Hemodynamics of Hypertension in Chronic End-Stage Renal Disease

By Kwan Eun Kim, M.D., Gaddo Onesti, M.D., Allan B. Schwartz, M.D., Joel L. Chinitz, M.D., and Charles Swartz, M.D.

SUMMARY
This study was undertaken to define the hemodynamic changes in hypertension of chronic end-stage renal disease. Mean cardiac index in 75 uremic patients was higher ($P < 0.001$) than that of 42 normal volunteers while stroke index was not different from normals. The higher cardiac indices of uremic patients were accounted for by increased heart rates. Despite the significantly higher blood pressure in the uremics, their mean total peripheral resistance index was not different from that of normals.

The total group of 75 patients included 52 hypertensive and 23 normotensive uremics. Cardiac index, heart rate, and stroke index were the same in 52 hypertensive and 23 normotensive uremics while mean total peripheral resistance index of hypertensive uremics was higher ($P < 0.001$) than normotensive uremics. Therefore, the hypertension in end-stage renal disease is sustained by a high total peripheral resistance.

Bilateral nephrectomy in 12 hypertensive uremics resulted in no changes in cardiac index; a consistent decrease in blood pressure ($P < 0.001$) and a decrease in total peripheral resistance index ($P < 0.001$) occurred. Bilateral nephrectomy in eight additional uremics with malignant hypertension resulted in an actual increase in cardiac index ($P < 0.001$) with a consistent reduction in blood pressures ($P < 0.001$) and an even more dramatic decrease in total peripheral resistance ($P < 0.001$). These findings imply that a vasopressor substance of renal origin increasing peripheral resistance is the major factor in the pathophysiology of renal hypertension in the late stage of its natural history.

Additional Indexing Words:
Cardiac output Total peripheral resistance Uremia
Maintenance hemodialysis Bilateral nephrectomy Kidneys
Vasopressor substance

Although the etiology of essential hypertension remains obscure, extensive studies have revealed a consistent hemodynamic pattern. Early essential hypertension is characterized by a high cardiac output and a normal total peripheral resistance. With advancing age, the patient with essential hypertension will change to a pattern of normal cardiac output and increased total peripheral resistance and finally, later in the natural course of the disease, into one of low cardiac output and further increase in total peripheral resistance.

In contrast with essential hypertension, not only is the etiology of hypertension in chronic renal parenchymal disease and uremia obscure, but also information regarding its basic

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hemodynamic derangement is limited and conflicting.

In 1961, Brod et al. described a cardiac output higher than normal in both chronic glomerulonephritis and polycystic kidney disease. A wide variation of cardiac output was, however, reported.

More recently, Frohlich and co-workers reported normal cardiac output and increased total peripheral resistance in 11 nonazotemic hypertensive patients with chronic renal parenchymal diseases of varying etiologies.

Hypertension associated with end-stage renal disease and uremia, a higher than normal cardiac output has been described by Goss et al. and by Mostert et al. In contrast, Del Greco and co-workers and Anthonisen and Holst described normal cardiac output in uremic patients.

A knowledge of the hemodynamic alterations in hypertension secondary to chronic renal disease is essential in order to understand the underlying pathophysiologic mechanisms. If the basic hemodynamic change in hypertension of chronic renal parenchymal disease is an increase in cardiac output, then the search for a renal vasoconstrictor material would remain fruitless. On the other hand, if the hemodynamic change is an increase in total peripheral resistance, then research efforts should be directed toward the causes of peripheral arteriolar constriction. It is possible that both mechanisms operate simultaneously or in chronologic sequence.

During the past 7 years we have had the opportunity to study the hemodynamic pattern of 75 patients with chronic end-stage renal parenchymal disease and uremia. During the same period 42 normal volunteers have been studied in the same laboratory.

It is the purpose of the present paper: (1) to report the hemodynamic changes of chronic end-stage renal disease, and (2) to assess the relative contribution of cardiac output and total peripheral resistance to the hypertension of chronic end-stage renal parenchymal disease.

