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Hemodynamics and Pathophysiology of Hypertension in Different Stages of Chronic Renal Parenchymal Disease

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INTRODUCTION

One of the serious complications of chronic renal parenchymal disease is hypertension. In patients with renal disease, the control of hypertension is mandatory in order to reduce morbidity and mortality from hypertensive cardiovascular complications. Blood pressure control also helps to preserve renal function for the longest possible interval between the onset of disease and the occurrence of uremia.

A precise knowledge of the hemodynamic alterations of hypertension secondary to renal parenchymal disease is essential in order to understand the underlying pathophysiologic mechanisms. Such an understanding is helpful in the rational and effective treatment of hypertension.

The hemodynamic derangement and mechanisms responsible for hypertension must be assessed in each of the different stages of renal disease. We have arbitrarily divided chronic renal parenchymal disease into four stages: 1) early-stage; 2) end-stage; 3) after bilateral nephrectomy; and 4) after successful renal transplantation.

The present report summarizes our studies on the hemodynamics and pathophysiology of blood presure regulation at each of the four stages of chronic renal parenchymal disease.

1. Hemodynamics and Pathophysiology of Hypertension in Early-Stage Renal Parenchymal Disease

a. Hemodynamics: Information regarding the hemodynamic changes in early-stage renal parenchymal disease is limited (Kim *et al.* 1976, Frolich *et al.* 1969, Brod *et al.* 1976). The hemodynamic factors regulating blood pressure may be expressed in the equation BP = CO × TPR, where BP is the mean arterial pressure, CO the cardiac output, the TPR the total peripheral resistance. Cardiac output represents the volume of blood propelled into the circulation per unit of time. Total peripheral resistance is a calculated value, and is estimated by the ratio of mean arterial pressure over cardiac output expressed in arbitrary resistance units. High blood pressure may result from a high cardiac output, a high total peripheral resistance or a combination of the two.

Frohlich and co-workers (1969) studied 11 patients when early-stage renal parenchymal disease and hypertension, and found that the hypertension was associated with a normal cardiac output and an elevated total peripheral resistance.

Brod and co-workers (1976) reported that cardiac output in patients with hypertension secondary to chronic non-uremic, non-anemic renal parenchymal disease was higher than in normotensive patients with renal parenchymal disease. Eleven of the 27 hypertensive patients had high cardiac output and stage I-II hypertension as defined by the World Health Organization. Of the eight patients in stage III, none had high cardiac output. There was no difference in total peripheral resistance between the normotensive and the hypertensive renal patients with stage I-II hypertension. In hypertensive renal patients with stage III hypertension, the total peripheral resistance was higher than that in patients with stage I-II. Therefore, Brod and co-workers (1976) postulated that hypertension secondary to renal parenchymal disease may be initiated by a high cardiac output, and at this stage total peripheral resistance is within normal range. The total peripheral resistance starts in increase only with the progress of hypertension to stage III. This is the reason for the cardiac output decreasing again to its original level.

We have studied 37 patients with chronic renal parenchymal disease without uremia or anemia (Kim *et al.* in press). There were 20 males and 17 females ranging in age from 16 to 55 years, with a mean age of 36 years. Of the 37 patients studied, 15 were normotensive and 22 were hypertensive. Patients were excluded from this study if they had

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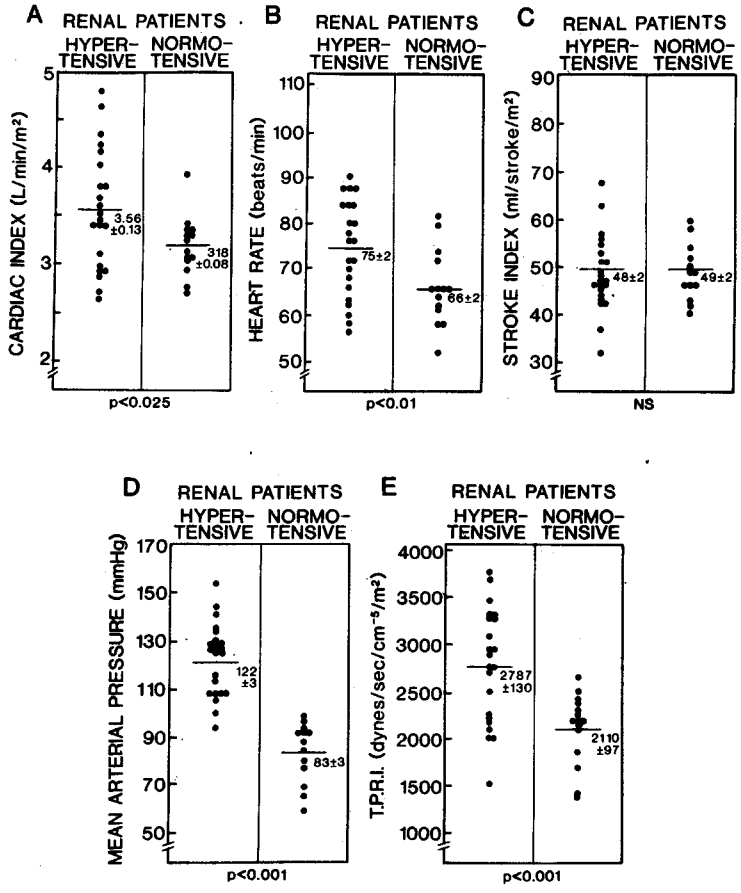

Fig. 1. *Comparison of cardiac index (A); heart rate (B); stroke index (C); mean arterial pressure (D) and total peripheral resistance index (TPRI) (E) of 22 hypertensive and 15 normotensive patients with early-stage renal parenchymal disease. Hemodynamic values are expressed as mean±S.E. From Kim et al. (in press).*

a documented family history of essential hypertension, were in the malignant phase of hypertension or had nephrotic syndrome. Only patients with a serum creatinine of 4 mg/dl or less and a hematocrit of 30% or more were included. All antihypertensive medication was discontinued at least two weeks prior to the study. The diagnoses were based on kidney biopsy except for eight patients with polycystic kidney disease in whom the diagnoses were made by intravenous pyelogram and ultrasound of the kidneys. Twenty five patients had chronic glomerulonephritis of different histologic types, eight had polycystic kidney disease and four had interstitial nephritis. The groups of hypertensive and normotensive patients were comparable for age, hematocrit and inulin clearance. The systemic hemodynamics of hypertensive and normotensive patients with chronic renal parenchymal disease are shown in Figure 1. The average mean arterial pressure was 122±3 mmHg (mean±S.E.) in hypertensive patients, and 83±3 mmHg in normotensive patients ($p<.001$) (Fig. 1D). The mean cardiac index in the hypertensive patients was 3.56±0.13 liters/min/m² (mean±S.E.).

