A Hemodynamic Evaluation of Bilateral Nephrectomy and Hemodialysis in Hypertensive Man

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SUMMARY
Three hypertensive men with end-stage primary renal disease were hemodynamically evaluated before and 3 to 4 weeks after bilateral nephrectomy and before and after 6 hours of hemodialysis with the twin coil artificial kidney. Conclusions include the following: (1) The height of the blood pressure and changes in plasma volume (P.V.) are not necessarily directly related in the early renoprival state. (2) Increased total peripheral resistance (TPR) plays an important role in maintaining elevation of blood pressure after nephrectomy. (3) We cannot document that bilateral nephrectomy has a beneficial effect on the hypertension of chronic renal failure during the first month of the anephric state. (4) Renin is not involved in maintaining elevated blood pressure after nephrectomy. (5) Increased sensitivity to ganglionic blockade may follow nephrectomy if P.V. decreases. (6) No evidence supports the existence of a "cardiodepressor" substance in uremia. (7) Increased blood pressure occasionally seen during hemodialysis is probably related to several factors (increased cardiac output, increased TPR). (8) P.V. may fall during hemodialysis even though body weight is maintained constant. (9) If P.V. is unchanged across hemodialysis, cardiac output usually does not change.

Additional Indexing Words:
Total peripheral resistance
Cardiodepressor substance
Valsalva maneuver
Renin

The long-term effect of chronically elevated blood pressure in man is poorly understood. Specifically, the effect of hypertension on the vasculature itself and the potential reversibility of such an effect need further study.

It has been stated that bilateral nephrectomy favorably influences the hypertension of end-stage chronic renal failure.1-3 It has also been suggested that in the anephric state there is a direct relationship between plasma volume and the height of the blood pressure.4 Furthermore, it has been demonstrated that with changes in plasma volume there is, in addition, an inverse relationship in peripheral vasoconstriction manifested by changes in sensitivity to ganglionic blockade.4

Because of problems of securing, managing, and controlling this type of patient, such

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This investigation was supported in part by Grants IR-01-HE-08260-01 from the U.S. Public Health Service, 5-RO1-AM-02657-08 from the National Institutes of Health, DA-49-193-MD-2497 and DA-49-193-MD-2337 from the U.S. Army Medical Research and Development Command, and AT-(30-1) 2265 from the Atomic Energy Commission. In addition, support was received from a John A. Hartford Foundation Grant. Studies were carried out in part in the Clinical Research Center and were supported by Grant 8-MD1-31-04 from the National Institutes of Health.
studies are understandably based on the evaluation of only one or two patients. We undertook the present investigation in order to examine, in a controlled manner, some of the points mentioned. Even though our series is also small, some definite "negative" impressions can be derived as well as several "positive" points as a guide for further study.

In addition, we have attempted to evaluate in a limited fashion the response of the cardiovascular system to uremia per se, the hemodynamic effects of hemodialysis, and the relationship of extracellular fluid and total body water to the hypertension of renal failure.

Methods

Three male hypertensive patients (ages 16 to 44 years) with chronic renal failure requiring periodic hemodialysis for maintenance of life were studied. These patients were candidates for bilateral nephrectomy in preparation for renal transplantation. The severity of hypertension was judged by funduscopic changes (table 1). All patients were known to have been hypertensive (diastolic pressure greater than 90 mm Hg) for 5 years or more, and each demonstrated cardiomegaly by chest x-rays and left ventricular hypertrophy by electrocardiogram. They were free from any complicating disease. Each had moderate to severe anemia (hematocrit, 17.6 to 28.6%).

All medications (except multi-vitamins) were withdrawn at least 7 days prior to study, and the patients were allowed (by changing the frequency of dialysis) to become azotemic. None of them had any edema or clinical evidence of congestive heart failure at any time during the study.

Prior to investigation, the patients were weighed. Femoral arterial blood pressure was measured with a Statham strain gauge (P-23AA) attached via a no. 18 Cournaud needle and recorded on one channel of a Lexington dual recorder. A small polyethylene catheter (Clay Adams PE-205) was inserted through an antecubital vein for measurement of central venous pressure (C.V.P.) and for dye injections. Either right atrial or C.V.P. was recorded with a strain gauge (Statham P-23BB) and connected to the other channel of the dual recorder. Cardiac output (C.O.) was determined from indicator-dilution curves (indocyanine green) connected to the Lexington analogue C.O. computer. The machine was calibrated at the beginning of each study and recalibrated after hemodialysis. Whenever possible, cardiac output was evaluated in groups of three curves and the average taken as the true output.

Base-line values of blood pressure, C.O., pulse rate, and venous pressure were taken.

The patient was instructed in the technique of the Valsalva maneuver. Alveolar pressure was measured by forceful expiration against a blood pressure cuff manometer. Average pressures of 30 to 40 mm Hg were maintained for 15 to 20 seconds during the Valsalva. Cardiac output, blood pressure, pulse rate, and C.V.P. were also recorded during this period. This procedure was repeated two to three times.

