Clinical-Physiological Correlations in the Development of Hypertensive Heart Disease

By Edward D. Frohlich, M.D., Robert C. Tarazi, M.D., and Harriet P. Duson, M.D.

SUMMARY

In order to understand more precisely the progression of ventricular dysfunction in hypertension prior to development of ventricular failure, 25 normal volunteer subjects and 97 untreated essential hypertensive patients (21 of whom had coronary arteriography and failed to show significant atherosclerosis) were classified into three groups: (I) normal-sized hearts, 54 patients; (II) left atrial enlargement (ECG criteria), 20 patients; and (III) left ventricular enlargement (ECG and chest X-ray criteria), 23 patients. Heart rate was elevated ($P < 0.001$) in all three groups; total peripheral resistance and arterial pressure increased progressively from group I to II to III ($P < 0.001$); cardiac index was reduced only in group III ($P < 0.001$). However, despite normal cardiac index in group II, left ventricular ejection rate was impaired ($P < 0.01$), and tension-time index and pressure-time per beat were greater than in patients with normal-sized hearts ($P < 0.001$). Thus, left atrial enlargement provided the initial evidence of left ventricular dysfunction. Later, when left ventricular hypertrophy became clinically apparent (always associated with left atrial abnormality) further impairment of left ventricular function was evident. Since these hemodynamic changes were observed in patients with normal coronary arteries, presence of left atrial and ventricular enlargement should provide useful criteria for classifying functional impairment in hypertensive heart disease.

Additional Indexing Words: Arteriography, Essential hypertension, Hemodynamics of hypertension, Left atrial abnormality, Left ventricular hypertrophy

Severity of hypertensive heart disease has been related primarily to electrocardiographic and chest X-ray observations and only to altered physiological indices when left ventricular decompensation occurs.$^1$ Thus, cardiac output has been said to remain normal in the presence of left ventricular hypertrophy even if systemic arterial pressure and total peripheral resistance rise to extremely high levels and only becomes reduced significantly when left ventricular failure supervenes.$^2,^3$ Previous studies from our laboratory seem to indicate otherwise; thus, cardiac output was reduced in patients with essential hypertension when obvious left ventricular hypertrophy was present.$^4$

We have also reported that, even in the absence of left ventricular enlargement, an abnormality of the left atrium may be demonstrated electrocardiographically.$^5$ This finding may be the sole evidence of left ventricular involvement in hypertension, and
it usually coexists with the auscultatory finding of an atrial diastolic gallop rhythm. 

Previous hemodynamic studies concerned with left ventricular hypertrophy were concerned with changes resulting from outflow tract obstruction, either from hypertrophic subaortic stenosis, from valvular aortic stenosis, or from experimentally induced ventricular hypertrophy produced by banding the outflow tract. These abnormalities are associated with either myocardial fibrosis or irregular distribution of myocardial hypertrophy. Therefore, little clinical information has been related to chronic eccentric left ventricular hypertrophy resulting from systemic hypertension in patients with essential or other forms of hypertension.

The present study was designed to correlate those clinical observations relating left atrial abnormality and left ventricular hypertrophy to hemodynamic functions in untreated essential hypertensive patients.

Materials and Methods

Ninety-seven untreated essential hypertensive patients and 25 normotensive volunteer individuals are the subjects of the present report. In all patients either they never had antihypertensive therapy prior to study or all medications (including diuretics and digitalis) had been discontinued for at least one month prior to study. Investigation in every instance failed to demonstrate a primary cause of hypertension, and renal arteriography and intravenous urography failed to demonstrate renal arterial or parenchymal disease. All patients had a standard 12-lead electrocardiogram and a 6-ft posterior-anterior and left lateral chest roentgenogram (timed in diastole) which formed the basis for classification of hypertensive heart disease.

Classification

Using body height and weight and the transverse cardiac diameter measured from the posterior-anterior chest X-rays, the Ungerleider index was determined for each patient. The electrocardiogram was used to determine the presence of left atrial abnormality by criteria reported previously. In brief, in order to satisfy diagnosis of left atrial abnormality at least two of the four following criteria were necessary: (1) terminal atrial forces in V1 must be equal to or more negative than $-0.04$ mm-sec as calculated from the depth and duration of the terminal negative deflection of the atrial complex; (2) the bipeak interval in deeply notched P waves should be wider than 0.04 sec in any lead; (3) the ratio of the duration of the P wave to the P-R segment should be greater than 1.6 in lead II; and (4) the P wave in lead II should be higher than 0.3 mv or longer than 0.12 sec.