In normotensive patients, the mean cardiac index was 3.18±0.08 liters/min/m² ($p<.025$) (Fig. 1A). The mean heart rate was 75±2 beats/min in hypertensive patients and 66±2 beats/min in normotensive patients ($p<.01$) (Fig. 1B). The mean stroke index in hypertensive patients was 48±2 ml/stroke/m². In normotensive patients, the mean stroke index was 49±2 ml/stroke/m² (Fig. 1C). The mean total peripheral resistance index was 2787±130 dynes/sec/cm^{-5}/m² in hypertensive patients and 2110±97 dynes/sec/cm^{-5}/m² in normotensive patients ($p<.001$) (Fig. 1E).

The patients with chronic renal parenchymal disease and hypertension were arbitrarily divided into two groups: those with hypertension less than 2 years' duration, and those with hypertension greater than 2 years' duration. The average mean arterial pressure was similar in these two subgroups (Fig. 2B). The mean cardiac index was higher in the patients with a more recent onset of hypertension (Fig. 2A), while the mean total peripheral resistance index was lower for this group (Fig. 2C). This study (Kim *et al.* in press) showed that the overall cardiac index and heart rate of hypertensive patients with chronic renal parenchymal disease were higher than those of normotensive patients with chronic renal parenchymal disease. These findings suggest that in some patients, the hypertension of early-stage renal parenchymal disease is associated with high cardiac output. When the hypertensive patients were divided into the two sub-groups according to the known duration of hypertension it appeared that the patients at an early stage of renal hypertension had a higher cardiac output.

These studies (Brod *et al.* 1976; Kim *et al.* in press) suggest that with the progression of hypertension, the cardiac output decreases, while total peripheral resistance increases. This hemodynamic natural history is similar to the well-documented natural history of essential hypertension (Eich *et al.* 1962; Sannerstedt 1966; Lund-Johansen 1967, 1976). However, more extensive studies of the hemodynamic changes in early stages of hypertension associated with chronic renal disease, and their possible evolution, are necessary for a definite conclusion.

b. Pathophysiology: pathophysiologic studies of hypertension secondary to early-stage renal parenchymal disease are limited and conflicting. Various factors and an abnormal relationship between them have been suggested as contributing to the hypertension.

The blood volume was 72±2 ml/kg body weight (mean±S.E.) in our hypertensive patients, compared to 71±5 ml/kg body weight in the normotensive patients. This difference is not significant. There was no correlation between blood volume and

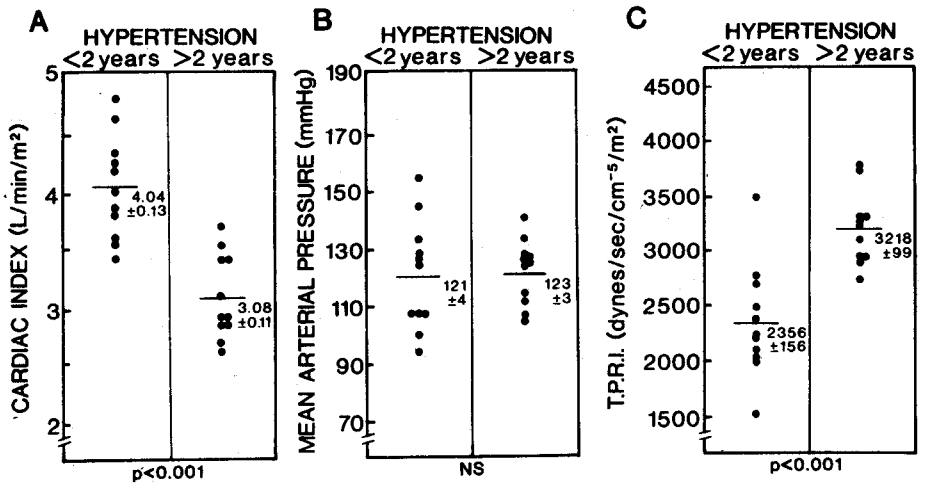

Fig. 2. *Comparison of cardiac index (A); mean arterial pressure (B) and total peripheral resistance index (TPRI) (C) of 11 patients with chronic renal parenchymal disease having hypertension of less than 2 year's duration and 11 patients with early-stage renal parenchymal disease having hypertension of longer than 2 years' duration. Hemodynamic values are expressed as mean±S.E. From Kim et al. (in press).*

mean arterial pressure. Our findings are in agreement with Brod and co-workers (1976), who also showed similar blood volumes in hypertensive and normotensive non-uremic patients. Beretta-Piccoli and co-workers (1976) showed blood volume to be normal. They demonstrated no correlation between blood pressure and blood volume. Tarazi and co-workers (1970) found plasma volume to be normal, but they showed a significant positive correlation between diastolic pressure and plasma volume. In our own experience, a significant positive correlation between blood pressure and blood volume is found only in patients with end-stage renal disease and anephric patients on hemodialysis (Kim *et al.* 1980; Onesti *et al.* 1975). Our data demonstrated that blood volume, per se, is not a primary determinant of blood pressure in hypertension of early-stage renal parenchymal disease. However, it is possible that the increase in cardiac output in a segment of our hypertensive patients may be the result of a redistribution of blood volume toward the cardiopulmonary section of the circulation. Such a central redistribution has been found to be associated with an increase in cardiac output in certain patients with essential hypertension (Ulrych *et al.* 1969; Safer *et al.* 1974). It is also possible that the increase in cardiac output and heart rate in some of our hypertensive patients is the expression of an increased activity in the adrenergic nervous system. This neurogenic factor has been reported in patients with borderline essential hypertension (Julius and Esler 1975).