After the hemodynamic measurements returned to control levels, the patient repeatedly lifted and lowered a 7-pound cylinder from a recumbent position for 3 to 5 minutes. C.O. was measured immediately after this exercise.

After return to base line, an intravenous drip of trimethaphan (Arfonad) (1 mg/ml at 60 gtt/min) was started. If there was no fall in blood pressure after 5 minutes, the patient was slowly "tilted" to 18° from the horizontal. This tilt was maintained for 30 seconds to 3 minutes depending upon the degree of hypotension.

Following a recovery period (approximately 1/2 hour), blood volume was determined by the summation method using Evans blue dye and 51Cr with equilibration times of 0, 5, 10, and 30 minutes. Blood was also drawn for determinations of hematocrit and serum concentration of urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, and creatinine by standard laboratory methods.

The patient was then transferred to a bed scale and hemodialysis was performed with the twin coil artificial kidney. The machine was primed with blood collected from the coil during the previous dialysis (with approximately the same hematocrit value as that of the patient). Blood pressure, pulse rate, and C.V.P. were recorded throughout the 6-hour dialysis. The chemical composition of the dialysate was as follows: sodium, 130 mEq/L; potassium, 4 mEq/L; calcium, 3 mEq/L; magnesium, 2 mEq/L; chloride, 103 mEq/L; acetate, 5 mEq/L; bicarbonate, 30 mM/L; and glucose, 500 mg/100 cc. A continuous drip of physiological saline (0.15 M) was infused during the dialysis in order to replace fluid removed by ultrafiltration. This was estimated in advance and adjusted every 30 minutes according to scale weights. After the first hour, we were able to predict the amount of fluid necessary to maintain constant body weight.

Thirty minutes after dialysis blood volume, BUN, serum electrolytes, hematocrit, and creatinine were measured again. The hemodynamic challenge of the Valsalva maneuver and exercise, and response to ganglionic blockade were determined.
Table 1

Clinical Summary of Patients Studied

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Duration of known hypertension (yr)</th>
<th>Hypertensive retinopathy*</th>
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<td>44</td>
<td>M</td>
<td>Chronic pyelonephritis</td>
<td>12</td>
<td>IV</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>M</td>
<td>Chronic glomerulonephritis</td>
<td>5</td>
<td>III</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>M</td>
<td>Chronic glomerulonephritis</td>
<td>5</td>
<td>II</td>
</tr>
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</table>

*The Keith-Wagener-Barker classification.5

a second time. The patient was weighed at the end of the study.

Plasma volume and red cell volume were determined in the week following the study. In addition, total body water was measured with tritium (2 to 3-hour equilibration time)12 and extracellular fluid with radiobromide (18 to 24-hour equilibration period) employing the single exponential decay slope for bromide reverse extrapolated to zero time.12 Bilateral nephrectomy as a one-stage operation was then performed.

Twenty-three to twenty-nine days following surgery, the entire procedure was repeated. An attempt was made to keep the hematocrit level the same in the postnephrectomy period.

Total peripheral resistance (TPR) was calculated by the formula:

$$TPR = \frac{\text{Mean arterial pressure (mm Hg) - central venous pressure (mm Hg)}}{\text{Cardiac output (ml/min)}} \times 1.332 \times 60$$

Normal values for plasma volume (PV), red cell volume (RV), large vessel hematocrit (LVH), total body water (TBW), extracellular water (ECW), and intracellular water (ICW) were taken from data obtained previously.12 Plasma renin was determined before and after nephrectomy in the week following the hemodynamic study. The method used for assay was that of Boucher and colleagues15 with minor modifications.16 The patients were maintained on a diet consisting of approximately 68 mEq of sodium and 40 mEq of potassium per day. No attempt was made to maintain the patient in the recumbent position prior to drawing blood for renin assay.

Results

Hemodynamic Changes with Dialysis

General (Table 2)

Two separate studies were performed on each patient. Pertinent clinical and laboratory data are shown in table 2. The concentration of BUN ranged from 85 to 180 mg/100 ml before dialysis. Severe acidosis (serum bicarbonate level less than 20 mM/L) was not present in any of the patients. Weight was maintained within 0.2 kg before and after dialysis in all patients. Serum potassium values did not fluctuate significantly with dialysis (pre-dialysis range, 4.0 to 5.2 mEq/L), and post-dialysis values were approximately 4.0 mEq/L, the concentration of potassium used in the dialysate.

Volume Changes (Figure 3)

Blood volume composition measured before and after dialysis is shown in table 3. Patient 1 was evaluated pre-nephrectomy (pre-N) on two separate occasions. Plasma volume was elevated in all patients before dialysis and ranged from 106.7% to 158% of the predicted normal value. Although total body weight did not change with dialysis more than 0.2 kg and in most instances less than 0.1 kg, plasma volume decreased more than 10% after dialysis in four instances (patient 1-pre-N, on two occasions, patient 2-pre-N, and patient 3-post-N) and was increased in one case (patient 1-post-N) and remained unchanged after the remaining two dialyses. Serum Na' was not significantly altered with dialysis (table 2).

