Hemodynamics in Labile Hypertension

A Follow-Up Study


PRELIMINARY WORK from this laboratory has suggested that the measurement of hemodynamics might have value as a prognostic test in labile hypertension.\(^1\) In patients with this abnormality, some will demonstrate a high cardiac output and a lower than normal total peripheral resistance. It was our feeling, based on this original work, that this pattern might be an early phase or a benign type of essential hypertension. This is a report of the first follow-up study done on a group of such labile hypertensive patients in whom the hemodynamics and clinical status have been studied over a period of 50 months to determine which one of the two possibilities mentioned might be true.

Methods

A total of 68 patients with initial hemodynamic measurements had follow-up studies, and in 48 of these, cardiac output and blood pressure were measured. Fifty-five of the subjects were part of the original group studied prior to 1960, and 13 were first studied between 1960 and 1961. The patients were initially selected as having labile hypertension by the following criteria: (1) a hospitalized patient less than age 30 with blood pressure, as measured by the admitting house officer, above 150/90 mm Hg; (2) a hospitalized patient over age 30 with blood pressure above 150/100 mm Hg; and (3) a patient, who, without treatment, had at least one blood pressure reading below the admitting levels in the first 3 days after hospitalization. No patient was included in the study who had evidence of renal disease, angina pectoris, prior myocardial infarction, or cerebral vascular accident by history, physical examination or laboratory studies. Only one patient was included with eye ground changes classified above grade II of the Keith, Wagener, and Barker method. The majority of the patients were selected from the general medical wards of a Veterans Administration Hospital. A complete history was obtained from all subjects; also physical examination, blood counts, urinalysis, and determination of blood nonprotein nitrogen were performed and chest x-rays and a 12-lead electrocardiogram were made. In addition, all had a determination of cardiac output.

Follow-up studies were started in 1962 and continued to the spring of 1965. Every effort was made to contact all 74 patients that were part of the initial study published in 1962. In all cases, an attempt was made to contact the patient by phone, and all the follow-up information is based on at least a phone conversation. The following historical information was obtained: age, occupation, change in family history of hypertension, symptoms of shortness of breath, chest pain on exertion, headache, dizziness, weakness or nocturia, treatment for hypertension, current status of blood pressure, and finally the name of the family physician. When necessary the family physician was called to clarify the points regarding clinical status and treatment. The patients were also asked to come to the hospital as outpatients for a more comprehensive history, and in addition, physical examination, urinalysis, chest x-ray, ECG, and a determination of the cardiac output. Fifty-five of the original 74 patients were contacted, and 35 of these came to the hospital for complete studies. An additional 13 patients studied between 1960 and 1961 also responded and came in for follow-up study.

All hemodynamic measurements were made in a similar manner. At the time of the initial study, the test was carefully explained to the patient in advance. On the following day, the patient was brought to the cardiovascular laboratory in the morning, and under local anesthesia, an 18-gauge Cournand needle was introduced into the right brachial artery, and an 18-gauge intravenous needle was placed in the left antecubital vein. The patient then rested 20 minutes, or longer if necessary, until the auscultatory blood pressure and pulse were stable over a 5-minute period. The first cardiac output was then determined, and
Hemodynamics with Follow-up Study

<table>
<thead>
<tr>
<th>Cardiac Group</th>
<th>No. of patients</th>
<th>Cardiac index (L/min/m²)</th>
<th>Pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I*</td>
<td>II†</td>
</tr>
<tr>
<td>Under age 50 yr</td>
<td></td>
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<tr>
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<td>16</td>
<td>5.97</td>
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<tr>
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<td>25</td>
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<td>3.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±0.53</td>
<td>±0.72</td>
</tr>
<tr>
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</tr>
<tr>
<td>Normal</td>
<td>6</td>
<td>3.55</td>
<td>3.25</td>
</tr>
</tbody>
</table>

*I = Initial study. †II = Follow-up study.

the study was repeated in 10 minutes. The two cardiac outputs were required to check within 12% or the study was discarded. In all cases, the first of the two cardiac outputs was used for statistical purposes and for calculation of total peripheral resistance. The cardiac outputs were measured by using radioactive iodinated human serum albumin as the indicator, and taking interrupted samples every 2 seconds. Details of the technique for injection, collection, analysis of the samples, and calculation of the results have been published.¹

For the follow-up hemodynamic studies, the procedure was as comparable as possible, although all the studies were done on an outpatient basis. The patients were familiar with the test. They were all studied after a light breakfast or lunch. Local anesthesia was used to cannulate the vessels, and the patients rested for 20 minutes or until the blood pressure and pulse were stable. Cardiac output measurements were again done in duplicate, as required to check within 12%, and the first cardiac output was used in the calculations and statistics. The oxygen consumption was measured in 16 patients with labile hypertension and in five normal subjects. Expired air was collected in a 120-L Collins gasometer and the contents were analyzed by the Scholander technique.

