A Hemodynamic Comparison of Essential and Renovascular Hypertension

Cardiac Output and Total Peripheral Resistance
Supine and Tilted Patients

By Edward D. Frohlich, M.D., Milos Ulrych, M.D., Robert C. Tarazi, M.B., B.Ch., M.D., Harriet P. Dustan, M.D., and Irvine H. Page, M.D.

SUMMARY
Systemic hemodynamic measurements were obtained in 15 normal subjects and 30 untreated hypertensive patients (15 with essential hypertension and 15 with fibrosing stenosis of renal arteries). The essential hypertensives were selected from a larger group solely on the basis of matching their mean arterial pressures and ages with those of the patients with renal arterial disease in matched pairs; cardiac index was consistently higher in patients with renovascular hypertension than in those with essential hypertension. The higher cardiac output was maintained in the group with renal arterial disease even when reduced by tilting the subjects to a 50° head-up position. Total peripheral resistance was increased in both hypertensive groups. The low cardiac indices and mean rates of left ventricular ejection found in essential hypertension may also implicate the heart in this form of hypertension. Hence, increased total peripheral resistance, long thought to be the hemodynamic hallmark of hypertension, may not be the sole systemic abnormality; cardiac output may be increased in renal arterial disease and even reduced in essential hypertension.

Additional Indexing Words: Angiotensin Blood volume Renal artery disease

Increased vascular resistance is considered the hemodynamic hallmark of diastolic hypertension.1, 2 With the exception of a few reports indicating that cardiac output participates in labile3-5 and mild essential hypertension,6-10 the heart is thought to play a secondary role. Lability of blood pressure is often associated with renal arterial stenosis suggesting that cardiac output might also be affected in this form of hypertension.

Important for description of characteristics of hypertensive diseases is the classification of patients into homogeneous groups by using selective renal arteriography11 for diagnosis of renal arterial lesions and by eliminating patients with malignant and reversed-malignant hypertension, thyrotoxicosis, primary aldosteronism, and “labile” hypertension. This study compares the systemic hemodynamics of normal subjects with those of patients having essential and renovascular hypertension.

Methods
Hemodynamic functions were studied in 15 healthy, normotensive subjects (not hospitalized) and 30 hypertensive patients (15 with essential hypertension and 15 with nonatherosclerotic renal arterial lesions). The known duration of hypertension between the groups was compared and there was no significant difference between the duration of hypertension in the essential and renovascular groups. The mean duration was 9.3 years for both groups with a range of 4 months to 24 years for essential hypertensives and a range of 2 months to 31 years for the patients with renovascular hypertension. Renal arteriography was performed in all patients and four normal subjects who were volunteer donors for

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renal homotransplantation. None of the patients had congestive heart failure and none had taken antihypertensive drugs (including diuretics) for at least 1 month prior to study. The 15 essential hypertensives were selected from a larger group because their mean arterial pressures could be matched with those of patients having renal arterial disease. Care was also taken to match for age and severity; such matching was not possible for sex (tables 1 and 2). Whereas there was similar sex distribution in the normal and essential hypertension groups, this was not the case for the group with nonatherosclerotic renal arterial lesions; these lesions occur more frequently in women.\textsuperscript{12} Patients with atherosclerotic renal arterial lesions were excluded lest they might also have unrecognized coronary arterial disease.

Each study was performed without premedication in the morning after an overnight fast. A polyethylene tubing was inserted through an antecubital vein into the subclavian vein, superior vena cava, or right atrium for injection of indocyanine-green dye, and an 18-gauge, thin-walled needle was inserted into the ipsilateral brachial artery for measurement of intra-arterial pressure and withdrawal of blood for indicator-dilution curves using the Gilford densitometer, cuvette,

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**Table 1**

*Characteristics of the Normal, Essential Hypertensives, and Renal Arterial Disease Groups with Respect to Number, Age, Sex, and Body Surface Area Which Permitted a Matching of the Patient Groups on the Basis of Mean Arterial Pressure and a Comparison of Cardiac Indices*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal</th>
<th>Essential hypertension</th>
<th>Renal arterial disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number 15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Male: female</td>
<td>13:2</td>
<td>13:3</td>
<td>3:12</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>33</td>
<td>48</td>
<td>41</td>
</tr>
<tr>
<td>Range 23-43</td>
<td>33-62</td>
<td>17-52</td>
<td></td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.90</td>
<td>1.90</td>
<td>1.69</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>3003</td>
<td>2662</td>
<td>3314</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>91</td>
<td>127</td>
<td>125</td>
</tr>
</tbody>
</table>