The results of plasma volume determinations were treated as paired data (pre-dialysis minus post-dialysis) and a t-value was calculated for the difference, $t = 2.23$ ($P < 0.1$). Changes in large vessel hematocrit (LVH) after dialysis were in the same direction as changes in plasma volume. Red cell volume was not altered significantly ($< 10\%$) following dialysis, except in one instance (patient...
2-post-N) when it increased by 15%. In this case, it was necessary to begin dialysis with bank blood containing a hematocrit of approximately 37%. This difference in hematocrit values explains the increase in red blood cell volume. Alterations in blood volume are largely explained by changes in plasma volume.

None of the patients (figs. 1 to 6) was felt to be in congestive heart failure clinically despite the large plasma volume. A normal C.V.P. and a rising C.O. with exercise further substantiate this conclusion.

**Response to the Valsalva Maneuver (Fig. 7)**

The Valsalva maneuver demonstrated a decrease in systolic pressure of greater than 50 mm Hg along with a lesser fall in diastolic blood pressure in all instances except one (patient 1-pre-N, pre-dialysis). There was a slight but definite increase of systolic and diastolic pressure over base-line levels immediately following the procedure. None of the patients demonstrated reflex bradycardia in conjunction with the “overshoot” in blood pressure. Except for patient 1, there was no appreciable change in the response to the maneuver following dialysis.

Cardiac output was markedly reduced during the procedure in each instance in which it was tested except for patient 1 (figs. 1 to 6). Patient 1 showed no fall in blood pressure with the Valsalva maneuver prior to dialysis before nephrectomy, but following dialytic treatment, when his plasma volume had decreased by 20%, he responded in a more normal way.

**Effects of Ganglionic Blockade (Figs. 1 to 6)**

The change in sensitivity to ganglionic blockage after dialysis was determined by the response to trimethaphan. Patient 1 (pre-N) did not respond to trimethaphan infusion before dialysis (total dose given, 100 mg), but following dialysis, he demonstrated a fair response to half that amount of the drug (50 mg). Patient 2 on both occasions showed only a slight fall in blood pressure with the ganglionic blocker, and this did not change after dialysis. In one instance (patient 1-post-N), although there was a hypotensive response pre-dialysis to 50 mg of trimethaphan, post-dialysis an equal response was achieved with less than half the dose (P.V. increased 7.2%). Patient 2 (pre-N) did not show an increased sensitivity to trimethaphan in spite of a fall in PV of 16%. These examples indicate no clear relationship between change in sensitivity to the drug and alteration in plasma volume.

**Table 2**

*Pre- and Post-Dialysis Values During Study*

<table>
<thead>
<tr>
<th>Days postnephrectomy</th>
<th>Patient 1 Pre-</th>
<th>Patient 1 Post-</th>
<th>Patient 2 Pre-</th>
<th>Patient 2 Post-</th>
<th>Patient 3 Pre-</th>
<th>Patient 3 Post-</th>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Weight (kg)</td>
<td>85.5</td>
<td>65.4</td>
<td>62.5</td>
<td>62.3</td>
<td>65.8</td>
<td>65.8</td>
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<tr>
<td>BUN (mg/100 ml)</td>
<td>90</td>
<td>23</td>
<td>180</td>
<td>59</td>
<td>88</td>
<td>28</td>
</tr>
<tr>
<td>Creatinine (mg/100 ml)</td>
<td>11.0</td>
<td>6.5</td>
<td>22.0</td>
<td>12.4</td>
<td>12.8</td>
<td>6.3</td>
</tr>
<tr>
<td>K⁺ (mEq/L)</td>
<td>4.8</td>
<td>4.2</td>
<td>4.9</td>
<td>4.1</td>
<td>4.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Na⁺ (mEq/L)</td>
<td>136</td>
<td>136</td>
<td>140</td>
<td>136</td>
<td>134</td>
<td>138</td>
</tr>
<tr>
<td>HCO₃⁻ (mM/L)</td>
<td>24</td>
<td>28</td>
<td>20</td>
<td>27</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>23.0</td>
<td>26.2</td>
<td>24.8</td>
<td>28.6</td>
<td>23.9</td>
<td>24.0</td>
</tr>
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</table>

