Hemodynamics of Uremic Anemia

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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 ele-
vated. 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 car-
diac output is generally attributed to a de-
creased 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, 12 may
both contribute to the elevated cardiac out-
puts.

A high cardiac output may be important in
the genesis of experimental renal hyperten-
sion14 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 sug-
gest 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, treat-
ment 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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blood pressure, and peripheral vascular resistance in a group of hypertensive and normotensive uremic patients and (2) to determine the hemodynamic effect of correction of anemia in a group of uremic patients.

Methods

**Group 1—Cardiac Output, Blood Pressure, and Peripheral Vascular Resistance in 40 Uremic Patients**

Forty patients being maintained on a chronic hemodialysis program were studied when their clinical condition was stable. There were 23 males and 17 females who ranged in age from 18 to 57 years (median 34). Diagnoses were chronic glomerulonephritis 27, primary malignant hypertension 5, chronic pyelonephritis 4, polycystic kidney disease 3, and hepatorenal syndrome 1. With the exception of vitamins and ferrous sulfate tablets, drugs were discontinued for at least 1 week prior to all studies. Most patients were studied several times at weekly intervals. Several patients were followed with ten or more studies over the course of a year, before and after bilateral nephrectomy.

Patients were placed at quiet bed rest for one-half hour prior to the determination of cardiac output and blood pressure. Each study consisted of the determination of three successive cardiac outputs, intra-arterial blood pressure, mean blood pressure, hematocrit, blood volume, and body weight. In 19 of the patients, total exchangeable sodium was also measured. Normal subjects were studied in the same laboratory under identical conditions.

Cardiac output was determined by the injection of indocyanine green through the venous side of the A-V shunt used for dialysis, and its withdrawal through a Gilford densitometer from the arterial side of the shunt. This technic has been described by us and validated by others. Arterial blood pressure was measured with a Statham strain-gauge transducer from the arterial side of the temporarily occluded shunt. Normal subjects were studied by cannulating the brachial artery with a Courand needle and injecting dye through a venous catheter. Mean pressure was recorded from the electronically dampened arterial pressure. Cardiac outputs and pressures were recorded on an Electronics for Medicine recorder. Peripheral vascular resistance index was calculated in dynes-sec-cm⁻⁵-m² as follows:

\[
\text{mean blood pressure} \times 1,332 \\
\text{cardiac index in ml/sec/m}^2
\]

Cardiac output was calculated by replotting the dye-dilution curve logarithmically to obtain

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**Table 1**

<table>
<thead>
<tr>
<th>Hemodynamic Studies in 40 Uremic Patients*</th>
<th>No.</th>
<th>C02</th>
<th>SI</th>
<th>PVR</th>
<th>BV</th>
<th>Ht</th>
<th>kg</th>
<th>BP</th>
<th>kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>21</td>
<td>3.29</td>
<td>0.55</td>
<td>50.5</td>
<td>10.6</td>
<td>87.2</td>
<td>9.4</td>
<td>2.166</td>
<td>417</td>
</tr>
<tr>
<td>Uremic patients</td>
<td>40</td>
<td>4.76</td>
<td>1.34</td>
<td>56.0</td>
<td>10.4</td>
<td>122</td>
<td>25</td>
<td>2.246</td>
<td>875</td>
</tr>
<tr>
<td>Females</td>
<td>23</td>
<td>4.83</td>
<td>1.16</td>
<td>58.2</td>
<td>10.5</td>
<td>68</td>
<td>19</td>
<td>2.120</td>
<td>761</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>4.83</td>
<td>0.81</td>
<td>50.3</td>
<td>10.2</td>
<td>127</td>
<td>27</td>
<td>2.304</td>
<td>986</td>
</tr>
<tr>
<td>Patients hypertensive at time of study</td>
<td>18</td>
<td>4.58</td>
<td>1.12</td>
<td>53.1</td>
<td>15.5</td>
<td>144</td>
<td>16</td>
<td>2.786</td>
<td>996</td>
</tr>
<tr>
<td>Patients not hypertensive at time of study</td>
<td>22</td>
<td>4.70</td>
<td>1.63</td>
<td>58.3</td>
<td>18.8</td>
<td>103</td>
<td>14</td>
<td>1.819</td>
<td>419</td>
</tr>
</tbody>
</table>

*Mean ± SE.

Abbreviations: C02 = cardiac index (liter/min/m²); SI = stroke index (ml/min/m²); PVR = peripheral vascular resistance index (dynes-sec-cm⁻⁵-m²); BV = blood volume (ml/kg body wt); Ht = hematocrit; Na+ = total exchange sodium (mEq/kg body wt).

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the circulation time and the average dye concentration.\textsuperscript{23} Hematocrit was measured by the capillary tube technic and blood volume using \textsuperscript{131}I albumin. Total exchangeable sodium was determined after a 24-hr equilibration using \textsuperscript{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 asuffy-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 ($P < 0.001$).
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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.24 This increase in resistance is seen with the infusion of angiotensin and pressor amines.25-27 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.2, 4-6, 28 A few studies have failed to demonstrate an increased cardiac output in uremic patients.12, 29, 30 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.15, 16 Several investigators believe that increased cardiac

Discussion

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.

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.

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Figure 4

Relation of diastolic blood pressure to cardiac index changes induced by varying the hematocrit (six patients): □ = B.P., ■ = L.W., □ = B.K., ▲ = V.F., ○ = L.R., △ = M.G.
output underlies all hypertension.\textsuperscript{14, 31–34} 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.\textsuperscript{14, 31, 34} 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.\textsuperscript{34}

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

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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 vasodilatation 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
protect patients from the effects of an otherwise devastating hypertension.

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