Materials and Methods

Seventy-five patients with chronic end-stage renal disease and uremia on maintenance hemodialysis programs were studied. There were 39 males and 36 females. The age ranged from 16 to 57 years with a mean of 36 years. Of the 75 patients studied, 23 were normotensive and exhibited no clinical, radiologic, or electrocardiographic changes of hypertensive cardiovascular disease. The remaining 52 were hypertensive. Of these, 44 had mild-to-moderate hypertension and eight were in the malignant phase of hypertension with retinal hemorrhages, exudates, and papilledema. Hypertension was defined as systolic blood pressure above 150 mm Hg or diastolic blood pressure above 90 mm Hg. Of the 23 normotensive uremic patients, 19 patients had chronic glomerulonephritis, three had polycystic kidney disease, and one had chronic pyelonephritis. Of the 52 hypertensive patients, 36 had chronic glomerulonephritis, six had malignant nephrosclerosis, six had chronic pyelonephritis, three had hereditary chronic nephritis, and one had polycystic kidney disease.

The studies were performed when the patients were clinically at dry weight and free of edema. There was no difference in the state of hydration between the hypertensive and the normotensive uremic patients. All the uremic patients studied were ambulatory, clinically stable, rehabilitated, and free of uremic complications. All antihypertensive medications were discontinued at least 2 weeks prior to the hemodynamic studies.

Studies were conducted in the morning, in the supine position, after 1 hour of bed rest. Because of possible acute hemodynamic changes induced by hemodialysis, all the studies were performed at least 48 hours after hemodialysis.

The control group included 42 normal, healthy volunteers. Twenty-two were males and 20 were females. Their age ranged from 22 to 57 years with a mean of 43 years. The group of uremic patients and normal subjects were of comparable age and sex.

Hemodynamic studies were performed through an external connector inserted between the arterial and venous ends of the A-V shunt used for hemodialysis. Cardiac output was determined by the dye-dilution technic using a Gilford densitometer with the injection of indocyanine green through the venous side of the external cannula and withdrawal of arterial blood from the arterial side of the external connection. Every cardiac output reported represents the average of at least three determinations. Arterial blood pressure was measured with a Statham strain gauge transducer from the arterial side of the temporarily occluded external connector. Normal subjects were studied through a Courmand needle inserted into the brachial artery. Mean arterial pressure (MAP) was obtained by electronic
integration. Dye-dilution and blood pressure curves were recorded on a photographic oscillograph.

Cardiac index (CI) was calculated by dividing the cardiac output by body surface area. Total peripheral resistance index (TPRI) was calculated according to the formula:

\[ \text{TPRI} = \frac{\text{MAP (mm Hg)}}{\text{CI (ml/sec/m}^2\text{)}} \times 1332 \]

and expressed as: dynes/sec/cm\(^{-5}\)/m\(^2\). Total exchangeable sodium was measured by isotope dilution using \(^{22}\)Na.\(^{13}\)

Twenty of 52 hypertensive uremic patients underwent bilateral nephrectomy in preparation for renal transplantation or for control of hypertension. Complete hemodynamic studies were repeated 1–3 months after bilateral nephrectomy. In each of these patients, the hemodynamic parameters before and after bilateral nephrectomy were compared at equivalent levels of total exchangeable sodium and body weight (dry weight).

**Results**

**Hemodynamic Pattern of Chronic End-Stage Renal Disease**

The mean value of the hematocrit in normal subjects was 43% while the uremic patients were all significantly anemic with a mean hematocrit of 23%.

In the 42 normal volunteers, the mean cardiac index was 3.39 ± 0.08 liters/min/m\(^2\) (mean ± 1 sd). In the 75 patients with end-stage renal disease, the mean cardiac index was 4.44 ± 0.11 liters/min/m\(^2\). The difference is statistically significant (P < 0.001) (fig. 1A).

