Systemic and Regional Hemodynamics in Low, Normal and High Cardiac Output Borderline Hypertension

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BARBARA CHRISTIE, AND EDWARD D. FROHLICH, M.D.

SUMMARY  Forty-one patients with borderline hypertension were subdivided into groups with low, normal, and high cardiac index. Cardiac output, intra-arterial pressure, renal blood flow, splanchnic blood flow, plasma volume, red cell mass and plasma renin activity were determined concomitantly, and derived hemodynamic indices were calculated. Cardiac output, arterial pressure and plasma renin activity were also measured after head-up tilt and isometric handgrip. Heart rate and stroke index were significantly higher in patients with normal and high cardiac output than in patients with low cardiac output. A significant difference was also found between the three groups in total blood volume, total peripheral resistance, renal and hepatic blood flow, whereas plasma renin activity and plasma volume did not differ significantly. Cardiac output correlated with plasma \( r = 0.500 \), total blood \( r = 0.630 \) and central blood volumes \( r = 0.782 \). In contrast, a negative correlation was observed between total peripheral resistance, plasma \( r = -0.440 \) and total blood \( r = -0.644 \) volumes. Furthermore, cardiac output, renal \( r = 0.550 \) and hepatic \( r = 0.625 \) blood flows correlated. The response of cardiac output and total peripheral resistance to tilt was more pronounced in high than in low cardiac output borderline hypertension \( P < 0.05 \) whereas handgrip responses were similar in the three groups. We conclude that the fluid volume state is a major determinant of cardiac output and/or peripheral resistance in borderline hypertension with renal and hepatic blood flow varying in parallel. The magnitude of cardiac output, renal and hepatic blood flow depends mainly on the shift of the circulating blood volume to the central circulation.

THE EARLY DEVELOPMENTAL STAGE OF ESSENTIAL HYPERTENSION has been described in various terms, including labile, juvenile, borderline and hyperkinetic high blood pressure. The common denominator of the definition is that all imply relatively young patients in whom alternatively normal and elevated arterial pressures can be measured. Although different criteria for defining borderline hypertension have been used by various investigators, it is well-documented that the hemodynamic pattern of these patients (as a group) show an increased cardiac output associated with a numerically normal total peripheral resistance.\(^1-9\) Several reports from our own and other laboratories have shown that among these borderline hypertensive patients there is a continuous spectrum from those with a very high heart rate and cardiac output, to those with normal values, and to a few others whose heart rate and cardiac output might even be somewhat reduced.\(^10-12\) Ulrych et al.\(^13\) have suggested that the increased cardiac output may be achieved through a redistribution of peripheral intravascular volume toward the cardiopulmonary circulation, presumably as a result of venoconstriction.

This study was designed to elucidate the relationship between the systemic and local hemodynamics and circulating intravascular volume in patients with borderline hypertension having low, normal and high cardiac output.
Methods

The borderline hypertension patients in this study had at least one value of arterial pressure below 140/90 mm Hg, with higher values on several occasions. In addition, intra-arterial pressure was consistently lower than 150/95 mm Hg during recumbency, when evaluated in the hemodynamic laboratory.

Each patient had a complete clinical evaluation to exclude any secondary form of hypertension. This evaluation included serum creatinine and electrolyte concentrations, fasting blood sugar, uric acid, serum lipid levels, routine urinalysis, creatinine clearance, chest x-rays, 12-lead electrocardiogram, vectorcardiogram, radioisotopic renal scan and determination of peripheral plasma renin activity in relation to 24-hour excretion of sodium. Blood for determination of plasma renin activity was obtained after 3 hours of stimulation by upright posture at noon in conjunction with a 24-hour urine collection to determine creatinine clearance and sodium excretion. No patient was older than 45 years or showed ECG or radiographic evidence of left ventricular hypertrophy, hypertensive funduscopic changes or renal involvement.

Most patients had never been treated previously. But in those who were treated, antihypertensive drugs (including diuretics) were discontinued at least four weeks before the study. In each instance the patient was informed of the nature of the investigative study and signed consent was obtained.