The mean plasma renin concentration was $0.22\pm0.05\times10^{-4}$ Goldblatt units (mean±S.E.) in our hyertensive patients, and $0.15\pm0.03\times10^{-4}$ Goldblatt units in the normotensive patients. This difference is not significant. The mean 24-hour urinary sodium excretion at the time of sampling plasma renin concentration was 136±16 mEq in the hypertensive patients, and 120±20 mEq in the normotensive patients. The role of the renin-angiotensin system in the pathogenesis of hypertension in chronic renal parenchymal disease is still the subject of considerable controversy. In patients with chronic renal parenchymal disease and hypertension, circulating renin has been found to range from low to high levels (Beretta-Piccoli *et al.* 1976; Wong *et al.* 1978; Nash 1977; Bank *et al.* 1978; Mitas *et al.* 1978). Some investigators reported a significant positive correlation between bood pressure and circulating renin or angiotensin II levels in these patients (Wong *et al.* 1978; Catt *et al.* 1970). Other investigators were unable to demonstrate such a relationship (Beretta-Piccoli 1976; Brown *et al.* 1965). It has also been suggested that plasma renin level, although normal or low, is often inappropriately high for the state of volume expansion in hypertensive patients with early-stage renal parenchymal disease (Beretta-Piccoli *et al.* 1976; Tarazi *et al.* 1970; Kim *et al.* 1980; Onesti *et al.* 1975; Ulrych *et al.* 1969; Safar *et al.* 1974; Julius and Esler 1975; Wong *et al.* 1978; Nash 1977).

Glomerular filtration rate determined by inulin clearence showed a wide scatter of values in both normotensive and hypertensive patients. There was no significant difference between the two groups: 55±7 ml/min/1.73 m^2 (mean±S.E.) in the hypertensive group, and 64±6 ml/min/1.73 m^2 in the normotensive group. Furthermore, no correlation was seen between blood pressure and glomerular filtration rate. These studies indicate that progressive loss of renal excretory function is not responsible for blood pressure elevation in patients with early-stage renal parenchymal disease. Our findings do not substantiate the theory of Guyton and associates (1972) that decreased renal excretory function overrides all other long-term pressure control mechanisms in hypertension of renal parenchymal disease. Only in patients with end-stage renal disease is the inability of the kidney to excrete a sodium chloride and water load responsible for blood pressure elevation (Kim *et al.* 1980; Onesti *et al.* 1975; Kim *et al.* 1976).

The interrelationship between blood pressure, exchangeable sodium, blood volume and plasma renin activity was studied in 40 normal subjects and 40 patients with early-stage renal disease by Beretta-Piccoli and associates (1976). Eight patients were normotensive. In the 32 hypertensives, there were significant increases in exchangeable sodium and in the products of the logarithm of plasma renin activity and exchangeable sodium or blood volume. In the 40 patients with renal disease, blood pressure correlated significantly with the blood volume-renin product, but not with blood volume or plasma renin activity individually. Furthermore, blood pressure showed a closer relationship with sodium-renin product than with exchangeable sodium alone. The authors concluded that hypertension accompanying early-stage renal disease might depend on subtle abnormalities in the sodium/volume-renin feedback mechanism.

2. Hemodynamics of Hypertension in Chronic End-Stage Renal Disease

The hemodynamic changes of hypertension in chronic end-stage renal disease are now well established (Kim *et al.* 1972; Neff *et al.* 1971; Kim *et al.*1973; Kim *et al.*1975).

In this section, we will discuss hemodynamic changes: a) in chronic end-stage renal disease with anemia; b) in hypertensive and normotensive patients with end-stage renal disease; c) after correction of anemia and d) after bilateral nephrectomy.

a. Hemodynamic changes in chronic end-stage renal disease with anemia: The hemodynamic studies of 75 patients with end-stage renal disease (hypertensive and normotensive) were compared with those of 42 normal subjects (Fig. 3). All antihypertensive medication was discontinued at least two weeks prior to the studies.

