Hemodynamics of Uremic Anemia

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Gaddo Onesti, M.D., and Charles Swartz, M.D.

SUMMARY
This study was undertaken to assess the importance of an elevated cardiac output in the generation of the hypertension associated with chronic renal failure. Forty stable uremic patients on a program of maintenance hemodialysis underwent hemodynamic studies. Cardiac index measured by dye dilution was found to be significantly elevated. Calculated peripheral vascular resistance was normal despite elevated blood pressure. Six patients underwent serial hemodynamic studies over a period of 6 to 12 weeks while being transfused with packed red blood cells to a normal hematocrit. Blood volume and body weight were constant during the study period. Cardiac index decreased during transfusion, reaching a normal level at a hematocrit of 30%. Diastolic blood pressure progressively rose, averaging an increase of 20 mm Hg at a hematocrit of 40%. Peripheral vascular resistance increased by 80% at a hematocrit of 40%.

We concluded that the elevation of cardiac index in uremic patients is secondary to anemia and is reversible when the hematocrit is raised over 30%. The high cardiac index is not responsible for hypertension because restoration of cardiac index to normal by transfusion raises blood pressure rather than lowers it.

Additional Indexing Words:
Cardiac output Anemia Uremia Hemodialysis Kidney
Hypertension Hemodynamics

Renal failure is frequently associated with an increased cardiac output and systemic hypertension.¹⁻⁶ The increased cardiac output is generally attributed to a decreased oxygen delivery secondary to anemia⁷ and decreased blood viscosity.⁸⁻¹⁰ Myocardial factors¹¹ and the presence of expanded plasma volumes in many of these patients⁶,¹²,¹³ may both contribute to the elevated cardiac outputs.

A high cardiac output may be important in the genesis of experimental renal hypertension¹⁴ and is usually present in the early phase of human essential hypertension.¹⁵,¹⁶ The peripheral vascular resistance is normal in many uremic hypertensive patients,¹,³,⁴ suggesting that the increased cardiac output may contribute to the development of hypertension in such patients.

Several studies have shown that in anemic patients with adequate renal function, treatment normalizes the high cardiac output.¹⁷⁻²¹ It seemed reasonable to expect that in uremic patients treatment of the anemia would result in a decrease in cardiac output. If the high cardiac output were contributing to the elevated blood pressure, then we would expect a lower blood pressure as hematocrit increased.

The purposes of this study were (1) to determine the cardiac output, intra-arterial

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Cardiac output was calculated by reporting the dye-dilution curve logarithmically to obtain mean blood pressure × 1.332 cardiac index in ml/sec/m².

Peripheral vascular resistance index was calculated in dynes-sec-cm⁻² as follows:

\[
\text{PVR} = \frac{\text{MAP} - \text{CVP}}{\text{CO}}
\]

where MAP is mean arterial pressure, CVP is central venous pressure, and CO is cardiac output.

**Table 1**

<table>
<thead>
<tr>
<th>Hemodynamic Studies in 40 Uremic Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>Uremic patients</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Patients hypertensive</td>
</tr>
<tr>
<td>at time of study</td>
</tr>
<tr>
<td>Patients not hypertensive at time of study</td>
</tr>
</tbody>
</table>

*Mean ± se.

Abbreviations: CI = cardiac index (liter/min/m²); SI = stroke index (ml/min/m²); DBP = mean blood pressure (mm Hg); Diast BP = diastolic blood pressure (mm Hg); PVR = peripheral vascular resistance index (dynes-sec-cm⁻²); BV/kg = blood volume per kg body wt (ml/kg); Ht = hematocrit; NaE/kg = total exchange sodium (mEq/kg body wt).
the circulation time and the average dye concentration. Hematocrit was measured by the capillary tube technic and blood volume using \(^{131}I\) albumin. Total exchangeable sodium was determined after a 24-hr equilibration using \(^{22}Na\).