Hemodynamic assessment was performed between 8 and 11 a.m., after overnight fasting and without premedication. The studies were performed after at least 1 hour of rest in the supine position as previously reported. Briefly, arterial and venous pressures were recorded continuously on a 12-channel Electronics for Medicine indirect writing recorder using a Statham P-23 DB pressure transducer. Cardiac output was determined in triplicate using indocyanine green dye. Mean arterial pressure was obtained by electrical integration. The usual hemodynamic indices were calculated by standard formula with a programmed Hewlett-Packard Computer Calculator.

Renal Blood Flow

Renal blood flow was determined concomitantly by the single injection clearance of Iodine para-aminohippuric acid (123I-PAH) on the basis of the model proposed by Sapirstein and associates. Forty μC/1.73 m² of 123I-PAH were injected into the venous line and eight heparinized 5 ml blood samples were drawn at exactly 5, 10, 15, 20, 30, 40, 50 and 60 minutes after injection. The plasma disappearance curve was resolved into two linear components and the renal plasma flow was calculated as proposed by Sapirstein. This value was subsequently corrected for total body hematocrit and body surface area.

Clearance of Indocyanine Green (Splanchnic Blood Flow)

Splanchnic blood flow was estimated as previously described, by injection of 50 mg of indocyanine green into the venous line and drawing blood at 4, 6, 8, 10, 12, 14, 16, 18 and 20 minutes, respectively, after the injection. Fractional clearance was calculated using the method of the least squares for the natural logarithmic values of the serum concentration. Subsequently, the fractional clearance was multiplied by the plasma volume to obtain plasma clearance of indocyanine green. This value was corrected for the total body hematocrit to obtain the total blood clearance. Indocyanine green clearance consistently underestimates total hepatic blood flow by a certain factor; however, in patients with normal hepatic function the clearance closely parallels any changes in total liver blood flow and provides a valid estimation.

Central Blood Volume

Central blood volume was determined from the dye dilution curve previously described. The procedure merely determines the tip-to-tip intravascular volume corresponding to the blood volume from the tip of the venous catheter (superior vena cava) to the tip of the arterial catheter (ascending aorta just proximal to the subclavian artery). Therefore, the central blood volume cannot be compared directly to the pulmonary blood volume, which is measured by catheterization of

<table>
<thead>
<tr>
<th>TABLE 1. Clinical and Laboratory Findings in 41 Patients with Borderline Hypertension and High (H), Normal (N), and Low (L) Cardiac Output (Mean ± 1 SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td><strong>H (n = 11)</strong></td>
</tr>
<tr>
<td>± sd</td>
</tr>
<tr>
<td><strong>N (n = 23)</strong></td>
</tr>
<tr>
<td>± sd</td>
</tr>
<tr>
<td><strong>L (n = 7)</strong></td>
</tr>
<tr>
<td>± sd</td>
</tr>
</tbody>
</table>

*After stimulation by ambulation for 3 hours.
†P <0.05 vs group with low cardiac output.
the pulmonary artery and the left atrium. However, our values do provide a good estimate of distribution of the total blood volume with regard to the central circulation.

Plasma Volume

Plasma volume was determined during the hemodynamic study by injecting \textsuperscript{125}I-labeled human serum albumin into the venous line and measuring the rate of radioactivity in the plasma after 15 and 30 minutes of equilibration.

Red Cell Volume

Red cell volume was measured simultaneously by injecting \textsuperscript{51}chromium-labeled red blood cells into the venous line and measuring the concentration of the isotope in the arterial blood after 20 minutes equilibration.

Plasma Renin Activity

Plasma renin activity was measured according to the method of Sealey and Laragh,\textsuperscript{11} and compared with a 24-hour urinary sodium excretion.\textsuperscript{18}

Isometric Exercise

The patient was asked to sustain handgrip for 3 minutes at one-third of his maximum force of contraction, which was determined before each study. Continuous recordings of arterial and venous pressure and ECG were obtained. The cardiac output was obtained during the last minute of handgrip. At the end of this procedure blood was drawn for determination of plasma renin activity.