Results

A total of 68 patients had follow-up studies. The results are summarized in tables 1 to 3 and figures 1 and 2. The detailed clinical and hemodynamic studies for the subjects under age 50 are shown in tables 4 and 5. The mean duration of follow-up for the entire group was 50.4 months. In analyzing the results, those for the 52 patients under age 50 were analyzed separately. Repeat hemodynamic studies were done in 41 of the 52, and these studies will be discussed first. In our initial report, the patients were separated into two groups using a cardiac index of 4.77 L/min/m² as the dividing line. This cardiac index, based on 28 normal subjects, is two standard deviations above the normal mean for this laboratory. The separation between the two groups by using cardiac index is obviously statistically significant (P < 0.001), and in addition, the separation between them for total peripheral resistance and heart rate is also significant (P < 0.001). There was no difference in blood pressure.

At the time of the follow-up study, the blood pressure had risen in both groups, as shown in table 1 and figure 2. Thirty-four patients now had blood pressure above 150/90 mm Hg. Only five, all in the normal cardiac index group, had blood pressures below 150/90 mm Hg at the time of both studies. In the patients with an initially high cardiac index, the cardiac index fell into the normal range in eight, while the total peripheral resistance and blood pressure rose (figs. 1 and 2). The difference in the cardiac index between the two groups was still statistically significant, but at a much lower level (P < 0.05). Two of the subjects, with a normal cardiac index at the initial study, now demonstrated a rise of cardiac index into the high range at follow-up. One of these two subjects had undergone nephrectomy for a lacerated kidney 2 years prior to the follow-up study.

In addition to the 41 subjects under age 50 who had repeat hemodynamic studies,
there were 11 in whom some clinical follow-up was available based on at least a phone call. The clinical information available for the 52 subjects is shown in tables 2 and 3. The 20 subjects with an initially high cardiac index were in generally good health and working. In the normal cardiac index group, one had died of a myocardial infarction, and the other had had cerebral thrombosis. The remaining 18 patients were in good health and working. There was no difference between the groups in terms of the duration of known hypertension, family history, or the presence of symptoms. In table 3, the results of the physical examination and laboratory studies are tabulated. In the high cardiac index group, in addition to the 16 subjects studied hemodynamically, one had been recently hospitalized for elective surgery whose chart provided sufficient information for us to use. There are, therefore, 17 subjects in this group. The following criteria were used for evaluation: (1) Eye grounds were graded by the classification of Keith, Wagener, and Barker; (2) the presence of a systolic murmur either apical or along the left sternal border was recorded; (3) left ventricular enlargement was determined by chest x-rays using the transverse diameter of the heart on the anteroposterior projection and the relationship between the inferior vena cava and the left ventricle on the lateral view; and (4) on the electrocardiogram, evidence for left ventricular enlargement either by the criteria of Sokolow and Lyon or nonspecific ST segment and T-wave depression or flattening. The one major complication of cerebral thrombosis and one death occurred in the normal cardiac index group. Otherwise, the two groups were similar. Detailed hemodynamic and clinical data are given in tables 4 and 5.

Sixteen patients over age 50 had follow-up studies and seven of these 16 patients had hemodynamic measurements. Only one patient was in the high cardiac index group, and on the repeat study, his cardiac index was within the normal range. He was the only patient with eye grounds above grade II in the entire study (grade IV), and is included because on treatment with reserpine his eye ground condition returned to grade II. He has lived for 77 months, continuing to work full time. However, at present he does have evidence of basilar artery insufficiency. In the six patients with an initially normal cardiac index, the hemodynamic findings remained the same on the repeat study. For the clinical follow-up study, there was, in addition to those studied hemodynamically, one patient in each group in whom a recent hospitalization provided sufficient information for their inclusion. The incidence of complications by history (table 2) is high in both groups. Of the five with the initially elevated cardiac index, two died of myocardial infarction, one has basilar artery insufficiency, and one developed congestive failure. In the normal cardiac index group, two died of myocardial infarction and one of an unknown cause. The complications by physical examination and