Mean heart rate was 66 ± 1.2 beats/min in the 42 normal volunteers, and 90 ± 1.1 beats/min in the 75 uremic patients (P < 0.001) (fig. 1B). The 42 normal subjects had a mean stroke index of 52 ± 1.4 ml/stroke/m\(^2\); in the 75 uremics, the mean stroke index was 50 ± 1.3 ml/stroke/m\(^2\) (fig. 1C).

The average mean arterial pressure in the 42 normal subjects was 91 ± 1.6 mm Hg, while in the 75 patients with end-stage renal disease, the average mean arterial pressure was 125 ± 3.2 mm Hg. The difference is statistically significant (P < 0.001), and reflects the presence of hypertension in 52 of the 75 end-stage renal disease patients (fig. 1D).

The calculated mean total peripheral vascular resistance index was 2187 ± 59 dynes/sec/cm\(^{-5}\)/m\(^2\) in the 42 normal subjects and 2389 ± 103 in the 75 uremic patients. The difference was not statistically significant (fig. 1E).

**Hypertensive Uremic Patients Compared to Normotensive Uremic Patients**

Within the total group of 75 patients with chronic end-stage renal disease (hypertensive and normotensive), the hemodynamic pattern of the 52 hypertensive patients was compared with that of 23 normotensive patients. The results are shown in figure 2.

The mean arterial pressure in the group of hypertensive patients with chronic end-stage renal disease averages 139 ± 2.9 mm Hg while in the group of normotensive patients with chronic end-stage renal disease, the mean arterial pressure was 93 ± 1.8 mm Hg, (P < 0.001) (fig. 2A).

The mean cardiac index in the hypertensive uremic patients was 4.39 ± 0.14 liters/min/m\(^2\) and in the normotensive uremic patients, 4.55 ± 0.15 liters/min/m\(^2\). The difference is not significant (fig. 2B).

The mean heart rate was 91.1 ± 1.4 beats/min in the 52 hypertensive patients and 89 ± 2.0 beats/min in the 23 normotensive patients. The 52 hypertensive patients showed a mean stroke index of 49 ± 1.6 ml/stroke/m\(^2\); mean stroke index in the 23 normotensive patients was 51 ± 1.6 ml/stroke/m\(^2\). Neither of these was significantly different.

Calculated mean total peripheral resistance index was 2703 ± 120 dynes/sec/cm\(^{-5}\)/m\(^2\) in the hypertensive patients and 1670 ± 61 dynes/sec/cm\(^{-5}\)/m\(^2\) in the normotensive uremic patients. The difference is highly significant (P < 0.001) (fig. 2C).

The mean hematocrit was 23% in both the hypertensive and normotensive uremic patients. In summary, the only significant differences between hypertensive and normotensive uremic patients were an elevated arterial blood pressure and an increased peripheral vascular resistance.

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A B

75 Uremic Patients 42 Normal Subjects

<table>
<thead>
<tr>
<th>Cardiac Index (L/min/m²)</th>
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<tr>
<td>Mean Hct 23% 23%</td>
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<td>Mean Hct 43% 43%</td>
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<td>P &lt; 0.001</td>
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C

75 Uremic Patients 42 Normal Subjects

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<th>Heart Rate (beats/min)</th>
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<td>Mean Hct 23% 23%</td>
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<td>Mean Hct 43% 43%</td>
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<td>P &lt; 0.001</td>
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75 Uremic Patients 42 Normal Subjects

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<th>Mean Arterial Pressure (mm Hg)</th>
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E

75 Uremic Patients 42 Normal Subjects

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<th>Total Peripheral Resistance Index (dynes/sec/cm²/m²)</th>
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<td>Mean Hct 23% 23%</td>
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Figure 1

Cardiac index (A), heart rate (B), stroke index (C), mean arterial pressure (D), and total peripheral resistance index (E) of 75 patients with end-stage renal disease (hypertensives and normotensives) compared with 45 normal control. Hemodynamic values are expressed as mean ± one standard error. TPRI = total peripheral resistance index.