Upright Tilting

Patients were tilted upright to 45° for 5 minutes, unless signs of vagovasal reaction occurred. ECG, arterial and venous pressures were monitored and cardiac output and blood for plasma renin activity were obtained during the fifth minute.

Patients were subdivided according to their cardiac index into groups with low (2.5 and less 1/min/m\(^2\), n = 7), normal (between 2.6 and 3.6 1/min/m\(^2\), n = 23), and high (3.6 and higher 1/min/m\(^2\), n = 11) cardiac index. These limits were arbitrarily chosen by comparison with our normal age-matched population showing a cardiac index of 3.05 ± 0.32 (sd). The extension of the limits to a value of ± 0.55 would include over 90% of all normal subjects in a population with a normal distribution. Statistical comparisons between the three groups were made by \(t\) test. Linear regression analysis was performed between the various hemodynamic values.\textsuperscript{19}

**Results**

Clinical, laboratory and hemodynamic characteristics of the three subgroups of borderline hypertension are detailed in tables 1 and 2. Patients with low cardiac output were somewhat older and had slightly higher levels of arterial pressure. Both heart rate and stroke index varied in parallel with cardiac index, the significance being more pronounced for the stroke index, and a significant difference also existed in total peripheral resistance. Plasma and blood volume were slightly (although not significantly) lower in women than in men when corrected for body surface or height. Although plasma volume did not differ significantly among the three groups, total intravascular volume was lowest in the low cardiac output and highest in the high cardiac output groups. Thus, cardiac output correlated directly with plasma volume (\(r = 0.500\)) and even closer with the total blood volume (\(r = 0.630\)) (fig. 1). Similarly, the central (cardiopulmonary) blood volume increased with cardiac output and a positive correlation was found between the two variables (\(r = 0.782\)) (fig. 2). The ratio between central blood volume and total blood volume varied in parallel with cardiac output.

In contrast, a negative correlation existed between total peripheral resistance and plasma (\(r = -0.440\)) and total blood (\(r = 0.644\)) volumes (fig. 3). However, arterial pressure did not correlate with plasma

### Table 2. Systemic and Regional Hemodynamic Findings in 41 Patients with Borderline Hypertension and High (H), Normal (N), and Low (L) Cardiac Output (Mean ± 1 SD)

<table>
<thead>
<tr>
<th>Arterial pressure</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
<th>Mean (mm Hg)</th>
<th>Heart rate (min(^{-1}))</th>
<th>CI (l/min/m(^2))</th>
<th>SI (l/min/m(^2))</th>
<th>TPR (mm Hg l/min/m(^2))</th>
<th>CBV (l/min/m(^2))</th>
<th>RBF (l/min/m(^2))</th>
<th>IGC (ml/min/m(^2))</th>
<th>PRA (ng/ml/h)</th>
<th>CBV/TVB</th>
<th>RBF/CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (n = 11)</td>
<td>138</td>
<td>80</td>
<td>99</td>
<td>81*</td>
<td>3982</td>
<td>51†</td>
<td>6.61</td>
<td>1696†</td>
<td>698†</td>
<td>437†</td>
<td>0.42</td>
<td>0.62†</td>
<td>0.18</td>
</tr>
<tr>
<td>*SD</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>253</td>
<td>9</td>
<td>1.2</td>
<td>148</td>
<td>138</td>
<td>108</td>
<td>0.30</td>
<td>0.07</td>
<td>0.04</td>
</tr>
<tr>
<td>N (n = 23)</td>
<td>137</td>
<td>81</td>
<td>99</td>
<td>71</td>
<td>2986</td>
<td>43†</td>
<td>4*</td>
<td>1378*</td>
<td>678*</td>
<td>367</td>
<td>0.52</td>
<td>0.57</td>
<td>0.23</td>
</tr>
<tr>
<td>*SD</td>
<td>16</td>
<td>9</td>
<td>11</td>
<td>8</td>
<td>305</td>
<td>6</td>
<td>2.6</td>
<td>164</td>
<td>172</td>
<td>103</td>
<td>0.37</td>
<td>0.08</td>
<td>0.55</td>
</tr>
<tr>
<td>L (n = 7)</td>
<td>144</td>
<td>87</td>
<td>105</td>
<td>65</td>
<td>2288</td>
<td>36</td>
<td>12.9</td>
<td>1186</td>
<td>440</td>
<td>263</td>
<td>0.29</td>
<td>0.50</td>
<td>0.19</td>
</tr>
<tr>
<td>*SD</td>
<td>9</td>
<td>6</td>
<td>6</td>
<td>9</td>
<td>165</td>
<td>4</td>
<td>1.8</td>
<td>194</td>
<td>64</td>
<td>28</td>
<td>0.25</td>
<td>0.11</td>
<td>0.04</td>
</tr>
</tbody>
</table>