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<th>Stroke volume (cc)</th>
<th>Blood pressure (mm Hg)</th>
<th>Total peripheral resistance (dynes sec cm⁻⁵)</th>
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<td>II</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
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<td>116.0</td>
<td>157/96</td>
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<td>167/96</td>
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<tr>
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<td>99.5</td>
<td>136/89</td>
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<td>149/95</td>
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### Table 2

**Complications by History**

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<th>No. of patients</th>
<th>Age, yr</th>
<th>Duration of hypertension, yr</th>
<th>Known hypertension, yr</th>
<th>Family history</th>
<th>Symptoms</th>
<th>Treatment for hypertension, yr</th>
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<td>39.2</td>
<td>55.9</td>
<td>4.0</td>
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<td>0</td>
<td>4</td>
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<td>46.6</td>
<td>5.4</td>
<td>10</td>
<td>1 headache</td>
<td>0</td>
<td>1 death</td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 stroke</td>
</tr>
<tr>
<td>Over age 50</td>
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<td></td>
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<td></td>
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<tr>
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<td>5</td>
<td>60.4</td>
<td>55.6</td>
<td>7.0</td>
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<td>0</td>
<td>BAI‡</td>
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<td>49.9</td>
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<td>1 PAT‡</td>
<td>1 PAT</td>
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</table>
*At the time of its initial study.

†BAI = basilar artery insufficiency; PAT = paroxysmal atrial tachycardia.

### Table 3

**Complications by Physical Examination and Laboratory Studies**

<table>
<thead>
<tr>
<th>Cardiac index</th>
<th>No. of patients</th>
<th>LVE by chest x-ray</th>
<th>ECG-LVE and / or ST and T-wave changes</th>
<th>Systolic murmur</th>
<th>Eye grounds</th>
<th>Albuminuria</th>
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<tr>
<td></td>
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<td>Follow-up</td>
<td>Initial</td>
<td>Follow-up</td>
<td>Initial</td>
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</tr>
<tr>
<td>High</td>
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<td>3</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
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<td>4</td>
<td>7</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Over age 50</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>2</td>
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<td>1</td>
<td>2</td>
<td>0</td>
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<td>3</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

*LVE = Enlarged left ventricle.
Figure 1
Relationship between cardiac index and peripheral resistance in labile hypertension.

Figure 2
Relationship between cardiac index and mean blood pressure in labile hypertension.
### Seventeen Patients with a High Cardiac Index

<table>
<thead>
<tr>
<th>Patients</th>
<th>Initial age, yr</th>
<th>Follow-up, mo</th>
<th>Family history</th>
<th>Complications</th>
<th>Initial</th>
<th>Follow-up</th>
<th>Treatment</th>
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</thead>
<tbody>
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<td>L.L.</td>
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<td>G-I, S</td>
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<td>None</td>
</tr>
<tr>
<td>I.H.</td>
<td>45</td>
<td>40</td>
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<td>None</td>
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<tr>
<td>J.Pa.</td>
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<td>E</td>
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<td>106</td>
<td>None</td>
<td>G-I</td>
<td>None</td>
<td>None</td>
<td>+</td>
</tr>
<tr>
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<td>70</td>
<td>M</td>
<td>None</td>
<td>G-I</td>
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<td>None</td>
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<tr>
<td>K.F.</td>
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<td>M</td>
<td>X, S</td>
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<tr>
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<td>X, G-II</td>
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<td>E</td>
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<td>F</td>
<td>S</td>
<td>G-I</td>
<td>R</td>
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</table>

Abbreviations: A, angina pectoris; E, ECG abnormality—left ventricular enlargement or ST & T-wave changes or both; S, systolic murmur; G, eye grounds (grades I and II); P, proteinuria; A, alpha-methyl dopa; R, reserpine; +, drug not known; BSA, body surface area; and X, LVE by x-ray.

### Twenty-five Patients with a Normal Cardiac Index

<table>
<thead>
<tr>
<th>Patients</th>
<th>Initial age, yr</th>
<th>Follow-up, mo</th>
<th>Family history</th>
<th>Complications</th>
<th>Initial</th>
<th>Follow-up</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
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<td>F &amp; M</td>
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<td>51</td>
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<td>G-I</td>
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Abbreviations: A, angina pectoris; E, ECG abnormality—left ventricular enlargement or ST & T-wave changes or both; S, systolic murmur; G, eye grounds (grades I and II); P, proteinuria; +, drug not known; BSA, body surface area and X, LVE by x-ray.
### LABILE HYPERTENSION

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<th>Cardiac output</th>
<th>Blood pressure, mm Hg</th>
<th>Pulse</th>
<th>Total peripheral resistance</th>
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**Cardiac output**

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laboratory studies are similar for the two groups, although only two subjects with high cardiac indices were examined.