In order to satisfy diagnosis of left ventricular enlargement, measurements from the conventional 12-lead electrocardiogram and Ungerleider index obtained from 6-ft posterior-anterior chest X-ray were used. The Ungerleider index was selected as one of the criteria for cardiac enlargement since any value 10% greater than normal indicates that cardiac enlargement is likely, and when 15% greater than normal it indicates that the heart is enlarged almost without exception. Several electrocardiographic criteria were selected to indicate left ventricular enlargement: (1) voltage, if the sum of the tallest and deepest precordial R and S waves exceeded 4.5 mv; electrical axis, if the frontal plane QRS vector axis was $0°$ or less; and left ventricular strain, if the S-T segment and T-wave vectors were $180°$ apart from the QRS vector. The high precordial voltage criterion was used because this index of left ventricular hypertrophy correlated very highly with autopsy findings of left ventricular hypertrophy and was shown to provide only a 1.6% false-positive diagnosis of left ventricular hypertrophy, although a higher prevalence of false-negative diagnoses was obtained. Thus, using both chest X-ray and electrocardiographic criteria, left ventricular enlargement was diagnosed if: the Ungerleider index exceeded 15%; all three electrocardiographic criteria were present (when this occurred the Ungerleider index invariably was greater than 10%); or if the Ungerleider index was greater than 10% and was also associated with at least two of the three electrocardiographic criteria. By employing these stringent criteria for left ventricular enlargement, we believed that all patients having cardiac enlargement did, in fact, have left ventricular hypertrophy, although there might well have been some patients in the groups with normal-sized hearts or with left atrial abnormality who could have had left ventricular hypertrophy. Thus, if left ventricular function were impaired significantly in the group with left ventricular enlargement as compared to the other groups, the finding would be all-the-more significant. On the basis of this classification the 97 essential hypertensive patients were divided into three groups: (I) normal-sized hearts, 54 patients whose average age was 39 years; (II) left atrial enlargement, including 20 patients whose average age was 49 years; and (III) left ventricular hypertrophy, comprising 23 patients whose average age was 48 years (table 1).
Table 1

Average Hemodynamic Data for the Normotensive Volunteer and Three Essential Hypertensive Groups

<table>
<thead>
<tr>
<th>Hemodynamic index</th>
<th>Normal</th>
<th>I†</th>
<th>II‡</th>
<th>III§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>25</td>
<td>54</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>20:5</td>
<td>37:17</td>
<td>14:6</td>
<td>20:3</td>
</tr>
<tr>
<td>Age and range (years)</td>
<td>34 (23–57)</td>
<td>39 (16–67)</td>
<td>49 (32–56)</td>
<td>48 (33–64)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.87</td>
<td>1.84</td>
<td>1.89</td>
<td>1.92</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>92 (1.5)</td>
<td>117 (2.7)</td>
<td>131 (3.7)</td>
<td>145 (3.7)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 (2.1)</td>
<td>75 (1.8)</td>
<td>79 (2.7)</td>
<td>74 (2.5)</td>
</tr>
<tr>
<td>Ejection time (msec)</td>
<td>310 (6)</td>
<td>282 (3)</td>
<td>270 (5)</td>
<td>271 (8)</td>
</tr>
<tr>
<td>Ejection time, corrected (msec)</td>
<td>330 (9)</td>
<td>315 (3)</td>
<td>309 (5)</td>
<td>298 (6)</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>3064 (87)</td>
<td>3129 (79)</td>
<td>2937 (91)</td>
<td>2528 (58)</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>84 (2.5)</td>
<td>77 (2.6)</td>
<td>71 (3.1)</td>
<td>67 (2.9)</td>
</tr>
<tr>
<td>LV ejection rate (ml/sec/m²)</td>
<td>152 (4.1)</td>
<td>149 (3.9)</td>
<td>135 (3.6)</td>
<td>129 (4.6)</td>
</tr>
<tr>
<td>Total peripheral index (mm Hg/ml/min)</td>
<td>0.017 (0.0005)</td>
<td>0.021 (0.0007)</td>
<td>0.024 (0.001)</td>
<td>0.031 (0.001)</td>
</tr>
<tr>
<td>Mean systolic pressure (mm Hg)</td>
<td>116 (2.3)</td>
<td>149 (3.3)</td>
<td>168 (4.9)</td>
<td>188 (4.4)</td>
</tr>
<tr>
<td>LV stroke work (g-m/m²)</td>
<td>77 (2.8)</td>
<td>90 (3.3)</td>
<td>92 (3.4)</td>
<td>96 (4.7)</td>
</tr>
<tr>
<td>LV stroke power (g-m/sec/m²)</td>
<td>248 (9.6)</td>
<td>319 (12.1)</td>
<td>342 (10.1)</td>
<td>355 (7.5)</td>
</tr>
<tr>
<td>LV tension-time index (mm Hg/sec/min)</td>
<td>2453 (128)</td>
<td>3172 (108)</td>
<td>3620 (150)</td>
<td>3673 (127)</td>
</tr>
<tr>
<td>Pressure-time/beat (mm Hg/sec)</td>
<td>36.9 (1.1)</td>
<td>41.8 (1.0)</td>
<td>46.0 (1.7)</td>
<td>50.9 (2.1)</td>
</tr>
<tr>
<td>Plasma volume (ml/cm)</td>
<td>18.3 (0.49)</td>
<td>17.0 (0.43)</td>
<td>18.0 (0.69)</td>
<td>18.0 (0.66)</td>
</tr>
</tbody>
</table>