\*P < 0.05.
\#P < 0.01 versus group with low cardiac output.
\$P < 0.001.

Abbreviations: CI = cardiac index (ml/min/m\(^2\)); SI = stroke index (ml/min/m\(^2\)); TPR = total peripheral resistance (units); CBV = central blood volume (ml/m\(^2\)); RBF = renal blood flow (ml/min/m\(^2\)); IGC = indocyanine green clearance (ml/min/m\(^2\)); TBV = total blood volume (ml/m\(^2\)); PRA = plasma renin activity (ng/ml/h after 1½ hours of recumbency); CBV/TVB = central blood volume/total blood volume; RBF/CO = renal blood flow/cardiac output.
volume, central or total blood volume, perhaps because of the very narrow range of arterial pressure in this selected group of patients. No significant difference between plasma renin activity, 24-hour urinary sodium excretion and calculated renin-sodium index was found between the three groups; and cardiac output, arterial pressure, total peripheral resistance, plasma and total blood volume did not correlate with plasma renin activity or the renin-sodium index in this study population.

Significant differences in renal and hepatic flow were seen between the three cardiac output groups. Thus, a positive correlation was found between cardiac output and renal blood flow \( r = 0.550 \) (fig. 4) and hepatic blood flow \( r = 0.625 \) (fig. 5).

Cardiac output, heart rate and arterial pressure increased during isometric exercise in all three groups \( (P \leq 0.05) \) (tables 3 and 4). Head-up tilt induced a significant fall in cardiac output and an increase in heart rate, but no significant change in mean arterial
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Figure 3. Correlation between total peripheral resistance and total blood volume in 38 borderline hypertensive patients with high (●), normal (○) and low (□) cardiac output.

pressure; however, the fall in cardiac output and increase in total peripheral resistance was significantly ($P < 0.05$) greater in the high than in the low cardiac output group. With this exception, the response to tilt and handgrip was similar in all three groups, and no other significant differences were determined. Also, plasma renin activity did not increase significantly after head-up tilt and isometric hand grip, perhaps because of the short duration of stimulation (5 and 3 minutes, respectively). A subdivision of the patient population with regard to diastolic pressure revealed no significant differences (with the exception of total peripheral resistance) (table 5).

Discussion

Three principal findings evolved from this study of patients with borderline hypertension: 1) an inverse correlation between total peripheral resistance and intravascular (and plasma) volume was found; 2) the magnitude of cardiac output correlated well with the total circulating and central (cardiopulmonary) blood

Figure 4. Correlation between cardiac output and renal blood flow in 25 borderline hypertensive patients with high (●), normal (○) and low (□) cardiac output.

Figure 5. Correlation between cardiac output and indocyanine green clearance (heptic blood flow) in 27 borderline hypertensive patients with high (●), normal (○), and low (□) cardiac output.
volume; and 3) the renal and hepatic blood flows varied in parallel to cardiac output with no evidence of redistribution between these two major circulations. Arterial pressure was purposely held constant by a very rigid definition of the study population. This approach permitted the elucidation of the interrelationships between the fluid volume state and systemic and local (renal and hepatic) blood flows and total peripheral resistance in this very early evolution stage of essential hypertension. Furthermore, separation of these patients with borderline hypertension into groups with low, normal, and high cardiac output permitted some clarification of the question of the so-called "cardiogenic hypertension" as opposed to high blood pressure primarily induced by an increase in total peripheral resistance.