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**Table 2**

*A Comparison of Patients with Nonatherosclerotic Renal Arterial Lesions and Essential Hypertension Demonstrating that, when Matched for Mean Arterial Pressure, Cardiac Index Was Consistently Higher in Each Patient with Renovascular Hypertension*

<table>
<thead>
<tr>
<th>No.</th>
<th>Essential hypertension</th>
<th>Renal arterial disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean arterial pressure (mm Hg)</td>
<td>Cardiac index (ml/min/m²)</td>
</tr>
<tr>
<td>1</td>
<td>119</td>
<td>2459</td>
</tr>
<tr>
<td>2</td>
<td>126</td>
<td>2407</td>
</tr>
<tr>
<td>3</td>
<td>128</td>
<td>2766</td>
</tr>
<tr>
<td>4</td>
<td>113</td>
<td>3004</td>
</tr>
<tr>
<td>5</td>
<td>166</td>
<td>2738</td>
</tr>
<tr>
<td>6</td>
<td>155</td>
<td>2456</td>
</tr>
<tr>
<td>7</td>
<td>137</td>
<td>2268</td>
</tr>
<tr>
<td>8</td>
<td>145</td>
<td>3260</td>
</tr>
<tr>
<td>9</td>
<td>119</td>
<td>2301</td>
</tr>
<tr>
<td>10</td>
<td>101</td>
<td>2892</td>
</tr>
<tr>
<td>11</td>
<td>111</td>
<td>2133</td>
</tr>
<tr>
<td>12</td>
<td>134</td>
<td>3110</td>
</tr>
<tr>
<td>13</td>
<td>102</td>
<td>2470</td>
</tr>
<tr>
<td>14</td>
<td>116</td>
<td>2805</td>
</tr>
<tr>
<td>15</td>
<td>129</td>
<td>2965</td>
</tr>
<tr>
<td>Average</td>
<td>127</td>
<td>2662</td>
</tr>
</tbody>
</table>
and withdrawal pump. Care was taken to keep the pressure transducer and needle at right atrial level.

After 40 minutes' rest in the supine position, arterial pressure and cardiac output determinations were obtained in duplicate (usually within 3 minutes of each other). The patient was then tilted to a 50-degree head-up position for 5 minutes and arterial pressure was continuously recorded except during blood withdrawal for cardiac output determination at 2 and 5 minutes. Five minutes following return to supine position cardiac output was again measured. Prior to each tilt for cardiac output determination, each patient was tilted in a similar fashion for continuous recording of blood pressure; in no instance were pressure responses different in the separate tilts.

Cardiac output was calculated using the Stewart-Hamilton method of reploting dye concentration semilogarithmically against time and cardiac index by correcting for body surface area. Mean arterial pressure was calculated from the sum of the diastolic pressure and one third of the arterial pulse pressure. Heart rate was measured from the electrocardiogram during cardiac output determinations. Total peripheral resistance was determined by dividing mean arterial pressure by cardiac output and expressed as mm Hg/ml/min. Left ventricular ejection time was measured from the brachial arterial pressure curve by averaging at least five consecutive pulses using a paper speed of 100 mm/sec, and was corrected for heart rate. Since left ventricular pressures were not obtained, this measurement of ejection time was used to give a reasonable estimate of mean rate of left ventricular ejection (stroke index divided by ejection time and expressed as ml/min/m²); none of the patients had evidence of aortic valvular disease.

Total blood volume was measured at the conclusion of each study by using radiiodinated human serum albumin and the technique of Williams and Fine. Absolute red blood cell masses were not measured but were calculated from the venous hematocrit measured by capillary microcentrifugation and corrected for total body hematocrit. The isotope was not injected until at least 15 minutes had elapsed following return to the supine position from the tilt position.

Results

Supine Studies

Average cardiac indices of essential and renovascular hypertensive patients were 2.662 and 3.314 ml/min/m², respectively; the average for normal subjects was 3.003 ml/min/m². Cardiac output in renal hypertensives was significantly higher than normal (P < 0.025) and lower than normal in essential hypertension (P < 0.02); the difference between the two hypertensive groups was highly significant (P < 0.001) (table 2 and fig. 1). Vascular resistance was increased in the hypertensives.
Heart rates were also higher in both groups than in normal subjects (table 3). When left ventricular ejection time was corrected for heart rate, there were no significant differences among the three groups; in contrast, mean rate of left ventricular ejection in essential hypertension was less than occurred normally (P < 0.001) or in renovascular hypertension (P < 0.02).