**Circulation, Volume XXXV, February 1967**
Blood Volume Distributions Before and After Dialysis

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Body weight (kg)</th>
<th>RV (ml/kg)</th>
<th>PV (ml/kg)</th>
<th>BV (ml/kg)</th>
<th>LVH (%)</th>
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<tbody>
<tr>
<td>1—pre-N</td>
<td>Predicted</td>
<td></td>
<td>27-31</td>
<td>40-50</td>
<td>70-80</td>
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<tr>
<td></td>
<td>Pre-dialysis</td>
<td>66.5</td>
<td>—</td>
<td>60.0</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Post-dialysis</td>
<td>66.5</td>
<td>—</td>
<td>50.7</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Pre-dialysis</td>
<td>65.5</td>
<td>20.6</td>
<td>54.0</td>
<td>74.0</td>
</tr>
<tr>
<td></td>
<td>Post-dialysis</td>
<td>65.4</td>
<td>19.3</td>
<td>43.3</td>
<td>62.7</td>
</tr>
<tr>
<td>1—post-N (23 days)</td>
<td>Pre-dialysis</td>
<td>61.9</td>
<td>14.0</td>
<td>40.1</td>
<td>63.1</td>
</tr>
<tr>
<td></td>
<td>Post-dialysis</td>
<td>61.8</td>
<td>14.4</td>
<td>52.7</td>
<td>67.1</td>
</tr>
<tr>
<td>2—pre-N</td>
<td>Pre-dialysis</td>
<td>62.5</td>
<td>13.7</td>
<td>61.1</td>
<td>74.9</td>
</tr>
<tr>
<td></td>
<td>Post-dialysis</td>
<td>62.3</td>
<td>14.9</td>
<td>51.3</td>
<td>66.3</td>
</tr>
<tr>
<td>2—post-N (26 days)</td>
<td>Pre-dialysis</td>
<td>54.3</td>
<td>13.4</td>
<td>54.3</td>
<td>67.8</td>
</tr>
<tr>
<td></td>
<td>Post-dialysis</td>
<td>54.5</td>
<td>15.4</td>
<td>52.1</td>
<td>67.5</td>
</tr>
<tr>
<td>3—pre-N</td>
<td>Pre-dialysis</td>
<td>65.8</td>
<td>18.2</td>
<td>68.0</td>
<td>86.3</td>
</tr>
<tr>
<td></td>
<td>Post-dialysis</td>
<td>65.8</td>
<td>19.9</td>
<td>67.8</td>
<td>85.7</td>
</tr>
<tr>
<td>3—post-N (29 days)</td>
<td>Pre-dialysis</td>
<td>67.2</td>
<td>19.3</td>
<td>75.9</td>
<td>95.2</td>
</tr>
<tr>
<td></td>
<td>Post-dialysis</td>
<td>67.2</td>
<td>18.6</td>
<td>67.7</td>
<td>86.3</td>
</tr>
</tbody>
</table>

Abbreviations: pre-N = pre-nephrectomy; post-N = post-nephrectomy; RV = red cell volume; PV = plasma volume; BV = blood volume (RV + PV); LVH = large vessel hematocrit; WBH = whole body hematocrit (RV + PV); Pre and Post = before and after dialysis.

Blood Pressure Change (Figs. 1 to 6)

There was no consistent change in blood pressure during or immediately following the dialysis. In one instance (patient 2-pre-N) a slight fall in blood pressure occurred during the last 2½ hours of the dialysis. Patient 1 on two occasions demonstrated a rise in blood pressure during the last hour of dialytic treatment, which was manifested primarily by a rise in systolic pressure. In patient 1 (pre-N), there was an increase in cardiac output of 1 L/min with no change in TPR. After operation an increased TPR was responsible for the increase in blood pressure. Patient 3 (post-N) had a slight fall in blood pressure during the midpoint of dialysis, with return to pre-dialytic levels prior to the end of the procedure. Patient 1 (post-N) developed unexplained hypotension shortly after beginning dialysis and required a transfusion of 100 ml of whole blood. The remainder of the dialysis was uncomplicated.

Cardiac Output (Figs. 1 to 6)

Cardiac output in the resting state was not significantly different pre-dialysis and post-dialysis in four of the six studies. Patient 1 (pre-N) increased his C.O. from 6.6 to 7.6 L/min following dialysis. This patient also had a slight rise in blood pressure. Patient 3 showed a change in cardiac output with dialysis after nephrectomy and resting C.O. increased from 10.3 to 11.4 L/min. He did not, however, show a significant change in blood pressure because of a fall in TPR. Both of these patients demonstrated a decrease in plasma volume with dialysis.

Effect of Bilateral Nephrectomy

Blood Pressure Change (Figs. 1 to 6)

Patient 1 showed no change in resting blood pressure during the hemodynamic evaluation following nephrectomy even though his plasma volume had been reduced by 30%. In addition, patient 2 with a plasma volume decrease of 13% after nephrectomy also showed no change in his resting blood pressure. Patient 3, who had an increase in plasma volume of 11% following nephrectomy, demonstrated a rise in systolic and diastolic blood pressures of 10 mm Hg.