**Group 2—Hemodynamic Effects of Correction of Anemia**

Six of the 40 patients volunteered for a further study to test the effect of increasing their hematocrit. Two of the patients (B.K. and L.W.) had chronic glomerulonephritis with secondary malignant hypertension and were studied prior to bilateral nephrectomy. Three patients (V.F., M.G., and L.R.) had chronic glomerulonephritis with known hypertension for 2 to 6 years. One patient had polycystic kidney disease and had never been known to be hypertensive. No patient received medication, beyond vitamins and iron, for at least 1 week prior to, and during the course of this study. All patients were free of congestive heart failure and clinically stable at the start of this study. Body weight was maintained within 4 lb in each patient during the entire study period.

Hemodynamic studies were performed twice a week prior to hemodialysis and at least 3 days after the patient had received packed red cell transfusions during the previous dialysis. Blood was administered during dialysis as buffy-coat free, packed red blood cells. The hematocrit was increased to at least 40% in each patient.

**Results**

**Group 1**

Table 1 presents the results of studies in these 40 patients with the mean values and standard deviations. Cardiac index was found to be significantly elevated \((P < 0.001)\), while stroke index was within the normal range. Despite the fact that mean blood pressure was elevated, the peripheral vascular resistance index was not different from normal. Male and female patients showed a similar hemodynamic pattern. Cardiac index and blood pressure tended to be lower with advancing age, but these changes were not statistically significant. Patients with hypertension differed from those without hypertension only with regard to peripheral vascular resistance index \((P < 0.001)\) and mean and diastolic blood pressures \((P < 0.001)\).

**Group 2**

Serial transfusion of packed red cells resulted in a linear decrease in cardiac index to a normal level: CI = 7.00 - 0.091Ht; \(r = -0.76\) \((P < 0.001)\) (fig. 1). Stroke index changed in the same direction as cardiac index, with a regression equation: SI = 78.3 -0.964Ht; \(r = -0.61\) \((P < 0.001)\). Mean blood pressure increased with transfusion but less significantly than diastolic pressure: BP (Diast) = 65.5 + 1.126Ht; \(r = 0.435\) \((P < 0.005)\) (fig. 2); for the mean pressure,
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An elevated blood pressure may be primarily due to an increase in cardiac output or an increase in peripheral vascular resistance. Most hypertension is traditionally attributed to an increase in resistance generated at the arteriolar level. This increase in resistance is seen with the infusion of angiotensin and pressor amines. Stable, fixed essential hypertension is also characterized by a normal cardiac output and increased peripheral resistance. In contrast, our uremic hypertensive patients have a hemodynamic pattern of high cardiac output and a normal to slight increase in peripheral vascular resistance. Most investigators have found a similar hemodynamic picture in patients with chronic renal failure. A few studies have failed to demonstrate an increased cardiac output in uremic patients. Careful review of these studies, however, reveals that in some patients anemia was not of a comparable degree to that found in our series, while in other patients circulatory overload and heart failure were present and cardiac output increased after dehydration dialysis.

The hemodynamic pattern of normal resistance and increased cardiac output is also reported in young patients with labile and early essential hypertension. Several investigators believe that increased cardiac output is due to an increase in cardiac index or to a decrease in peripheral vascular resistance. The latter explanation appears to be the case with our patients.

Discussion

A typical patient study is presented in figure 5. The patient represented was studied while the hematocrit was increased by transfusion and then allowed to fall to baseline levels over a period of 3 weeks. This study demonstrates that the hemodynamic changes induced by transfusion are reversible.

Change in peripheral vascular resistance index induced by raising the hematocrit (six patients): □ = B.P., ● = L.W., ■ = B.K., ▲ = V.F., ○ = L.R., △ = M.G.

BP = 108.4 + 0.976Ht; r = 0.297 (P < 0.05).
Peripheral vascular resistance index increased markedly as hematocrit increased: PVRI = 345.4 + 80.04Ht; r = 0.675 (P < 0.001) (fig. 3). Under the conditions of increasing hematocrit, as cardiac index decreased, blood pressure rose (fig. 4). Neither body weight nor blood volume changed significantly during the study.