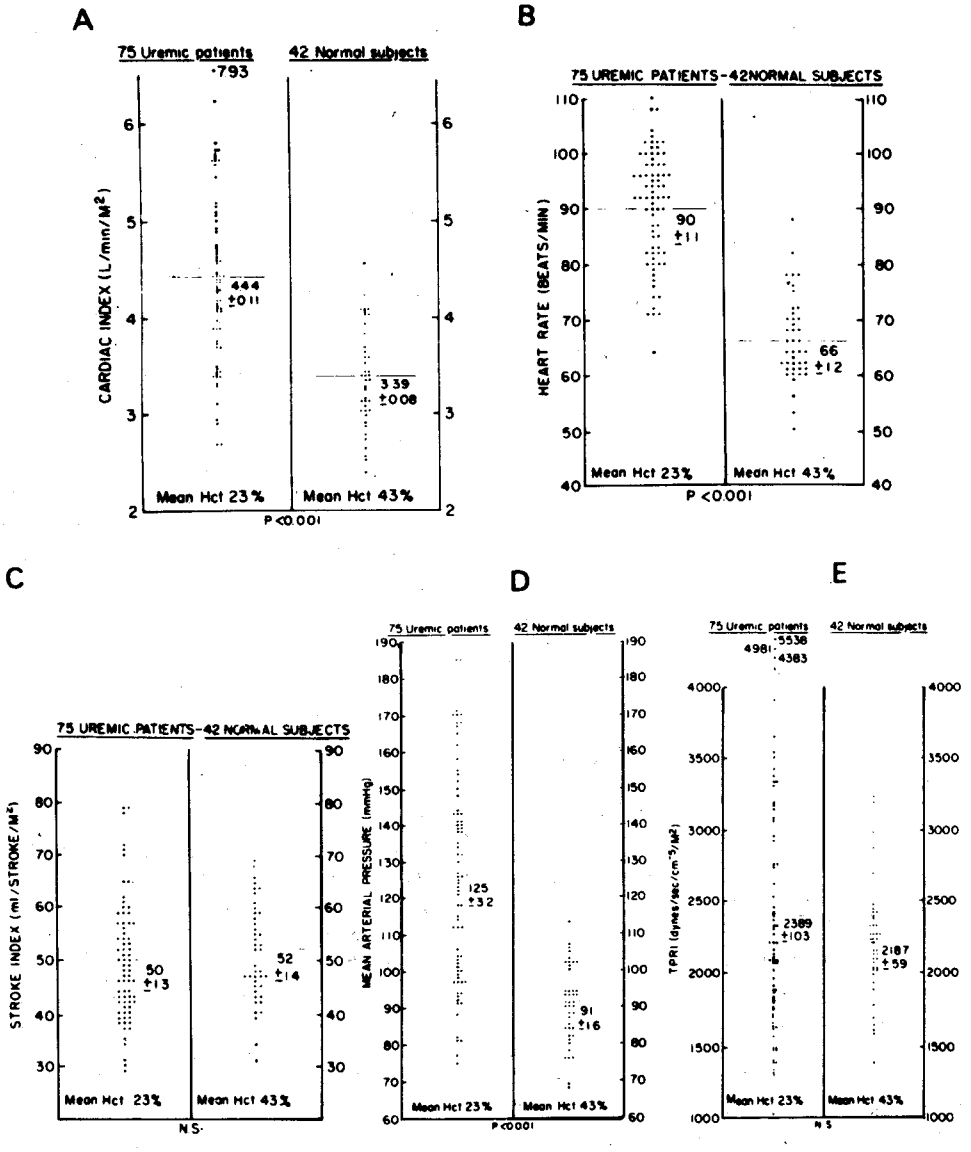

Fig. 3. *Cardiac index (A); heart rate (B); stroke index (C); mean arterial pressure (D) and total peripheral resistance index (TPRI) (E) of 75 patients with end-stage renal disease (hypertensives and normotensives) compared with 42 normal controls. Hemodynamic values are expressed as mean±S.E.; N.S.=not statistically significant. From Kim et al (1972).*

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%. The average mean arterial pressure of uremic patients was significantly higher than that of the normal subjects, reflecting the presence of hypertension in 52 of the 75 patients with endstage renal disease (Fig. 3D). patients with end-stage renal disease had significantly higher cardiac indices than did normal controls (Fig. 3A). The higher cardiac indices of uremic patients were accounted for by increased heart rates with normal stroke volume (Figs. 3B-C). Despite the significantly higher blood pressure in the uremics, their mean total peripheral resistance index was not different from that of normals (Fig. 3E).

b. Hemodynamic comparison between hypertensive and normotensive patients with end-stage renal disease: Of the 75 patients studied, 52 were hypertensive and 23 were normotensive. The hemodynamic patterns of these two groups were compared in order to evaluate the role of cardiac output and total peripheral resistance in hypertension of end-stage renal disease. The results are shown in Figure 4. The mean hematocrit was 23% in both the hypertensive and normotensive uremic patients.

This comparative evaluation of the hemodynamic pattern of the hypertensive uremic patients vs the normotensive uremic patients showed that the cardiac index was the same in these two groups (Fig. 4B), whereas, mean total peripheral resistance index of the hypertensive uremics was significantly higher than that of the normotensive uremics (Fig. 4C). Therefore, the hypertension in end-stage renal disease is sustained by a higher total peripheral resistance.

c. Hemodynamic effects of correction of anemia: Six of the 75 patients with end-stage renal disease underwent further study to evaluate hemodynamic effects of correction of anemia. Hemodynamic studies were performed twice a week prior to hemodialysis and at least 48 hours after the patient had received red cell transfusion during the previous hemodialysis. Blood was administered during hemodialysis as buffy-coat-free packed red cells. Hematocrit was increased to at least 40% in each patient. Body weight was maintained within 1.8 kg in each patient during the entire study period. The effect of increase in hematocrit on cardiac index, total peripheral resistance index, and mean arterial pressure in a representative patients is shown in Figure 5. With the increase in hematocrit, there was a progressive decrease in cardiac index and a progressive increase in both the total peripheral resistance and mean arterial pressure. Blood volume did not change significantly during the study. The most likely explanation for the increasing total peripheral resistance and the decreasing of cardiac output as a result of correcting the anemia is related to the oxygen delivery and the viscosity of the blood. Severe anemia is

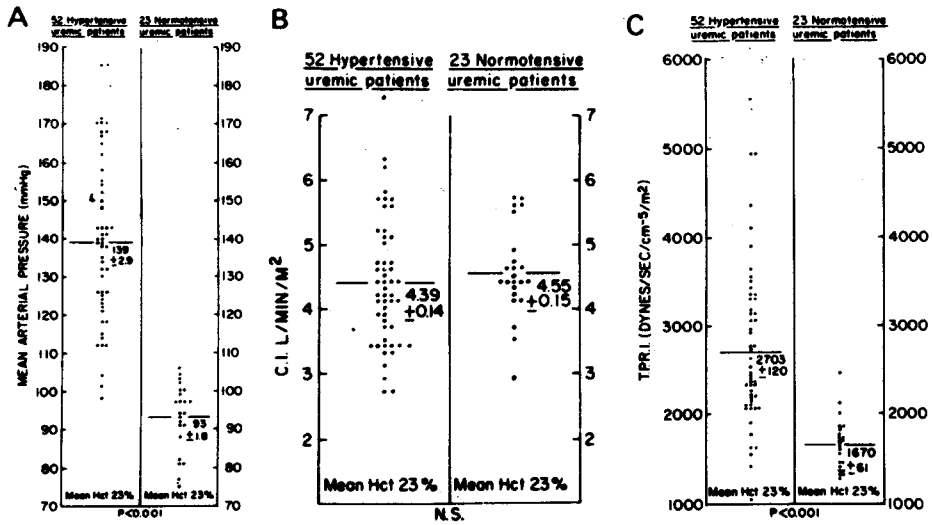

Fig. 4. Comparison of mean arterial pressure (A), cardiac index (CI) (B), and total peripheral resistance index (TPRI) (C) of 52 hypertensive and 23 normotensive patients with end-stage renal disease. From Kim et al. (1972).