**Tilt Studies**

Cardiac output was decreased in every instance after 5 minutes of tilt. In essential hypertensives cardiac index fell 21%, in patients with renal arterial disease, 17%, and in normals 9% (table 3). Even though diminished, the cardiac output of patients with renal arterial disease continued to be significantly higher than in essential hypertension (P < 0.001); mean rate of left ventricular ejection remained less in essential hypertension. When tilted, the heart rate of essential hypertensives was increased, but this was no longer significantly greater than in normal subjects. The response was significantly different from that of patients with renal arterial disease who continued to maintain a higher heart rate in the tilted position than normal subjects or patients with essential hypertension (P < 0.001).

**Blood Volume Studies**

Differences in cardiac output between normal subjects and hypertensive patients were not explained by parallel differences in intravascular volume (table 4). These data are presented as total blood and derived plasma and red blood cell volumes expressed per kilogram of body weight. The only significant differences observed were among the patients with renovascular hypertension whose total blood volumes were lower than those of normal subjects (P < 0.05) and whose red blood cell volumes were lower than those found in normal individuals (P < 0.02) and patients with essential hypertension (P < 0.05). Presumably, these differences reflected the greater number of women in the renovascular hypertension group in contrast with the other groups.¹⁹

**Discussion**

This study demonstrates that increased vascular resistance was not the sole systemic

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**Table 3**

<table>
<thead>
<tr>
<th>Normal</th>
<th>Normal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure (mm Hg), mean se*</td>
<td>Arterial pressure (mm Hg), mean se*</td>
<td>Arterial pressure (mm Hg), mean se*</td>
</tr>
<tr>
<td>Supine</td>
<td>2 min</td>
<td>5 min</td>
</tr>
<tr>
<td>91</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>66</td>
<td>1.9</td>
<td>3.8</td>
</tr>
<tr>
<td>0.292</td>
<td>0.004</td>
<td>0.241</td>
</tr>
<tr>
<td>Corrected</td>
<td>Corrected</td>
<td>Corrected</td>
</tr>
<tr>
<td>Eject. time (sec)</td>
<td>0.307</td>
<td>0.281</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>3030</td>
<td>2552</td>
</tr>
<tr>
<td>Stroke volume (ml/min), mean se</td>
<td>99</td>
<td>108</td>
</tr>
<tr>
<td>LV ejection rate (ml/sec/m²)</td>
<td>86</td>
<td>60</td>
</tr>
<tr>
<td>Total periph. resist. (mm Hg/ml/min)</td>
<td>2.9</td>
<td>4.3</td>
</tr>
<tr>
<td>0.016</td>
<td>0.001</td>
<td>0.019</td>
</tr>
<tr>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Each average is expressed ± 1 standard error of the mean. Mean is on upper line and se is on next line in each measurement.
hemodynamic abnormality in these hypertensive patients. Although total peripheral resistance was increased, cardiac output was elevated in those with fibrosing renal arterial disease and reduced in patients with essential hypertension.

At present there is no way of determining whether a patient with renal arterial disease has renal hypertension other than remission of hypertension following appropriate surgery. This criterion can be applied to only two of our patients who were treated surgically and became normotensive postoperatively. The rest have not been operated upon because of diffuse bilateral disease or ease of arterial blood pressure control with drugs. In these, however, a renal cause for hypertension seems likely since they had nonatherosclerotic renal arterial stenoses which in our experience are more often associated with remiurable hypertension than the atherosclerotic ones.20, 21

Our findings in essential hypertension may be compatible with previous reports describing normal or low-normal cardiac output;5, 7, 10, 22-36; the few patients in those reports who had higher than expected cardiac indices may well have had renal arterial disease since renal arteriography had not been performed in all, and juvenile, early, and labile hypertensives were included; these types of hypertensives were excluded from our essential hypertension group. Moreover, subclinical cardiac failure did not seem to be the explanation of low cardiac output in our patients since in none was there suggestive history, abnormal Valsalva maneuver response,37 or compatible physical or radiographic findings.

Renal arterial disease, especially of the fibrosing types, is more often found in women, whereas men predominate among the essential hypertensive patients referred to us for study. The demonstration of higher cardiac indices in renal arterial disease associated with hypertension is all the more striking since in groups matched for age and pressure lower output is expected where females predominate.38 Another cardiac difference between the two hypertensive groups concerns the mean rate of left ventricular ejection, which was normal in hypertension associated with renal arterial disease but low in essential hypertension. These low ejection rates and cardiac output.
indices may suggest some functional myocardial abnormality in essential hypertension. The differences in heart rate among the three groups in both supine and tilted positions remain unexplained.