None of the patients demonstrated a significant change in blood pressure when we compared average pressures in the period immediately preceding and in the 4 weeks following nephrectomy. Figure 8 shows the
### HEMODYNAMIC RESPONSE TO HEMODIALYSIS BEFORE NEPHRECTOMY

**Effect of Valsalva, Exercise and Arfonad + Tilt**

**PATIENT #1**

<table>
<thead>
<tr>
<th>WBH (%)</th>
<th>WBH/LVH</th>
<th>RV (%) observed</th>
<th>PV (%) observed</th>
<th>BV (%) observed</th>
<th>RV (%) Pre—Post</th>
<th>PV (%) Pre—Post</th>
<th>BV (%) Pre—Post</th>
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<tr>
<td>38-44</td>
<td>0.88-0.94</td>
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<td>—</td>
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<tr>
<td>27.6</td>
<td>0.88</td>
<td>73.8</td>
<td>118.0</td>
<td>101.9</td>
<td>— 6.7</td>
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<td>—16.3</td>
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<tr>
<td>30.9</td>
<td>0.93</td>
<td>68.9</td>
<td>94.3</td>
<td>85.2</td>
<td>— 2.3</td>
<td>+ 7.2</td>
<td>+ 6.1</td>
</tr>
<tr>
<td>22.3</td>
<td>0.93</td>
<td>50.0</td>
<td>106.0</td>
<td>85.2</td>
<td>+ 9.0</td>
<td>—16.2</td>
<td>—12.0</td>
</tr>
<tr>
<td>22.8</td>
<td>0.78</td>
<td>45.0</td>
<td>123.0</td>
<td>93.4</td>
<td>+15.1</td>
<td>— 3.7</td>
<td>0</td>
</tr>
<tr>
<td>19.9</td>
<td>0.85</td>
<td>43.5</td>
<td>106.9</td>
<td>82.7</td>
<td>— 1.7</td>
<td>— 0.4</td>
<td>— 0.7</td>
</tr>
<tr>
<td>22.9</td>
<td>0.88</td>
<td>50.0</td>
<td>102.9</td>
<td>82.7</td>
<td>— 1.7</td>
<td>— 0.4</td>
<td>— 0.7</td>
</tr>
<tr>
<td>21.1</td>
<td>0.88</td>
<td>61.9</td>
<td>141.8</td>
<td>111.4</td>
<td>— 1.7</td>
<td>— 0.4</td>
<td>— 0.7</td>
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<tr>
<td>20.8</td>
<td>0.87</td>
<td>60.8</td>
<td>141.1</td>
<td>110.6</td>
<td>— 1.7</td>
<td>— 0.4</td>
<td>— 0.7</td>
</tr>
<tr>
<td>20.3</td>
<td>0.88</td>
<td>66.0</td>
<td>158.9</td>
<td>123.6</td>
<td>— 3.8</td>
<td>—10.8</td>
<td>— 9.4</td>
</tr>
<tr>
<td>21.6</td>
<td>0.88</td>
<td>63.5</td>
<td>141.7</td>
<td>112.0</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Figure 1**

*Patient 1 (pre-nephrectomy). Note the abnormal response to the Valsalva maneuver before dialysis, increase in blood pressure late in dialysis, and fall in plasma volume after dialysis.*

*Circulation, Volume XXXV, February 1967*
course of patient 1, correlating blood pressure, weight, and time after nephrectomy. There was no decrease in mean blood pressure in the 3 weeks following surgery. There was, however, a significant decrease in systolic and diastolic pressures 4½ months after nephrectomy while he was being maintained with biweekly hemodialysis.

**Hemodynamic Response (Figs. 1 to 6)**

No consistent difference in the response to the Valsalva maneuver or to exercise was noted pre- and post-nephrectomy. A reflex bradycardia was not associated with the Valsalva maneuver either in the pre- or post-nephrectomy state. The resting cardiac output was slightly increased after operation in patients 1 and 3 and decreased in patient 2.

The patients with decreased plasma volume post-nephrectomy had increased sensitivity to ganglionic blockade and increased TPR. Patient 1 had no response to 100 mg of trimethaphan before nephrectomy but responded to 50 mg after nephrectomy. Patient 2 demonstrated minimal response to 75 mg of the drug prior to operation but developed marked hypotension with only 10 mg after surgery.

**Volume Changes (Table 4)**

ECW and TBW were increased above normal in all patients before and after nephrectomy. ICW, on the other hand, was consistently within the normal range. Body weight had decreased in all patients post-nephrectomy. In patient 1 the relationship of TBW, ECW, and ICW to total body weight did not change appreciably. Patients 2 and 3, whose weight decreased following operation, demonstrated an increase in TBW manifested by a rise in ECW, and a fall in ICW. The increase in ECW, however, was not reflected by an increase in plasma volume in patient 2.

**Renin Assay (Table 5)**

Renin levels were low in all patients following operation. Patient 1 demonstrated a slight increase in the enzyme from 38 nanograms (ng)/100 ml to 110 ng/100 ml after nephrectomy, and patient 2 demonstrated the highest value for the group prior to nephrectomy (560 ng/100 ml).
Discussion