Abbreviation: LV = left ventricular.
*Data presented represent the average for each group; numbers in parentheses = ± 1 standard error of the mean.
†Normal-sized hearts.
‡Left atrial abnormality.
§LV enlargement.

Hemodynamic Studies

The hemodynamic studies were performed in all patients in the morning after an overnight fast and without premedication as described previously.18, 19 In brief, catheters were introduced percutaneously into an antecubital vein and usually the ipsilateral brachial artery and advanced to the level of the subclavian vein, superior vena cava or right atrium, and shoulder levels, respectively. Cardiac output was determined at least in duplicate, usually in triplicate, with the subject in the supine position and then during the fifth minute of 50° upright tilt from indicator-dilution curves obtained by using 5 mg indocyanine green dye, which had been introduced already into the venous catheter and flushed centrally in a bolus using 5 ml normal saline. This technique of extracardiac dye injection has been shown to provide cardiac output values which are different from more central injections.20 Arterial pressure was recorded on a multichannel Sanborn polygraph, and mean arterial pressure was determined from the sum of the diastolic pressure and one-third of the pulse pressure. Mean systolic pressure was measured planimetrically. Left ventricular ejection time was determined from a rapid recording of the arterial pressure wave (100 mm/sec) by averaging the time from the onset of the upstroke of the pulse to the nadir of the dicrotic notch in 10 consecutive pulsations; this time was also corrected for heart rate from the square root of the R-R interval of the electrocardiogram recorded simultaneously with the arterial pressure pulse. Left ventricular ejection rate (index) was calculated by dividing the stroke index by the ejection time (ml/sec/m²); heart rate from the continuously recorded electrocardiogram (beats/min); left ventricular stroke work from the product of mean systolic pressure, 13.6, the stroke index, and 1.055, divided by 1000 (g-m/m²); the 13.6 is the factor used to convert from the mercury to water reference and 1.055 is the accepted specific gravity of blood; left ventricular stroke power (index) from the result of dividing the stroke work index by ejection time (g-m/sec/m²); tension-time index from the product of the mean systolic pressure, ejection time, and heart rate (mm Hg-sec/min); and the pressure-time per beat from the product of the mean systolic pressure and ejection time (mm Hg-sec). Plasma volume was determined prior to each hemodynamic study using radioiodinated human serum albumin after the patient had been resting supine for at least 30 min, according to techniques reported previously.21 Prior to obtaining the supine and upright tilt studies, Valsalva maneuvers were performed in duplicate by...
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B instructing the patient to blow against a fixed resistance of 40 mm Hg for 30 sec. All statistical comparisons were made using the Student t-test.

Results

Hemodynamic Characteristics

A summary of the averaged hemodynamic data for the normotensive and each of the three hypertensive groups is presented in table 1 and figure 1. In general, age increased with increasing severity of hypertensive heart disease although those patients with normalized hearts were not significantly older than those individuals of the normal volunteer group, and patients with left atrial enlargement were not significantly different from those with left ventricular hypertrophy.

Heart rate was faster than normal in all essential hypertensive groups and the differences among these groups were not significant (fig. 1). Mean arterial pressure and total peripheral resistance, however, increased progressively from groups I to II to III (the level of statistical significance between each group was \( P < 0.001 \)).