No explanation is presently available for the higher cardiac output in renovascular than in essential hypertension or in normal subjects. These findings are consistent with those of Ledingham and Cohen\textsuperscript{38, 40} showing in rats elevated cardiac output in the early stages following experimental induction of renovascular hypertension. It would be erroneous though to suggest that these findings confirm the rat experiments since Ledingham and Cohen failed to demonstrate continued elevated cardiac output after the initial 5 to 10 days; none of our patients had hypertension of such acute onset. Our findings are also at variance with observations in trained, unanesthetized dogs made hypertensive by partial occlusion of one renal artery and unilateral nephrectomy.\textsuperscript{41} In the dog studies, which lasted up to 42 days, an initial fall in cardiac output was followed by its normalization; both stages were associated with increased peripheral resistance. While these studies may be considered long term, they are of relatively short duration when compared with clinical hypertension due to renal arterial disease (even when corrected for average life span of each animal species).

The several possible mechanisms causing elevated cardiac output include expanded intravascular volume, increased adrenergic activity, a circulating agent which can mimic the hemodynamic changes observed, increased responsiveness of the myocardium and vascular smooth muscle, or a combination of any or all of these factors.

The blood volume studies reported herein tend to exclude expanded intravascular volume as a mechanism. In fact, to the contrary, total blood volume was lowest in renovascular hypertension which may be explained by predominance of women in this hypertensive group since women normally have lower red blood cell volumes than men.\textsuperscript{19} Elevated hematocrit values, such as we have previously reported to occur in patients with renal arterial disease, were not found.\textsuperscript{42}

Recent studies have suggested that experimentally produced renovascular hypertension in dogs is associated with alterations in neural control of vascular resistance.\textsuperscript{43, 44} During the chronic phase of hypertension (average, 58 days) in contrast to the acute phase, vascular resistance seemed to be more dependent on neural control,\textsuperscript{44} a finding suggested in the present study. A neurogenic mechanism increasing cardiac output in renovascular hypertension seems possible because heart rate was also increased and both higher output and heart rate were maintained on tilt.

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### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Weight (kg)</th>
<th>Hematocrit (%)</th>
<th>Total blood volume (ml/kg*)</th>
<th>Plasma volume (ml/kg*)</th>
<th>Red blood cell mass (ml/kg*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Mean 73 SE 39</td>
<td>81</td>
<td>49</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>Mean 77 SE 41</td>
<td>77</td>
<td>45</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Renal arterial disease</td>
<td>Mean 63 SE 37</td>
<td>72</td>
<td>45</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

*Milliliters per kilogram of body weight.
Angiotensin decreases cardiac output in man following injections or during short-term infusions,\(^4\) but there is no information about effects of sustained infusions of small doses in normotensive or hypertensive man. However, evidence is available indicating angiotensin has a positive chronotropic myocardial effect in dogs,\(^48\) and other studies have shown that it has a positive inotropic effect on feline myocardium which is not mediated by action on \(\beta\)-adrenergic receptor sites.\(^50\) Finally, angiotensin may act by releasing catecholamines from the adrenal medulla,\(^51\) thereby increasing cardiac output.\(^54\)

**Acknowledgment**

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**References**


The Necropsy on Dr. Johnson

Wednesday, December 15th, 1784: Opened the body of Dr. Samuel Johnson . . .

On opening into the cavity of the chest, the lungs did not collapse as they usually do when air is admitted, but remained distended, as if they had lost the power of contraction; the air-cells on the surface of the lungs were also very enlarged; the right lobe adhered very strongly to the diaphragm; the internal surface of the trachea was somewhat inflamed; no water was found in the cavity of the thorax. The heart was exceedingly large and strong, the valves of the aorta were beginning to ossify; no more fluid than was common was contained in the pericardium. In the abdomen seemed to be incipient peritoneal inflammation and ascites; the liver and spleen were firm and hard; the spleen had almost the feel of cartilage. A gall stone about the size of a pigeon’s egg was taken out of the gall bladder; the omentum was exceedingly fat; nothing remarkable was found in the stomach; the folds of the jejunum adhered in several places to one another; there was also a strong adhesion by a long slip between the colon and the bladder; the pancreas was remarkably enlarged; the kidney of the left side tolerably good, some hydatids beginning to form on its surface; that of the right side was almost entirely destroyed, and two large hydatids formed in its place.—RUSSELL BRAIN: Some Reflections on Genius and Other Essays. London, Pitman Medical Publishing Co. Ltd., 1960, p. 99.
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