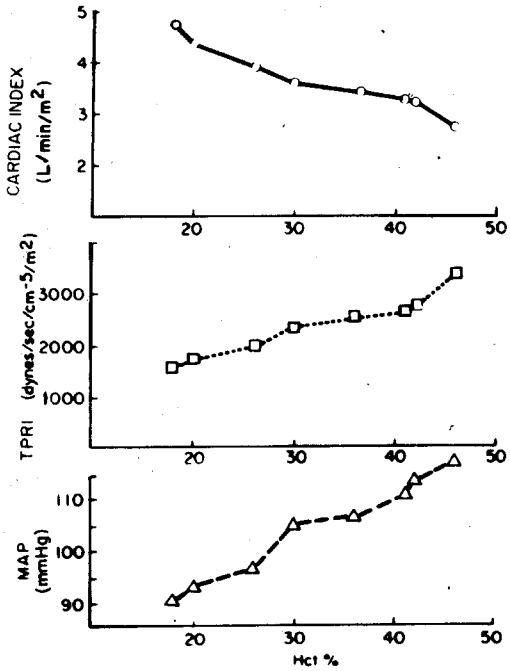

Fig. 5. Effects of increase in hematocrit on cardiac index (O), total peripheral resistance index (TPRI). (□) and mean arterial pressure (MAP) (Δ) in one respresentative patient. From Kim et al. (1973).

associated with inadequate oxygen delivery to the tissue. This condition produces peripheral vasodilatation. The hypoxic vasodilatation decreases the total perpheral resistance. Anemia also decreases the viscosity of the blood which decreases resistance to venous flow and, therefore, increases venous return and cardiac output (Whittaker and Winton 1933; Guyton and Richardson 1973; Guyton *et al.* 1973). Correcting the anemia abolishes vasodilatation and increases the viscosity of the blood. This increases the peripheral resistance and blood pressure and decreases the venous return and cardiac output. The effect is probably magnified in previously hypertensive uremic patients.

The role of anemia in high cardiac output was also evaluated in 11 anephric patients before and after a successful renal transplantation (Kim *et al.* 1980). Mean hematocrit of 11 patients before renal transplantation was 21% and after transplantation was 35.2% (Fig. 6A). With the increase in hematocrit after the renal transplantation, the mean cardiac index decreased from 4.62 liters/min/m² to 3.68 liters/min/m² (Fig. 6B).

These studies indicate that the major factor responsible for the high cardiac output in anephric patients and those with end-stage renal disease is anemia itself.

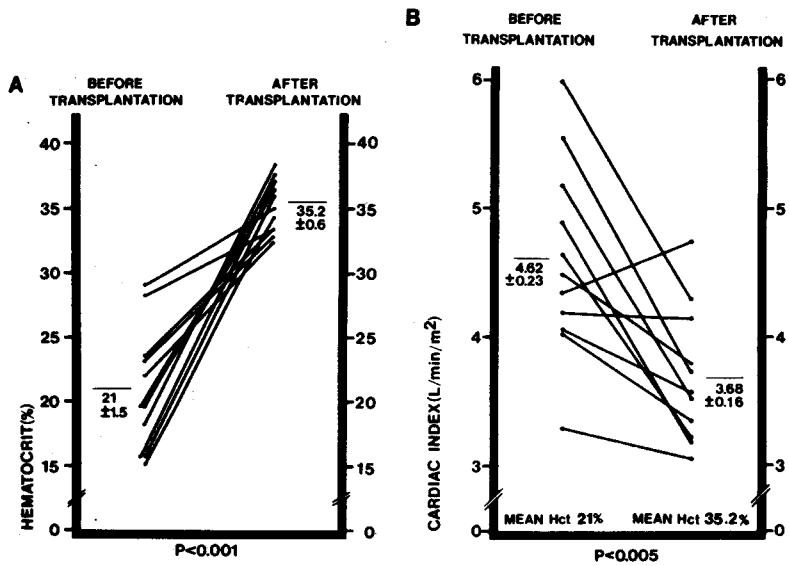

Fig. 6. Hematocrit (A) and cardiac index (B) of 11 anephric patients before and after a successful renal transplantation. Hemodynamic values are expressed as mean±S.E. From Kim et al. (1980).

Duke and Abelmann (1969) found cardiac index values of 4.73 liters/min/m² and low total peripheral resistance in anemic patients with normal kidney function (a mean hematocrit of 20.3%). The hemodynamic pattern of their anemic patients and the degree of their anemia are very similar to those of the normotensive uremic patients in our 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.

d. Hemodynamic effects of bilateral nephrectomy: Hemodynamic studies in 12 patients with chronic end-stage renal disease and severe but nonmalighant hypertension who underwent bilateral nephrectomy are shown in Fig. 7. The hemodynamic studies are compared at equivalent level of total exchangeable sodium and body weight for each patient before and after bilateral nephrectomy. Bilateral nephrectomy resulted in a significant reduction of blood pressure in all 12 patients. The average mean arterial pressure decreased from 147 mm Hg to 93 mm Hg ($p > 0.001$) (Fig. 7A). Changes in cardiac index (Fig. 7B), 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/cm^{-5}/m² to a mean of 1746 dynes/sec/cm^{-5}/m² ($p < .001$) (Fig. 7C).

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 blood pressure reduction in every case the average mean arterial pressure decreased from 158 mmHg to 112 mmHg ($p < .001$) (Fig. 8A). In contrast to the group of patients with nonmalignant hypertension in whom the cardiac index was not changed by bilateral nephrectomy, cardiac index increased after bilateral nephrectomy in each case of malignant hypertension. The mean cardiac index was 3.45 liters/min/m² before bilateral nephrectomy, and rose to 4.40 liters/min/m² after billateral nephrectomy (<.001) (Fig. 8B) Changes in heart rate were minor and inconsistant, while the stroke index increased after nephrectomy in every case. The mean stroke index rose from 38 ml/stroke/m² following bilateral nephrectomy ($p < .001$) (Fig. 8C). For equivalent level of total exchangeable sodium, the total peripheral resistance index was invariably lower in the absence of renal tissue (Fig. 8D).

Bilateral nephrectomy reduced blood pressure by reducing total peripheral resistance. This implies that a vasopressor substance or substances of renal origin which act to increase total peripheral resistance are major factors in the pathophysiology

