockade conditions in all three groups. Among the NT volunteers, PWP increased during HG in contrast with the decrease observed before propranolol. Among patients with EH, the PWP reached levels of 11.6 and 19 mm Hg in groups I and II, respectively, both of which were higher than levels attained before propranolol.

These averages concealed some individual variations. After propranolol, one EH-I patient increased mean PWP by 9 mm Hg during maximum HG. It was therefore, thought that in this patient, cardiac performance before propranolol was maintained within normal limits by an adrenergic mechanism. On the other hand, another EH-II patient slowed his heart rate markedly (58 from 68 bpm) and dropped his systolic blood pressure (132 from 168 mm Hg) after propranolol injection. As a result, the product of SBP \( \times \) HR was decreased, but the mean PWP at rest remained almost unchanged (12 from 13 mm Hg). When maximum HG was performed in this patient after propranolol, the level of the product SBP \( \times \) HR reached was markedly lower than that obtained during preinjection HG; under these conditions, his mean PWP rose by only 2 mm Hg (compared to 12 mm Hg in the prepropranolol HG).

Calculation of Changes Induced by Beta-Adrenergic Blockade

The response to maximum HG can be defined by the slope of a line joining two points, the first defined by the baseline values of the \( (SBP \times HR) \) product and PWP and the second point by the values reached by the same indices during maximum HG (fig. 1). A comparison of responses before and after propranolol could reveal either no shift in that slope or a distinct alteration following beta-blockade. The first response suggests minimal contribution of the sympathetic adrenergic activity to cardiac response to static exercise while the second would imply that the cardiac response depended to a large extent on adequate cardio-adrenergic support. The slope of that line could be defined mathematically as the ratio of the change in the two measured variables [mean PWP and \( (SBP \times HR) \)] between rest and maximum handgrip: \( \Delta mPWP/\Delta SBP \times HR \), where \( m \) equals the mean value.

To define more precisely the level of sympathetic contribution to cardiac performance, the ratio \( \Delta mPWP/\Delta SBP \times HR \) obtained before propranolol was compared with the ratio obtained after the beta-blocker (fig. 2). The higher the changes induced by propranolol in this ratio, the greater would be the dis-
distance from the identity line and therefore, the greater the contribution of sympathetic activity to cardiac function during static exercise. The distance from the identity line of a point referring to the comparison of ∆mPWP/∆SBP × HR ratio before and after propranolol could also be calculated according to the formula (fig. 3):

\[ d = \sin 45° (S_a - S_b) = 0.707 (\Delta S) \]

where \( d \) = distance, \( S = \Delta mPWP/\Delta SBP \times HR \), \( b \) = before and \( a \) = after propranolol. The mean distance from the identity line of the three groups tested averaged: NT = 0.83 ± 0.3; EH-I = 0.40 ± 0.12; EH-II, 1.11 ± 0.20. There was an obvious overlap between values for the NT subjects and the EH-I group of patients, and the difference between the two was not significant. However, the values for patients in EH-II were on the whole higher than both the NT and the EH-I group, and this difference was statistically significant (1.11 ± 0.20 vs 0.554 ± 0.48 for pooled value for NT and EH-I, \( p < 0.05 \)).

One patient deserves a special mention; his cardiac performance appeared to improve following i.v. propranolol (slope of 2.8 before and 0.7 after). This was due to the fact that he was the only one in whom i.v. propranolol led to a marked reduction in systolic blood pressure (from 168 to 132 mm Hg) within 10 to 15 minutes of the injection.

**Discussion**

Various studies have revealed a wide spectrum of cardiac function among hypertensive patients. All too often, however, these conclusions were based on determinations of cardiac output alone, possibly because of the ethical problems involved in subjecting asymptomatic patients to left ventricular catheterization. In this study, PWP was used as an index of left ventricular filling pressure since none of the patients had any evidence of mitral disease or of mechanical obstruction in the left atrium or pulmonary veins. This approach which is more acceptable ethically and practically in asymptomatic subjects allowed a more complete evaluation of left ventricular performance by determining the response of left ventricular filling pressure to static exercise. The alterations of that pressure in response to a sudden increase in pressure load were shown to be a valid index of cardiac performance, whether the increase in arterial pressure is induced pharmacologically by vasopressor agents or reflexly by static exercise.