Generally differences in hemodynamic response following dialysis can be explained by changes in plasma distribution. It is curious that without a corresponding alteration in body weight, we observed differences in the distribution of vascular volume in four of the seven dialyses studied. The plasma volume in these instances decreased appreciably after dialysis in the face of a stable serum Na concentration (table 2), implying an increased permeability of the vasculature to circulating fluid. These changes, although not statistically significant \((P < 0.1)\) in this small series, are suggestive and indicate the need for further study. The degree of uremia (BUN and serum creatinine) range from moderate to severe. The patients with the greatest elevation in BUN did not have a different hemodynamic response when the azotemia was less severe. It is possible, although unlikely, that some substance present in uremia directly affects the small vasculature, and that removal of such a "toxin" in some patients increases the permeability of the vessel wall. Our failure to demonstrate consistent elevation in TPR or increased sensitivity to ganglionic blockade following dialysis would make it unlikely that any generalized vasoconstrictive element is responsible for the volume change.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre-nephrectomy (nanograms/100 ml)</th>
<th>Post-nephrectomy (nanograms/100 ml)</th>
</tr>
</thead>
<tbody>
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<tr>
<td>3</td>
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*Normal = 200 to 500 ng/100 ml.

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It is possible that in some patients there is a fall in serum albumin following dialysis with a resultant decrease in oncotic pressure and intravascular volume. Protein is known to adhere to the cellophane membrane used for dialysis, but this has not been quantitated. Information concerning albumin kinetics in the uremic, non-nephrotic patient is not available. Our data do not shed any light on this point. Serum albumin may be decreased in patients with long-standing hypertension, and it is conceivable that in some patients an added loss of plasma protein with dialysis, although slight, may be enough to affect plasma oncotic pressure and intravascular fluid distribution.

Del Greco and associates demonstrated an increase in cardiac output following dialysis in five of nine patients studied. Their study is not directly comparable to ours, however, as body weight was not maintained constant and several of their patients were in congestive heart failure. The improved cardiac output in their series may have been secondary to the fall in plasma volume effected by ultrafiltration. We found no consistent change in cardiac output after dialysis and would conclude that, if plasma volume remains constant, there is no change in output. This is evidence against the existence of a uremic cardiodepressor factor. Anemia, hypertension, fluid balance, and changes in serum potassium before and after dialysis were constant in our patients. Therefore, if a cardiodepressor substance were removed by dialysis, we would expect a rise in cardiac output. It may be that the myocardial depression was not severe.
HEMODYNAMIC RESPONSE TO HEMODIALYSIS AFTER NEPHRECTOMY

Effect of Valsalva, Exercise and Arfonad

Patient 2 (post-nephrectomy, 26 days). There was no change in blood pressure as compared to that in the pre-nephrectomy study (fig. 3) even though PV decreased. Sensitivity to ganglionic blockade has increased greatly.

Malmberg and colleagues evaluated the Valsalva maneuver in a group of patients with chronic pulmonary disease. These investigators suggested that pulmonary hypertension with or without right ventricular failure is likely when a combination of a normal peripheral artery response and an abnormal heart rate (lack of bradycardia) is obtained.

The Valsalva maneuver was abnormal in our patients primarily because of a lack of reflex bradycardia accompanying the pressure overshoot. This was a consistent finding in all patients without relationship to dialysis or nephrectomy. None of the patients studied had any evidence of acute or chronic pulmonary disease. We cannot explain the response to the Valsalva maneuver with certainty but would doubt if these patients had isolated pulmonary hypertension. A more likely explanation is that the stimulus to the autonomic nervous system caused by the hypotension and pressure overshoot produced during the maneuver was not strong enough to evoke a reflex slowing of heart rate. Most normal persons will develop bradycardia with the hypotensive response seen in our patients, and this suggests some derangement of function of the autonomic nervous system. The cause or degree of any such dysfunction is not at all clear.

The Valsalva maneuver did not suggest...
left ventricular failure except in one instance. In patient 1 (fig. 7) the test was abnormal prior to nephrectomy and was the only parameter measured to indicate a degree of failure. This test improved following dialysis when plasma volume decreased.

No consistent change in blood pressure was noted with dialysis. It is not uncommon to observe an increase in blood pressure in a patient undergoing hemodialysis. This usually occurs after the first hour. The reason for such an increase was not detected from this study. The blood pressure was high in all individuals and generally remained so throughout the dialysis. Patient 1 on most occasions when he is having a "routine" dialysis will experience a significant rise in blood pressure associated with headache and occasional nausea. This pattern persisted during the study both before and after nephrectomy. Before nephrectomy there was a slight rise in cardiac output, which may have accounted for the increase in mean pressure. Following nephrectomy, however, cardiac output did not change, but TPR rose. In addition, there was an increase in sensitivity to ganglionic blockade, implying that sympathetic vasomotor activity was responsible for the post-dialytic rise in blood pressure. It is probable that the rise in blood pressure occasionally seen with dialysis is due to multiple factors (increased cardiac output, peripheral vasoconstriction, central nervous system changes, and others), and that one or a combination of such factors is responsible for the hypertension in the individual patient.