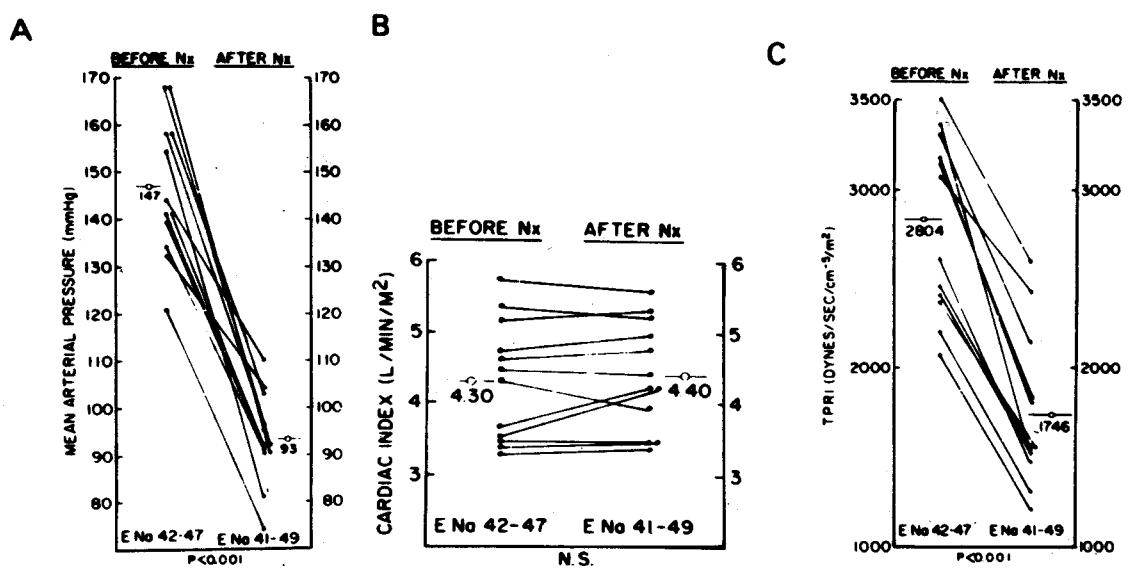

Fig. 7. Mean arterial pressure (A), cardiac index (B), and total peripheral resistance index (C) before and after bilateral nephrectomy in 12 hypertensive patients (nonmalignant) with end-stage renal disease. The hemodynamic values of each patient are compared at an equivalent level of total exchangeable sodium and body weight. Nx=bilateral nephrectomy; E Na=total exchangeable sodium (mEq/kg). From Kim et al. (1972).

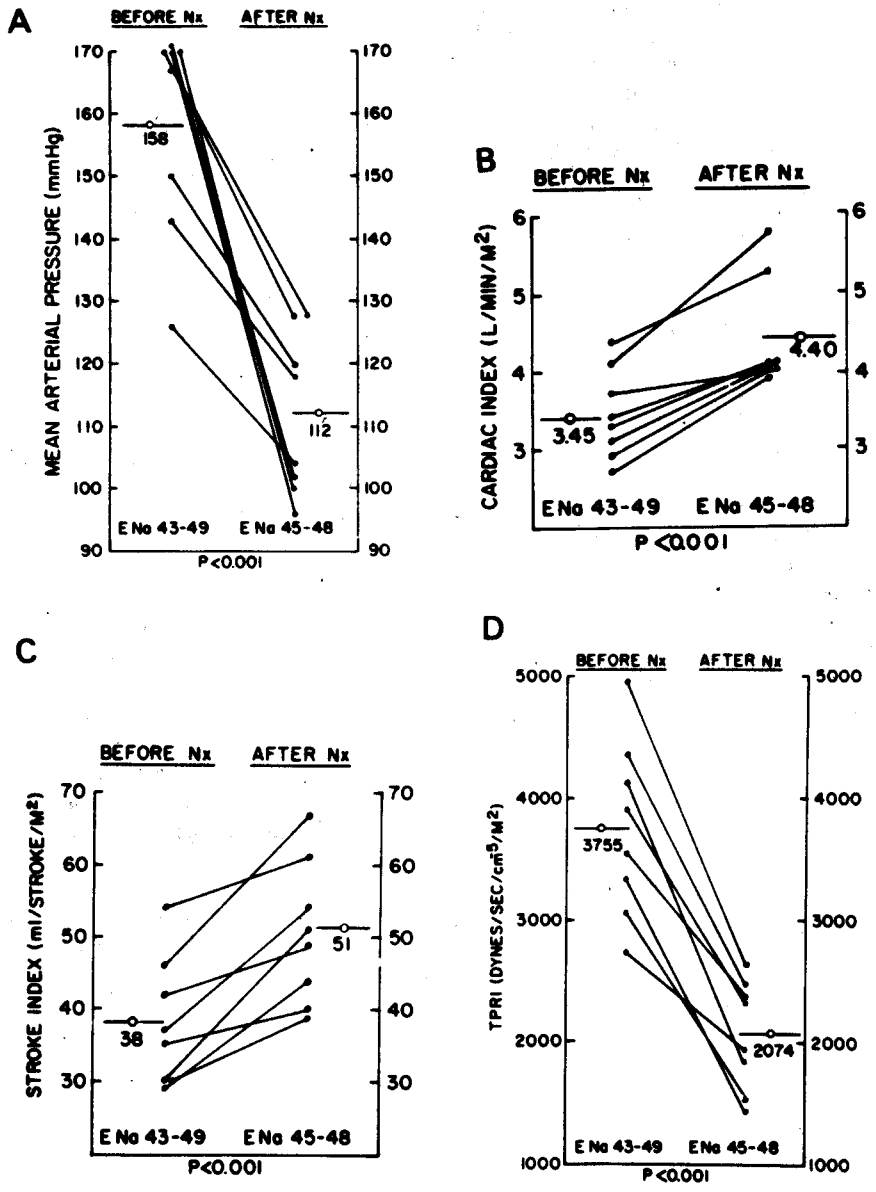

Fig. 8. *Mean Arterial pressure (A), cardiac index (B), stroke index (C) and total peripheral resistance index (D) before and after bilateral nephrectomy in eight patients with end-stage renal disease and malignant hypertension. Hemodynamic values of each patient are compared at an equivalent level of total exchangeable sodium and body weight. From Kim et al. (1972).*

of severe and malignant hypertension in end-stage renal disease.

The difference in hemodynamic patterns in malignant and nonmalignant renal hypertension warrants some comments. Cardiac output and stroke index are lower in the malignant Hypertension group, and total peripheral resistance is higher. A similar hemodynamic pattern of low cardiac output and high total peripheral resistance has been described in experimental malignant hypertension (Ledigham and Pelling 1967; Ferrario *et al.*1970; Ferrario 1974). The hemodynamic dif-

ferences observed in our patients, as well as those reported in the experimental animal (Ledigham and Pelling 1967; Ferrario *et al.*1970; Ferrario 1974), suggest qualitatively different vasopressor mechanism in malignant hypertension.

Bilateral nephrectomy was performed in eight normotensive patients with end-stage renal disease and no history of hypertension. The hemodynamic studies were compared for each patient at the same body weight, before and after bilateral nephrectomy. Bilateral nephrectomy resulted in no significant change in mean arterial pressure, cardiac index and total peripheral resistance index. Therefore, end-stage kidneys of normotensive patients without a prior history of hypertension, do not exert either a vasopressor or a depressor effect.