Arterial pressure is determined by the amount of blood within a vascular segment and by the compliance of this same segment. Hence, the fluid volume state of the body is directly involved in the regulation of arterial pressure; and numerous reports (in part contradictory) on fluid volume state and systemic hemodynamics in arterial hypertension have been published. This issue has also been the subject of two recent, extensive and careful reviews. The present findings of an inverse relationship between plasma or blood volume and total peripheral resistance confirm previous findings in borderline and established hypertension. In patients with borderline hypertension, plasma volume seems to be more closely related to total peripheral resistance than to diastolic pressure. This most likely reflects the extremely narrow range of arterial pressure in the study population. Total blood volume is determined, to a much greater extent, by the capacitance vessels (which do not significantly influence vascular resistance) than by the resistance vessels. Hence, an inverse relationship between total peripheral resistance and blood volume indicates that arteriolar constriction could be associated with a decrease in the venous capacity, whereas a low arteriolar tone might parallel a dilatation of the capacitance vessels.

We designed our study to minimize variation of arterial pressure on the relationship between the systemic and regional hemodynamics and the fluid volume state. Under these conditions (i.e., of relative constancy of arterial pressure), cardiac output varied inversely with the total peripheral resistance, and we found a positive correlation between cardiac output and total blood or plasma volumes. It was important to ascertain that the correlation between cardiac output and central (cardiopulmonary) blood volume was more significant than between cardiac output and total blood volume. A similar correlation has been found previously in borderline hypertension. Thus, the patients with high cardiac output showed a significantly higher ratio between central and total blood volume than patients with lesser outputs. Although cardiac output paralleled total blood volume in borderline hypertension, it seems to be considerably more dependent on the intravascular volume redistribution to the central circulation from the

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**Table 3. Response to 45° Head-up Tilt in 41 Patients with Borderline Hypertension and High (H), Normal (N), and Low (L) Cardiac Output (Mean ± 1 SD)**

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (min⁻¹)</th>
<th>Cardiac index (ml/min/m²)</th>
<th>Stroke index (ml/min/m²)</th>
<th>Total peripheral resistance (units)</th>
<th>Central blood volume (ml)</th>
<th>Plasma renin activity (ng/ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>98</td>
<td>93</td>
<td>3058</td>
<td>35</td>
<td>8.3</td>
<td>1211</td>
<td>0.54</td>
</tr>
<tr>
<td>% Change</td>
<td>-1</td>
<td>14.8</td>
<td>-23.3*</td>
<td>-31.4</td>
<td>26.5*</td>
<td>-28.6</td>
<td>28.6</td>
</tr>
<tr>
<td>N</td>
<td>99</td>
<td>84</td>
<td>2493</td>
<td>30</td>
<td>10.8</td>
<td>1071</td>
<td>0.75</td>
</tr>
<tr>
<td>% Change</td>
<td>0</td>
<td>18.3</td>
<td>-17.3</td>
<td>-30.2</td>
<td>22.1</td>
<td>-22.3</td>
<td>44.2</td>
</tr>
<tr>
<td>L</td>
<td>103</td>
<td>77</td>
<td>2067</td>
<td>28</td>
<td>14.2</td>
<td>961</td>
<td>0.43</td>
</tr>
<tr>
<td>% Change</td>
<td>-1.9</td>
<td>18.5</td>
<td>-9.5</td>
<td>-22.2</td>
<td>10.1</td>
<td>-18.9</td>
<td>48.3</td>
</tr>
</tbody>
</table>

*P <0.05 vs group with low cardiac output.

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**Table 4. Response to 3-Minute Isometric Exercise (Handgrip) in 41 Patients with Borderline Hypertension and High (H), Normal (N), and Low (L) Cardiac Output (Mean ± 1 SD)**