It has been shown recently in an anephric patient studied by Dustan and Page that changes in blood volume are reflected by similar changes in blood pressure. This observation coupled with earlier work from this and other laboratories suggesting such a correlation leaves little doubt that blood pressure and blood volume are closely related. It is

Figure 5

Patient 3 (pre-nephrectomy). No significant change in hemodynamic function with dialysis.
HEMODYNAMIC RESPONSE TO HEMODIALYSIS AFTER NEPHRECTOMY

Figure 6

Patient 3 (post-nephrectomy, 29 days). There is an increase in PV and blood pressure as compared to that in the pre-nephrectomy study (fig. 5). PV is decreased following hemodialysis.

noteworthy that there was little change in blood pressure in patients 1 and 2 following nephrectomy. In these two patients the plasma volume was considerably decreased after nephrectomy, and in both was only 106% of predicted normal. The reason for a lack of fall in measured blood pressure is not certain, but the implication is clear that, although the relation between blood volume and blood pressure may hold in certain instances, other factors (such as total ECF?), perhaps equally as important, affect the height of arterial pressure.

Total peripheral resistance was increased in both patients 1 and 2 following nephrectomy and this was substantiated by the demonstration of increased sensitivity to ganglionic blockade. Dustan and Page4 showed an increase in sensitivity to trimethaphan with a decrease in blood volume in their patient. Our findings after bilateral nephrectomy are in general agreement with theirs. Patient 3, who had no decrease in plasma volume following nephrectomy, did not demonstrate a change in response to the drug. We could not, however, substantiate such a correlation of increased sensitivity to ganglionic blockade when the change in plasma volume occurred after dialysis. Our finding in two patients of no change in blood pressure with increased TPR and increased sensitivity to ganglionic blockade in spite of a significant fall in plasma volume strongly suggests a change in sympathetic vasomotor activity. An increase in vascular tone seems to be playing a major role in maintaining hypertension in spite of the absence of renal tissue and any hypertensive factor that the diseased kidney tissue may elaborate. It certainly suggests that plasma volume itself may be only a secondary factor in maintaining elevated blood pressures in the early renoprival state.26

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EFFECT OF VALSALVA ON ARTERIAL BLOOD PRESSURE

PATIENT #3 BEFORE DIALYSIS, AFTER NEPHRECTOMY

ALVEOLAR PRESSURE 40 mm Hg
PLASMA VOLUME 5100 ml

PATIENT #1 BEFORE NEPHRECTOMY

BEFORE DIALYSIS

ALVEOLAR PRESSURE 75 mm Hg
PLASMA VOLUME 4720 ml

Figure 7
Representative tracing obtained during the Valsalva maneuver is shown in the upper part of this figure. Note the absence of bradycardia accompanying the overshoot. The bottom tracings demonstrate the change in the response to the Valsalva in patient 1 (pre-nephrectomy) after a decrease in plasma volume effected by dialysis.

Our data do not shed any light on the role of a renal vasodepressor substance in the hypertension seen with renal disease. Since this substance is probably not elaborated in sufficient amounts by the chronically diseased kidney or possibly is overshadowed by a vasopressor element, no effect on blood pressure would be expected by removing kidney tissue in an already “autonephrectomized” patient with chronic renal disease.

There is evidence to indicate that the renin-angiotensin system plays a role in some types of hypertension. However, the low level of renin activity in the anephric state demonstrated in this study with the low but definite levels found pre-nephrectomy indicates little importance for this system in the maintenance of hypertension after nephrectomy. Even though renal vein blood was not examined, this observation, coupled with the fact that patients with this form of hypertension do not show increased sensitivity to angiotensin, casts doubt on its etiological importance in the chronically hypertensive patient with renal failure. To date, studies fail to show a consistent increase of this enzyme in most forms of hypertension.

The slightly elevated renin level found in patient 3 before nephrectomy might be due to changes in sodium balance or the upright position or both (both factors known to affect renin production). This patient suffered from chronic glomerulonephritis, and this condition has not been associated with increased renin levels. The increase in plasma renin in patient 1 following nephrectomy, although small and considerably below normal, may be related...
NEPHRECTOMY AND HEMODIALYSIS IN HYPERTENSION

Figure 8

Relationship of blood pressure and weight to nephrectomy in patient 1. Pressures did not differ before and immediately following the operation. Four and one half months later, however, there was a significant difference in both systolic and diastolic pressures ($P < 0.01$).

to recent transfusions or to extrarenal production of this enzyme. A repeat renin determination several weeks after nephrectomy was 68 nanograms/ml. Extrarenal production of renin, or a renin-like substance, has been demonstrated only in lower animals, but such a site, if present in man, would explain why there is any detectable renin in the renal prival state.