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output underlies all hypertension. They cite evidence that early in the development of experimental renal hypertension, increased cardiac output is present, and when the experimental hypertension is reversed, the earliest hemodynamic change is a decrease in cardiac output. These investigators postulate that the underlying event in hypertension is an increase in cardiac output, which eventually stimulates a sustained increase in peripheral vascular resistance and a return of cardiac output to normal.

If hypertension associated with chronic renal disease were causally related to the increased cardiac output, we would expect that (1) hypertensive uremics would have higher cardiac indices than normotensive uremics; (2) when the cardiac index is reduced by correction of the anemia, blood pressure should decrease; (3) bilateral nephrectomy, which is a therapeutic maneuver known to decrease blood pressure, should decrease cardiac output. In fact, none of these actually occurs. As can be seen in table 1, there is no difference between the cardiac indices of normotensive and hypertensive uremics.

Transfusion with packed red blood cells did decrease cardiac output but actually raised blood pressure instead of lowering it. Increasing the hematocrit from 20 to 40% increased diastolic blood pressure an average of 20 mm Hg despite a reduction of cardiac index to normal in five of six patients. It is interesting to compare the findings of patients with

Serial evaluation of cardiac index, stroke index, mean blood pressure, diastolic blood pressure, peripheral vascular resistance index, and plasma volume, while the hematocrit was raised by transfusion of packed red cells. Patient V.F.
normal renal function and severe anemia undergoing transfusion with those of our uremic series. Table 2 summarizes the results obtained by investigators studying the hemodynamic effect of blood transfusion on anemia in patients with adequate renal function. In most of the studies, not only was cardiac output reduced by transfusion, but small increases in blood pressure were consistently recorded. In most series the investigators felt that the increase in blood pressure was due to an increase in blood volume. In our dialysis patients we attempted to maintain a constant body weight. We found that blood volume did not change over the course of the study despite red blood cell transfusion. In studies in both uremic patients and those with normal renal function, peripheral resistance always increases when anemia is corrected. Similar effects have been noted after oxygen breathing in anemic children. We believe the most likely explanation for the increasing resistance is related to the fact that severe anemia is associated with inadequate oxygen delivery to the tissues. This produces peripheral vasodilation. Correcting the anemia abolishes hypoxic vasodilation and increases arteriolar resistance and blood pressure. This effect is magnified in previously hypertensive uremic patients.

Finally, bilateral nephrectomy has been repeatedly demonstrated to be effective in the control of hypertension in uremic patients. Hemodynamic studies in some of our patients were performed prior to bilateral nephrectomy and weeks to months later when conditions had again stabilized after surgery (unpublished data). Cardiac index was unchanged despite relief of hypertension, and the major hemodynamic adjustment was a decrease in peripheral vascular resistance.

In summary, we believe the basic cause of hypertension in chronic renal disease is an inappropriately increased peripheral vascular resistance. The high cardiac output state in uremia is predominantly due to anemia and can be lowered by transfusion. The anemia of chronic renal failure may actually serve to

### Table 2

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. studied</th>
<th>Pre-Rx</th>
<th>Post-Rx</th>
<th>Effect on cardiac index</th>
<th>Effect on blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bragg12</td>
<td>4 patients</td>
<td>7.1</td>
<td>2.1</td>
<td>3.8</td>
<td>20% decrease</td>
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<tr>
<td>Richardson13</td>
<td>14 dogs</td>
<td>226 ml/min/kg</td>
<td>135 ml/min/kg</td>
<td>5.4</td>
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<tr>
<td>18 patients = CI</td>
<td>7.4</td>
<td>4.6</td>
<td>1 hr = 10.9 CO</td>
<td>3.44</td>
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<tr>
<td>8 patients = BP</td>
<td>8.97 CO</td>
<td>4.73</td>
<td>6 hr = 10.9 CO</td>
<td>4.58</td>
<td></td>
</tr>
<tr>
<td>7 children</td>
<td>4.71</td>
<td>7.71</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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