3. Regulation of Blood Pressure in End-Stage Renal Disease and the Anephric State

Hypertension in anephric patients and those with end-stage kidneys is sustained by a high total peripheral resistance (Onesti *et al.*1975; Kim *et al.*1972). The most important factors responsible for the increase in total peripheral resistance in patients with end-stage kidneys are the vasopressor function of the kidney (Onesti *et al.* 1975; Kim *et al.* 1972) and an increase in body salt and water (Kim *et al.*1980; Onesti *et al.* 1985; Vertes *et al.* 1969; Weidmann *et al.* 1971). In anephric patients, salt and water balance plays a major role in the regulation of blood pressure (Kim *et al.* 1980; Onesti *et al.* 1975; Dustan and Page 1964; Merrill *et al.* 1961; DelGreco and Burgess 1973; Coleman *et al.*1970). The final effect of salt and water loading in the anephric patient has been found to be an increase in total peripheral resistance (Onesti *et al.* 1975; Coleman 1970). The precise mechanism, however, by which expansion of body fluid increases blood pressure is not known (Onesti *et al.* 1975; Coleman *et al.* 1970).

In 1963, Borst and Borst-De Geus (1963) and Ledingham and Cohen (1963) introduced the autoregulation theory of the pathogenesis of hypertension. The theory proposes that expansion of body fluid volume with consequent Increase in cardiac output results in perfusion of tissues above their metabolic needs. This, in turn, elicits myogenic constriction of peripheral vessels, thereby producing an increase in total peripheral resistance with a gradual lowering of cardiac output toward the normal level (Borst and Borst-de Geus 1963; Ledingham and Cohen 1963). According to this theory, the initial increase in cardiac output with expansion of body fluid volumes is the cause of hypertension. The subsequent rise in total peripheral resistance is the result.

Subsequently, Guyton and associates (Guyton and Coleman 1969; Coleman *et al.*1971; Guyton *et al.*1975) proposed the theory of whole body autoregulation as the pathogenesis of many forms of hypertension.

Coleman and co-workers (1970) reported their sequential hemodynamic studies during volume expansion in three anephric patients. They showed that the increase in blood pressure during volume expansion was associated with an initial increase in cardiac output followed by an increase in total peripheral resistance. A similar sequence of hemodynamic events has also been reported in different models of renal hypertension in different species (Ferrario *et al.*1970; Ledingham and Cohen 1963; Bianchi *et al.*1970; Bianchi *et al.*1972).

In contrast, in two-kidney, two wrapped hypertension in rabbits, Fletcher and associates (1976) described variable changes in cardiac output at the onset of hypertension, with elevation of total peripheral resistance as the final event. Bravo and co-workers (1977) found that a sustained rise in blood pressure during administration of metyrapone was associated with three different hemodynamic patterns of response. Terris and co-workers (1976) reported that in six of seven pigs, elevations of blood pressure induced by deoxycorticosterone were entirely the result of increased total peripheral resistance.

These conflicting data on the sequence of hemodynamic events in renal hypertension and in salt- and water-induced hypertension may be due to different species and different pathophysiologic mechanisms in different models.

To determine the precise sequence of hemodynamic events, four anephric patients and six patients with end-stage kidneys on maintenance hemodialysis were studied sequentially at: a) stable, dry control weight ($control_1$); b) during progressive volume expansion; c) during the period of sustained volume expansion; d) during volume depletion and e) again at dry control weight ($control_2$) (Kim *et al.*1980).

Introduction of the artificial kidney and arteriovenous shunt for maintenance hemodialysis in patients with end-stage renal disease has made it possible to perform sequential hemodynamic studies. Anephric patients and those with end-stage kidneys on maintenance hemodialysis have no renal excretory function. Their body fluids are controlled by their salt and fluid intake and by the amount of salt and fluid removed by the artificial kidney. Therefore, patients' body weights can be controlled by varying these

parameters. Hemodynamic studies and sampling of blood can be performed noninvasively through an external connector inserted between the arterial and venous side of the arterio-venous shunt used for hemodialysis.

Seven patients underwent a hemodynamic study three times a week immediately before each dialysis. In three patients, hemodynamic studies, were done daily. During hemodialysis, desired body weights were achieved by adjustment of ultrafiltration pressure and infusion of 0.9% saline solution. Between hemodialysis, body weights were controlled with adjustment of salt and fluid intake. The entire study period lasted an average of 36 days.

Body weight was maintained within total range of 1 kg in each patient during the control period. At least