Based on previous studies, cardiac performance was considered normal if in response to a static effort, PWP did not change by more than 4 mm Hg; it was considered impaired if static exercise led to a PWP increase by more than 5 mm Hg. A wide spectrum of results was observed among our subjects. In normal volunteers, PWP did not change or was even decreased during an effective steady HG which increased the SBP × HR product by more than 25%. Among 31 hypertensives, eight had a frankly abnormal response (∆PWP > 5 mm Hg) indicating an impaired cardiac performance (EH-II). However, all the others (EH-I) including all seven patients with BLH, showed a definite increase in PWP (albeit still within the normal ± 4 mm Hg) during static exercise; consequently, the rise in PWP on effort was statistically greater among these hypertensives with "normal cardiac performance" than in the NT group (table 1). These results were all the more remarkable inasmuch as the patients with BLH showed no significant difference from NT volunteers with regard to the level of cardiac index, blood pressure or heart rate recorded during the study (table 2). Evidence for a subtle impairment of cardiac response in hypertension to stress had been reported in both experimental animals and EH patients. Lund-Johansen reported a lower stroke index during dynamic exercise even in young hypertensives compared to age-matched controls. To this reduced capacity of increasing stroke volume and cardiac output, with dynamic exercise, our study added the observation that even in early hypertension, an acute arterial
pressure rise leads to a greater increase in PWP than in NT subjects. Together with reports of cardiac hypertrophy in BLH, these observations seem to indicate an early involvement of the heart in hypertension sometimes out of proportion to the level of blood pressure. We do not think that this subtle reduction in level of cardiac performance is necessarily due to an "incipient cardiac insufficiency" since it might conceivably reflect only an early reduction in ventricular compliance in hypertension. Fouda et al. have recently reported a significant reduction in left ventricular filling rate in hypertensive patients who otherwise showed no significant difference in cardiac output, left ventricular ejection rate and ejection fraction from NT controls.

Apart from differences among patients as regards cardiac response to static exercise, other important differences were uncovered by propranolol concerning the dependence of this cardiac response on adrenergic influences. Static exercise is associated with reflex sympathetic activation, the importance of adrenergic participation in cardiac response to static exercise was, therefore, evaluated by determining the change in that response following beta-adrenergic blockade. Again, a wide spectrum of findings were noted from little or no change in ventricular performance following intravenous propranolol to marked depression of performance in some patients. To allow for possible changes in heart rate or blood pressure due to propranolol, results were analyzed in terms of the ratio of ΔPWP to Δ(SBP × HR) product, in effect, normalizing the change in wedge pressure for the load imposed on the heart. The effect of propranolol on that ratio was used as an index of the dependence of cardiac performance on adrenergic activity in the same way as the effect of propranolol on systolic time intervals gave a measure of cardioadrenergic influences. An important caveat in this approach is to restrict analysis only to those patients with unchanged systolic pressure during the test following acute beta-adrenergic blockade. A significant change in that pressure may so alter the cardiac load as to induce changes in performance irrespective of the beta-blockade. This was clearly demonstrated in the only patient whose systolic pressure fell and cardiac performance improved after propranolol (fig. 2).

In individual patients, it was not possible to prognosticate the effect of propranolol on cardiac response to static exercise (fig. 1). However, as a group those patients with "impaired cardiac performance" before propranolol (EH-II) had a greater reduction in performance following propranolol than both EH group I and the NT subjects. The importance of adrenergic activity in supporting the performance of failing hearts is well recognized. This study suggests that it might be also important in some hypertensive patients with no signs or history of heart failure. Given the frequency with which sympatholysis are used in the treatment of hypertension, the clinical relevance of these observations hardly needs stressing. Guazzi et al. have pointed out the relative frequency with which guanethidine or propranolol led to marked increases in PWP. In this context, it is particularly important to note that there was no obvious clinical difference in our patients between those with "impaired" and those with "normal" cardiac performance.

In those patients, therefore, whose cardiac status causes some concern, a minimally invasive test of cardiac performance would be helpful in better evaluation of their condition and choice of therapy. Indications for antiadrenergic treatment should be very carefully weighed in hypertensive patients whose cardiac performance is markedly dependent on sympathetic support. The study of PWP response to static exercise would be particularly appropriate in that regard. Arterial puncture is not required; indirect determination of systolic blood pressure is easier and more accurate than of diastolic pressure. Further, the quick abating of the raised blood pressure and tachycardia on release of the HG adds to the safety of the procedure.

Acknowledgment

The authors gratefully acknowledge the invaluable help of B. Vbrakar, M.D., M. K. Kruchan, R.N., and S. Vaughn, R.N., as well as the secretarial help of S. Bir and A. Raulinaitis.

References

30. Spech MM, Ferrario CM, Tarazi RC: Cardiac pumpng ability following reversal of hypertrophy and hypertension in spontaneously hypertensive rats. Hypertension 2: 75, 1980
34. Frohlich ED, Tarazi RC: Is arterial pressure the sole factor responsible for hypertensive cardiac hypertrophy? Am J Cardiol 44: 959, 1979
Sympathetic contribution to the cardiac response to stress in hypertension.
C Alicandri, F M Fouad, R C Tarazi, E L Bravo and R L Greenstreet

Hypertension. 1983;5:147-154
doi: 10.1161/01.HYP.5.1.147

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 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/5/1/147

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/