Increased arterial pressure and total peripheral resistance were associated with normal cardiac index despite a significant reduction in left ventricular ejection rate in patients with
left atrial enlargement (group II). Thus, even though normal cardiac output was preserved in these patients, left ventricular ejection rate was reduced from 149 to 135 ml/sec/m² ($P < 0.01$) and was related to a relatively greater fall in stroke volume than in ejection time (table 1). The reduction in left ventricular ejection rate in the patients with left atrial enlargement (group II), as compared with those having normal-sized hearts (group I) was significant ($P < 0.02$); however, the decrease in stroke volumes between these groups was not significant.

Only with development of left ventricular enlargement did cardiac index fall significantly to 2.5 liters/min/m² from the normal level of 3.0 liters/min/m² ($P < 0.001$); associated with this reduction was a further impairment of left ventricular ejection rate (129 ml/sec/m²). Since heart rate remained no different from the other two hypertensive groups and was significantly faster than normal, this reduction can be explained primarily by a further fall in stroke volume.

Associated with these hemodynamic changes were significant increases in left ventricular stroke work and stroke power, in tension-time index, and in the pressure-time per beat indices (table 1 and fig. 1C). Left ventricular stroke work and stroke power must be greater than normal in hypertensive patients; mean systolic pressure is increased in hypertension. Significant differences among the three hypertensive groups were not evident, however, because as arterial pressure and total peripheral resistance increased, stroke volume progressively fell. Thus, external cardiac work and power failed to increase progressively with increasing pressure and resistance. However, when tension-time index and pressure-time per beat were used to compare hypertensive groups, the significant differences observed among groups with respect to pressure and total peripheral resistance once more became evident with respect to left ventricular function. Each of these indices increased progressively from one hypertensive group to the next, and these changes were more evident with the pressure-time per beat expression since the insignificant, but measurable, group variations in heart rate were taken into consideration.

### Neural Indices

There was no difference in the increase of diastolic arterial pressure during the overshoot phase of the Valsalva maneuver between the groups of normal subjects and patients with normal-sized hearts or atrial enlargement; however, the response was significantly attenuated in those patients with cardiac enlargement with respect to normal individuals ($P < 0.05$) and other hypertensive groups ($P < 0.005$) (table 2). The patients with cardiac enlargement (group III) responded to upright tilt with a 22% increase in total peripheral resistance. This response was similar to that observed in the normal subjects.
(21%), but less than in the other two hypertensive groups (28 and 30%, respectively). The responses of diastolic-pressure overshoot during theValsalva maneuver and total peripheral resistance during upright tilt reflect either reflex adrenergic activity or vasomotor responsiveness to adrenergic stimulation during these physiological stresses. More specific physiological indices of cardiac adrenergic activity might be inferred from resting cardiac rate or left ventricular ejection rate. Thus, left ventricular ejection rate (index) was normal in those patients with normal-sized hearts but was reduced significantly in those with both left atrial (group II) and left ventricular (group III) enlargement \( (P < 0.05) \). Resting supine cardiac rate was always faster than normal in all hypertensive groups (group I, \( P < 0.01 \); group II, \( P < 0.005 \); group III, \( P < 0.05 \)); however, during upright tilt these differences no longer were observed. Thus, whereas cardiac rate increased significantly in all groups (normal and hypertensive) during upright position, the only hypertensive group to continue to demonstrate a faster heart rate than normal during tilt were those with normal-sized hearts (group I, \( P < 0.01 \)); the left atrial \( (P < 0.10) \) and ventricular enlargement \( (P < 0.25) \) groups no longer were different from the normal.

**Coronary Arteriography**

Because 23 of these 97 patients had certain complaints suggesting coronary arterial disease (e.g. chest pain suggesting coronary insufficiency), selective coronary cineangiographic studies were performed in the laboratories of Dr. F. Mason Sones. Of 21 patients who failed to demonstrate significant occlusive coronary arterial disease, 12 had normal-sized hearts, four had left atrial abnormality, and five, left ventricular enlargement. Averages of these groups reflected the same changes observed in the larger groups to which they belonged (table 3). These findings, therefore, provide greater credence that the hemodynamic changes described for the various hypertensive groups are attributable to systemic hypertension rather than to associated coronary atherosclerosis.