Hemodynamic Changes following Bilateral Nephrectomy in Hypertensive Patients with Chronic End-Stage Renal Disease

Studies in 12 patients with chronic end-stage renal disease and hypertension who underwent bilateral nephrectomy are reported in figure 3. The hemodynamic studies reported are compared at equivalent levels of total exchangeable sodium and body weight for each patient before and after bilateral nephrectomy.

Bilateral nephrectomy resulted in a consistent and significant reduction of blood pressure in all 12 cases. Average mean arterial pressure decreased from 147 to 93 mm Hg (P < 0.001) (fig. 3A). Changes in cardiac index (fig. 3B), heart rate, and stroke index were not statistically significant. As a consequence, a reduction in total peripheral resistance index occurred after bilateral nephrectomy in every case, from a mean of 2804 dynes/sec/cm²/m² to a mean of 1746 dynes/sec/cm²/m² (P < 0.001) (fig. 3C).
Bilateral nephrectomy was performed in an additional group of eight patients with chronic end-stage renal disease and hypertension in the malignant phase. Removal of both kidneys resulted in a dramatic decrease of the blood pressure in every case. The average mean arterial pressure decreased from 158 to 112 mm Hg ($P < 0.001$) (fig. 4A). Unlike the group of patients with nonmalignant hypertension whose cardiac index was unchanged by bilateral nephrectomy, cardiac index increased after bilateral nephrectomy in each case of malignant hypertension. The mean cardiac index was 3.45 liters/min/m$^2$ before bilateral nephrectomy and rose to 4.40 liters/min/m$^2$ after bilateral nephrectomy ($P < 0.001$) (fig. 4B). Changes in heart rate were minor and inconsistent while the stroke index increased after nephrectomy in every case. The mean stroke index was 38 ml/stroke/m$^2$ before bilateral nephrectomy and became 51 ml/stroke/m$^2$ after bilateral nephrectomy ($P < 0.001$) (fig. 4C). In this group of malignant hypertensive patients for equivalent levels of total exchangeable sodium, the blood pressure and the total peripheral resistance were invariably lower in the absence of renal tissue (fig. 4D).

**Discussion**

The hemodynamic data reported in the present study in 42 normal volunteers are similar to those obtained with the same methods by other investigators$^1$-$^7$ in their normal controls. This confirms the reproducibility of cardiac output studies with the dye-dilution technic.

The data obtained in our chronic end-stage renal disease patients demonstrate that at this stage of the natural history of renal parenchymal disease, the cardiac index is significantly higher than normal. This increase in cardiac index is associated with an increase in heart rate whereas the stroke index is not different from controls. The mean cardiac index of 4.44 liters/min/m$^2$ in our 75 uremic patients is very close to the value of 4.28 liters/min/m$^2$ reported by Goss et al.$^9$ with the dye-dilution method. Similarly, a mean cardiac index of 4.19 liters/min/m$^2$ was
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reported in 21 uremic patients by Mostert and co-workers. In contrast, Del Greco et al. reported cardiac index in uremic patients not different from their normal controls. The technic for cardiac output used in that study, however, was external isotopic counting. This technic in their study gave a cardiac index in normal controls of 4.10 liters/min/m² which is significantly higher than the normal values obtained by the dye-dilution technic in several studies. Anthonisen and Holst in 1960 reported that nine patients with chronic uremia had a cardiac index equal to their control subjects. However, at the time of their study their uremic patients were not rehabilitated by maintenance hemodialysis and had a uremic syndrome that appeared to be more severe than in the 75 patients reported in the present study.

We conclude that patients with chronic end-stage renal disease and uremia (hypertensive and normotensive) on maintenance dialysis have a higher than normal cardiac output. This increase in cardiac output is associated with an increase in heart rate, whereas the stroke volume remains within the normal limits.