Discussion

There is now considerable evidence in the literature demonstrating that some subjects with elevated blood pressure will have an elevated cardiac output and lower than normal peripheral resistance. This differs from the usual hemodynamics in hypertension in which the cardiac output is normal and the total peripheral resistance is elevated. It has been suggested by us as well as others that the high cardiac output pattern may represent the initial stage in the development of fixed essential hypertension. Ledingham and Cohen found an elevated cardiac output as the first hemodynamic change in the development of experimental renal hypertension in the rat, although this was not shown by Olmsted and Page in dogs with renal hypertension. Wilson postulated that the initial abnormality in hypertension may be an excessive retention of sodium by the kidney. This leads to an increased extracellular volume and a rise in cardiac output by the Starling mechanism. Eventually, the high cardiac output is compensated by autoregulation, and the peripheral resistance rises, leading to the usual hemodynamic condition in hypertension, a normal cardiac index, and a high total peripheral resistance. Certainly hypertensive patients do have an abnormal response to a salt load, both in terms of excretion and hemodynamics.

The present study is part of a continuing project by means of long-term follow-up studies to test the hypothesis that the high cardiac output pattern is an earlier or more benign process than the normal cardiac index pattern is. The group of patients studied had labile hypertension. The initial blood pressure was elevated, but at least one normal pressure was found within 3 days. This type of patient was chosen in order to study subjects early in the course of the disease who might demonstrate the elevated cardiac output pattern. It is probably true that all of these subjects do not have essential hypertension. Five subjects had normal blood pressure both times they were studied. However, the blood pressure was elevated on the repeat study in 34 of the other 43 subjects and had been elevated on the initial study in the remaining four subjects. The mean blood pressure rose during the follow-up period in the subjects under age 50, and it would appear that the majority of subjects chosen do demonstrate a consistent elevation of blood pressure.

Whether or not patients with the high cardiac indices are a separate group, with earlier or more benign hypertension, is difficult to prove. At the time of the initial study, efforts were made to rule out possible causes for the elevated cardiac output. Thyroid status was assessed by determining the concentrations of protein-bound iodine, and all were within the normal range. Plasma norepinephrine and epinephrine were measured, and they did not relate to hemodynamics. Certainly it is possible that the patients with high cardiac indices were more anxious, for the pulse was significantly elevated, and remained so on repeat studies. Anxiety is difficult to quantitate, but these patients did not appear more anxious, nor did they admit to more anxiety. Oxygen consumption in these subjects showed a linear relationship with the cardiac output, which would not be expected with anxiety (fig. 3). Finally, if anxiety were the only cause of the elevated cardiac output, then this hemodynamic pattern would still represent a different response to the stress of the test than that seen in subjects with the normal cardiac indices.

This study appears to document that high cardiac output tends to fall with time. For patients under 50 years of age, eight of the 16 had repeat cardiac indices in the normal range, and as the index fell the total peripheral resistance rose. This suggests that the process is an earlier phase and not a separate entity. That the two groups are not mutually exclusive is emphasized by two of the subjects whose cardiac indices rose from normal into the high range. Whether these two pat-

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LABILE HYPERTENSION

Relationship between oxygen consumption and cardiac output.

Figure 3

Relationship between oxygen consumption and cardiac output.

-patterns are truly different in terms of prognosis will have to await longer follow-up. In those under age 50, in the normal cardiac index subjects, one had a stroke and one died. However, other than that, the two groups were similar. For those over age 50, complications were high in both patterns, probably a reflection of their increased age.

Summary

A preliminary follow-up study has been carried out in 68 labile hypertensive patients followed for an average of 50.4 months. The high cardiac output pattern found initially tended to revert toward a normal cardiac output and higher total peripheral resistance. This suggests that the high cardiac output pattern is an early hemodynamic abnormality. No difference between those groups could be shown on the basis of complications at the time of this study.

References

Hemodynamics in Labile Hypertension: A Follow-Up Study
ROBERT H. EICH, RICHARD P. CUDDY, HAROLD SMULYAN and RICHARD
H. LYONS

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