**Discussion**

The results of this study clearly demonstrate that left ventricular function is not normal either in hypertensive left ventricular hypertrophy or even immediately before ventricular hypertrophy becomes clinically obvious (left

**Table 3**

Averages of Hemodynamic Indices in Twenty-One Hypertensive Patients Included in the Present Study and in whom no Evidence of Significant Coronary Arterial Atherosclerosis was Demonstrated

<table>
<thead>
<tr>
<th>Hemodynamic index</th>
<th>I*</th>
<th>II†</th>
<th>III‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>12</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>9:3</td>
<td>2:2</td>
<td>5:0</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>44</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.82</td>
<td>1.76</td>
<td>1.95</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>107</td>
<td>128</td>
<td>140</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72</td>
<td>81</td>
<td>83</td>
</tr>
<tr>
<td>Ejection time (msec)</td>
<td>297</td>
<td>266</td>
<td>259</td>
</tr>
<tr>
<td>Ejection time, corrected (msec)</td>
<td>323</td>
<td>309</td>
<td>297</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>2990</td>
<td>2783</td>
<td>2572</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>78</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>LV ejection rate (ml/sec/m²)</td>
<td>144</td>
<td>131</td>
<td>123</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg/ml/min)</td>
<td>0.020</td>
<td>0.027</td>
<td>0.028</td>
</tr>
</tbody>
</table>

*Normal-sized hearts.
†Left atrial abnormality.
‡LV enlargement.
atrial abnormality). Included in our current concept of hypertensive heart disease is the notion that cardiac output remains normal until left ventricular failure supervenes. The data presented indicate that cardiac output is significantly reduced in hypertensive patients with left ventricular hypertrophy without evidence of cardiac decompensation. That these changes occurred without evidence of left ventricular decompensation is shown by failure of plasma volume and heart rate to increase with development of left atrial abnormality or left ventricular enlargement as well as the absence of clinical signs and symptoms of failure or radiological evidence of pulmonary congestion. Moreover, when cardiac output was reduced, there was no measurable change in cardiopulmonary volume (in those patients whose catheterization included placement of arterial and venous catheters just distal to aortic valve and in the right atrium, respectively). Furthermore, none of the patients demonstrated the abnormal square-wave Valsalva phenomenon of cardiac failure. That these changes are most likely related to systemic hypertension and not to atherosclerotic cardiac disease is indicated by confirmation of these hemodynamic findings in 21 of these patients who had selective coronary arteriography and failed to demonstrate evidence of significant occlusive coronary arterial disease.

Early in the development of left ventricular involvement in hypertension, when left atrial abnormality only is evident clinically, left ventricular ejection rate was reduced, and arterial pressure, total peripheral resistance, and pressure-time per beat were increased significantly in comparison with patients having no cardiac abnormalities (group I); but resting cardiac output remained normal. Only when left ventricular hypertrophy became evident clinically did cardiac output fall. That ventricular hypertrophy seems to be a succeeding stage in the development of hypertensive heart disease from the preceding one of left atrial enlargement is strongly suggested by the presence of left atrial abnormality in all patients with left ventricular hypertrophy.

An additional clinical index of left atrial abnormality is the presence of the fourth heart sound (atrial diastolic gallop), which is found with a high degree of concordance in association with at least two electrocardiographic criteria of the left atrial abnormality. We emphasize that these two findings do not indicate atrial disease but rather reflect atrial manifestations of diminished left ventricular compliance of the “hypertrophying” left ventricular myocardium. Perhaps at this stage of the development of ventricular hypertrophy the atrium is providing that extra “kick” which is helping to maintain cardiac output at normal levels.

Such a clinical description of a physiological grouping is arbitrary since the spectrum from patients having a normal heart to those with obvious clinical ventricular hypertrophy must be gradual. Hence, one would expect the variation of such a transitional grouping to be such that only statistical significance would be shown. By classifying this group of patients with left ventricular abnormality as one of left ventricular dysfunction we mean to emphasize that, to maintain normal cardiac output in the presence of persistent increasing arterial pressure and peripheral vascular resistance and diminished rate of ventricular ejection, the myocardium must be initiating some of its adaptive mechanisms (i.e., hypertrophy) and the “booster action” of atrial systole.