The three patients in this study had persistent hypertension for more than 5 years. The permanent effect on the blood vessels of such an elevation in pressure is unknown. Although there was little change in the vasculature of dogs maintained hypertensive for several years, the situation in man may be different. Circumstantial evidence indicates that chronic elevation in blood pressure produces atherosclerotic lesions. This is suggested by the development of severe changes in the aorta above a coarctation and by the atherosclerotic plaques that occur in the pulmonary artery of patients with chronic pulmonary hypertension. In some patients with long-standing hypertension secondary to unilateral renal arterial disease, a fall in blood pressure after nephrectomy or arterial reconstruction may be dramatic and may be demonstrating immediate reversibility of the hypertension. On the other hand, in other patients a fall in blood pressure may become apparent only after some months. Our patients were anephric 3 to 4 weeks between studies, but during that time there was no significant change in mean blood pressure. It is possible that the factor(s) in the kidney that initiated the process of hypertension is no longer necessary to sustain the elevation. This may represent a "resetting" of the baroreceptors, as has been postulated, and may require considerable time for readjustment. This is suggested by the experience of some that hypertension is easier to control after bilateral

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nephrectomy and that a fall in blood pressure may require several weeks to become manifest. Our own experience gives no clear answer but would support this observation in part. Patient 7 (fig. 8) remained hypertensive in spite of antihypertensive medication for more than 3 months following nephrectomy while being maintained with bi-weekly hemodialysis. After that time, he gradually required less antihypertensive medication until 5 months after operation he was maintained normotensive without drugs. At this point, there appeared to be good correlation between the state of hydration and the level of blood pressure. A similar course has been reported previously in an anephric patient. Such experience suggests a gradual amelioration of chronic renal hypertension with nephrectomy and is consistent with the idea of a readjustment of vascular baroreceptors. However, we have also noted in other chronically hypertensive patients who are not nephrectomized and who are maintained with chronic hemodialysis, a similar gradual fall in blood pressure over many months.

The distribution of body fluids is not changed significantly with nephrectomy. In our cases there was an excess of total body water and specifically there was a marked increase in extracellular water. The increase in extracellular water was proportionally larger than that of intracellular water (which was normal). One would expect most patients being maintained with the artificial kidney to show an increase in extracellular fluid. This seems to be the case even when negative nitrogen balance has been reversed and the patient is assimilating body mass. With the limitation in excretory function it is difficult to maintain the patient completely "dry" between dialyses and the removal of fluid by ultrafiltration during the procedure to some degree selectively removes fluid from the circulating volume. Over the relatively short time during which dialysis is performed, extracellular fluid may not be mobilized completely and the patient tends to maintain a state of chronic overhydration. This appears to be so as immediately following renal transplantation in some patients who are "dry" by clinical standards (including dialysis to the point of hypotension), we have observed diuresis and the patient may lose several kilograms of body weight without depleting circulating volume.

As stated, the volume distributions seen in these patients are not specific and suggest overhydration and after surgery a loss of body mass (decreased ICW).

In summary, the following points may be said of this study: (1) The height of the blood pressure and changes in plasma volume are not necessarily directly related in the early renoprival state. (2) An increase in TPR plays an important role in maintaining an elevation of blood pressure after nephrectomy despite a fall in plasma volume. (3) We cannot document that bilateral nephrectomy has a beneficial effect on the hypertension of chronic renal failure during the first month of the anephric state. In addition, even though in some patients hypertension becomes easier to control several weeks to months following operation, it is not clear that the procedure has unquestionably benefited them. This reservation is based on the fact that some patients maintained with the artificial kidney undergo an identical amelioration in their hypertension without surgery. (4) Renin is not involved in maintaining an elevated blood pressure after nephrectomy. (5) An increased sensitivity to ganglionic blockade may be present following nephrectomy if plasma volume decreases. However, there is no consistent correlation between an increased sensitivity to trimethaphan and changes in plasma volume if the plasma volume falls during dialysis without a change in body weight. (6) We can find no evidence to support the existence of a "cardiodepressor" substance in uremia. (7) The increase in blood pressure occasionally seen during hemodialysis is probably related to several factors (increased cardiac output, increased TPR). (8) Plasma volume during hemodialysis may fall even though body weight is maintained constant. The cause of such a redistribution of fluid is unknown but does not appear to be...
secondary to generalized vasoconstriction. (9) Hypertensive patients with chronic renal failure, being maintained with periodic hemodialysis, are overhydrated with an increase in TBW and ECF. (10) If plasma volume is unchanged across hemodialysis, there is usually no change in cardiac output.

Acknowledgment

We thank Dr. F. D. Moore for his continued support and encouragement throughout this study and for his generosity in making his laboratory facilities available to us. Without his kind cooperation this study would not have been possible. We also thank Dr. R. Hickler for the plasma renin determinations.

References
Allan Burns on Cardiac Resuscitation, 1809

Where however, the cessation of vital action is very complete, and continues long, we ought to inflate the lungs, and pass electric shocks through the chest: the practitioner ought never, if the death has been sudden, and the person not very far advanced in life, to despair of success, till he has unequivocal signs of real death.—ALLAN BURNS: Observations on Some of the Most Frequent and Important Diseases of the Heart. New York, Hafner Publishing Co., 1964, p. 147.
A Hemodynamic Evaluation of Bilateral Nephrectomy and Hemodialysis in Hypertensive Man
CONSTANTINE L. HAMPERS, JOHN J. SKILLMAN, JOHN H. LYONS, JOHN E. OLSEN and JOHN P. MERRILL

Circulation. 1967;35:272-288
doi: 10.1161/01.CIR.35.2.272
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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