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (min⁻¹)</th>
<th>Cardiac index (ml/min/m²)</th>
<th>Stroke index (ml/min/m²)</th>
<th>Total peripheral resistance (units)</th>
<th>Central blood volume (ml)</th>
<th>Plasma renin activity (ng/ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>121</td>
<td>89</td>
<td>4330</td>
<td>49.5</td>
<td>7.3</td>
<td>124</td>
<td>0.427</td>
</tr>
<tr>
<td>% Change</td>
<td>22.2</td>
<td>9.9</td>
<td>8.9</td>
<td>2.9</td>
<td>12.4</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>N</td>
<td>121</td>
<td>80</td>
<td>3446</td>
<td>43.8</td>
<td>9.5</td>
<td>6.4</td>
<td>5.8</td>
</tr>
<tr>
<td>% Change</td>
<td>22.2</td>
<td>12.7</td>
<td>15.7</td>
<td>1.9</td>
<td>6.4</td>
<td>5.8</td>
<td>5.8</td>
</tr>
<tr>
<td>L</td>
<td>120</td>
<td>68</td>
<td>2521</td>
<td>37.1</td>
<td>13.5</td>
<td>0.300</td>
<td>3.4</td>
</tr>
<tr>
<td>% Change</td>
<td>14.3</td>
<td>4.6</td>
<td>10</td>
<td>3.1</td>
<td>5.3</td>
<td>3.4</td>
<td>3.4</td>
</tr>
</tbody>
</table>
peripheral vascular beds. However, central blood volume and cardiac output are calculated from the same curve and are not independent determinations.

Several groups working with different methods have observed a significant increase in renal blood flow in patients with borderline hypertension. The present data, indicating a close correlation between cardiac output and renal blood flow, support the findings of Kioschos and his associates who also observed an increased cardiac output in patients with a greater renal blood flow. However, our findings are in contrast with the data of Tuck et al., who reported a normal cardiac output together with an increase in renal blood flow. Nevertheless, our present findings show that the renal blood flow seems to parallel the changes in cardiac output and that the fraction of cardiac output perfusing the renal vascular beds remains similar in patients with high, normal or low cardiac output borderline hypertension. These data, demonstrating no local redistribution of cardiac output, were also confirmed with regard to the splanchic circulation. Similar data from our laboratory have been previously reported in established essential hypertension. Moreover, these findings in early and later stages of essential hypertension are also consistent with our observations in genetic, spontaneously hypertensive rats.

These data seem to indicate and support our thesis of a continuum or spectrum of the hemodynamic alterations in the progressive development of essential hypertensive disease. Early on, the increased cardiac output is associated with a faster heart rate and stroke volume (and perhaps enhanced myocardial contractility) associated by a translocation of intravascular volume from the periphery to the cardiopulmonary circulation. This seems to be attributable to peripheral venoconstriction. But, as vascular resistance progressively increases with time, intravascular and plasma volume contracts, possibly on the basis of the vascular ultrafiltration factors elucidated by Pappenheimer and Soto-Rivera.

Response of cardiac output and total peripheral resistance to upright tilt was significantly greater in high cardiac output patients than in the low cardiac output group. Thus, these subjects exhibit an increased cardiovascular reactivity which could be secondary to an imbalance between vagal and sympathetic outflow. The same pathophysiological mechanism could, at least to some extent, account for the increase in cardiac output under baseline conditions. The response to isometric exercise was similar in the three groups; this maneuver does not seem to unmask the dysregulation of the autonomic nervous system.

Neither plasma renin activity nor the renin-sodium index correlated with any of the systemic or regional hemodynamic or fluid volume factors. A weak positive correlation had been found previously between cardiac output and plasma renin activity in essential hypertension in patients with relatively constant sodium intake, whereas renal blood flow and total peripheral resistance correlated negatively with plasma renin activity. However, it should be noted that the analysis presented here is restricted to a rather homogenous group of young subjects with borderline hypertension whose arterial pressure levels were restricted to a narrow range. Thus, in this early stage of the disease plasma renin activity seemed to be relatively independent of sodium-fluid volume state and may be influenced predominantly by autonomic (adrenergic) factors.

Acknowledgments

The authors thank the Medical Editorial Department for assistance in preparation of the manuscript, and Barbara Siede of the Department of Medical Illustrations for preparation of the graphs.

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Systemic and regional hemodynamics in low, normal and high cardiac output borderline hypertension.
F H Messerli, J G De Carvalho, B Christie and E D Frohlich

_Circulation_. 1978;58:441-448
doi: 10.1161/01.CIR.58.3.441
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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