The present data do not explain the cause of high cardiac output state in uremia. The anemia, however, which was present in all the uremic patients studied (mean hematocrit 23%), may be considered to be an important factor in the production of increased cardiac output and tachycardia. Duke and Abelmann found values of cardiac index of 4.73 liters/min/m² and low total peripheral resistance in nonuremic anemic patients with a mean hematocrit of 20.3%. The hemodynamic pattern of their nonuremic anemic patients and the degree of their anemia appear to be very similar to the normotensive uremic patients discussed in this study. In their study, the correction of anemia in the same patients resulted in a decrease of cardiac index to normal (3.44 liters/min/m²) and a significant increase in total peripheral resistance. Furthermore, our previous study of the hemodynamic effects of the correction of anemia in

Figure 3

Mean arterial pressure (A), cardiac index (B), and total peripheral resistance index (C) before and after bilateral nephrectomy in 12 hypertensive patients (nonmalignant) with end-stage renal disease. The hemodynamic values of each patient are compared at an equivalent level of total exchangeable sodium and body weight. Nx = bilateral nephrectomy; E Na = total exchangeable sodium (mEq/kg).
uremic patients indicated that the most important factor in the high cardiac output state of uremia is indeed the anemia itself.\textsuperscript{17}

Thus, the patients with end-stage renal disease and uremia are characterized by a high cardiac output. Their calculated total peripheral vascular resistance falls within the normal limits. It may, therefore, be suggested that the hypertension, which is present in the majority of these patients, is sustained by such an elevation of the cardiac output. The comparative evaluation of the hemodynamic pattern of the hypertensive uremic patients vs the normotensive uremic patients has now clarified the role of cardiac output in this hypertensive state. Cardiac index, heart rate, and stroke index were entirely similar in these two uremic groups. The 52 hypertensive patients with chronic end-stage renal disease, however, showed a total peripheral resistance

\textit{Figure 4}

\textit{Mean arterial pressure (A), cardiac index (B), stroke index (C), and total peripheral resistance index (D) before and after bilateral nephrectomy in eight patients with end-stage renal disease and malignant hypertension. Hemodynamic values of each patient are compared at an equivalent level of total exchangeable sodium and body weight.}
index much higher than the normotensive patients with chronic end-stage renal disease. Anemia and uremia were equivalent in the two groups. These data support the conclusion that the hypertension of chronic renal parenchymal disease at this stage is sustained by an elevated resistance.

Additional information on the role of cardiac output in this stage of renal hypertension is offered by the studies of the hemodynamic effects of bilateral nephrectomy in the hypertensive uremic patients.

Bilateral nephrectomy in 12 hypertensive uremic patients (nonmalignant hypertension) resulted in consistent and significant reduction of blood pressure with a decrease in TPRI. Cardiac index, heart rate, and stroke index did not change. At equivalent levels of total exchangeable sodium and body weight, mean arterial pressure and total peripheral resistance index were invariably lower in the absence of renal tissue. Since exchangeable sodium remained in the same range after bilateral nephrectomy, the hemodynamic effects described cannot be attributed to sodium balance.

Bilateral nephrectomy in eight additional hypertensive patients, with the malignant phase of hypertension, also resulted in a significant reduction of the blood pressure in every case. Unlike the nonmalignant hypertension group, cardiac index and stroke index increased after nephrectomy in all these patients. Total peripheral resistance underwent a dramatic reduction in every case. Again, for equivalent levels of total exchangeable sodium and body weight, the mean arterial pressure and the total peripheral resistance were significantly lower in the absence of renal tissue.

The comparative analysis of the hemodynamic pattern of hypertensive uremic patients vs normotensive uremic patients and the reported hemodynamic effects of bilateral nephrectomy demonstrate that the hypertension of chronic end-stage renal disease is sustained by an elevated total peripheral resistance. The high cardiac output, characteristic of the uremic patient and due predomi-
The data obtained in the present study leave no doubt that at the end-stage of the natural history of hypertension of chronic renal disease in man the blood pressure elevation is associated with an elevated resistance. The presence of a vasoconstrictor substance produced by the end-stage kidney appears to be the predominant pathophysiologic factor in operation. Studies of the hemodynamic changes of the early stages of hypertension in chronic renal disease and of their possible evolution appear to be necessary.

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