It comes as no surprise that stroke work and stroke power are higher in hypertensive patients than in normal individuals; by definition, mean systolic pressure must be greater in hypertension. When more sensitive indices of left ventricular function (tension-time index and pressure-time per beat) were used, significant and progressive group differences became evident among the hypertensive groups. These latter indices are in direct relation to myocardial oxygen consumption because pressure has been shown to be the most costly determinant of left ventricular work. This was best demonstrated with the pressure-time per beat index, because with
this expression of tension-time index the insignificant, but measurable, group variation in heart rate is taken into consideration. While direct left ventricular pressure and volume measurements were not obtained to provide more precise calculation of tension, left ventricular enlargement was evident between the normal-sized group and the ventricular enlargement groups of hypertensive patients (by definition); and it therefore seems obvious that myocardial tension must have increased progressively from group to group. Thus, the significant gradations between the three hypertensive groups were evident both in pressure-time per beat and left ventricular ejection rate.

It may be argued that without direct left ventricular pressure and volume measurements the indices of left ventricular function are less accurate. This, is admittedly true; but it is most difficult to justify direct left ventricular studies in hypertensive patients without other indications for left ventricular studies. Our procedure involved insertion of catheters to shoulder level and, when compared with simultaneously recorded carotid arterial pulse waves, significant differences in ejection time were not measured. Special effort was made to insure that the subjects were undisturbed by extraneous stimuli; the laboratory was restricted to individuals concerned with the study, noise was minimal, temperature was relatively constant, each patient remained at complete supine rest for 30 min following insertion of the catheters, the room remained well lit, and the patients were not premedicated. These situations are difficult to duplicate in the circumstances involving left ventricular catheterization and biplane ventriculography, because a darkened room with fluoroscopy, premedication, and extraneous noise and conversation are frequently necessary.

Question may always arise concerning the influence of increasing age of the groups as an explanation for the hemodynamic changes observed. The reduction of cardiac index in patients with left ventricular enlargement (group III) most likely is unrelated to the older age of this group as compared to the other groups, since this group's mean age was not different from the patients with left atrial abnormality (group II; 49 and 48 years, respectively); and cardiac output was significantly lower in those with left ventricular hypertrophy ($P < 0.001$). Alternatively, this same argument may be used to explain the maintenance of normal cardiac output in the patients with left atrial abnormality (group II, 2937 ml/min/m²) if these individuals are compared with those patients with normal-sized hearts who were on the average 10 years younger but whose cardiac index was 3129 ml/min/m². Finally, cardiac index was normal in patients with normal-sized hearts who were of the same age as the normotensive group.

The left ventricular ejection rate characterizes only one aspect of cardiac contractility; it reflects only an average rate of flow, provides no information concerning the instantaneous rate of ejection, and is obviously far removed from the original "velocity" of Hill. However, it is an easily obtained and useful index of contractility$^{26–29}$ when adequately interpreted in relation to other factors. Studies of aortic root velocity$^{30–32}$ have shown that the curves obtained were not asymmetrical and their shape was such that derived mean velocities did not introduce any gross misinterpretation.

As ejection time and stroke volume are closely correlated,$^{28}$ their association in the calculation of left ventricular ejection rate allows more precise evaluation of ventricular ejection than consideration of ejection time alone. Weissler et al. and Levine et al. concluded that in enlarged hearts even the finding of a normal ejection time index$^{27, 28}$ or normal rate of ventricular ejection$^{28}$ would indicate impaired contractility. The same reasoning obviously applies to reduction of left ventricular ejection rate below normal values. Whether this reduction depends on primary myocardial factors, excessive systyolic load, or altered neurogenic influences obviously depends upon the particular conditions of that instance.

Responses of total peripheral resistance to upright tilt, of diastolic pressure during the
overshoot phase of the Valsalva maneuver, supine and upright-tilt heart rate, and resting left ventricular ejection rate were used to compare differences in neurogenic reflex activity between groups. The data from the Valsalva maneuver indicate that patients with ventricular hypertrophy demonstrate a diminished supine peripheral reflex adrenergic responsiveness, although intrinsic in the overshoot response is the increase of cardiac output with resumption of venous return. These data, then, together with the lesser increase in heart rate during upright tilt, the lesser increase in peripheral resistance during upright tilt, and the reduced left ventricular ejection rate, suggest that neurogenic reflex activity is significantly reduced in patients not only with ventricular hypertrophy but also perhaps even when the ventricle has not manifested this hypertrophy clinically (left atrial abnormality group). These in vivo findings of reduced neurogenic reflex activity and impaired hemodynamic function in left ventricular hypertrophy are reminiscent of the in vitro studies on cat papillary muscle from hypertrophied nonfailing myocardium.33

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