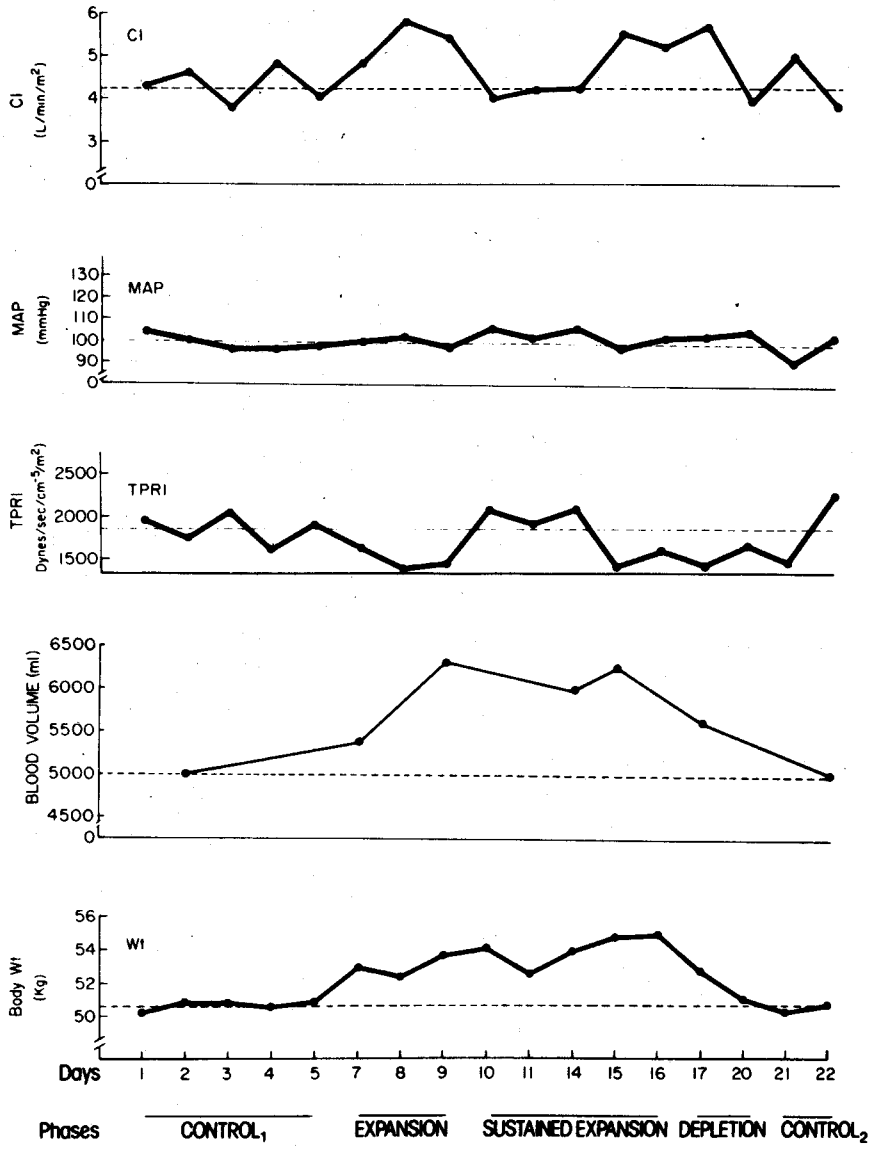

Fig. 9. Sequential hemodynamic changes during volumes expansion and depletion. Increases in body weight and blood volume did not increase mean arterial pressure (MAP). Cardiac index (CI) and total peripheral resistance (TPRI) show reciprocal changes. Control₁ = control phase of beginning of the study. The dashed lines indicate control₁ values. From Kim et al. (1980).

two control studies were performed, which lasted an average of one week. During the progressive volume-expansion phase, which lates from 10-14 days, patients gained weight, with a mean increase of 6.9±3.5% (mean±S.D.) of the control body weight. The constant volume-expansion phase lasted a mean of 16 days. The volume-depletion phase lasted an average of 10 days. When the patients' body weight decreased to the control levels, at least two studies were performed over a period of one week.

The sequential studies of the 10 patients showed four different patterns of hemodynamic change (Figs.

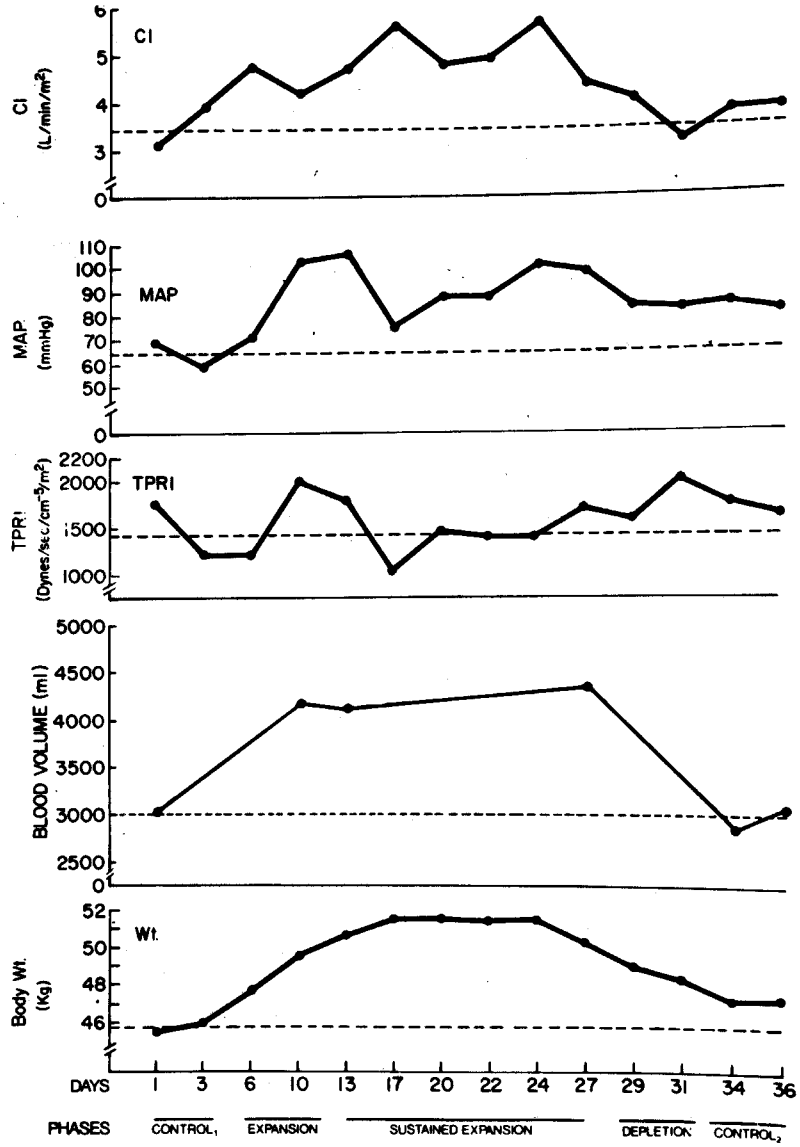

Fig. 10. *Sequential hemodynamic changes during volume expansion and depletion. Increases in body weight and blood volume raised mean arterial pressure. There was a concomitant increase in cardiac index (CI), which remained elevated throughout the volume expansion. Decreases in body weight and blood volume reduced mean arterial pressure and CI toward control level. Total peripheral resistance index did not show any consistent change. The dashed lines indicate control, values. From Kim et al. (1980).*

9-12). Pattern 1 occurred in two patients and is shown in Fig. 9. pattern 2 occurred in two patients and is shown in Fig. 10. Pattern 3 occurred in five patients and is shown in Fig. 11. Pattern 4 occurred in one patient and is shown in Fig. 12.

In two patients, volume expansion failed to significantly increase blood pressure (Fig. 9). Body weight and blood volume increased in the same proportion, in these two patients, as in the eight remaining patients in whom salt- and water-loading increased

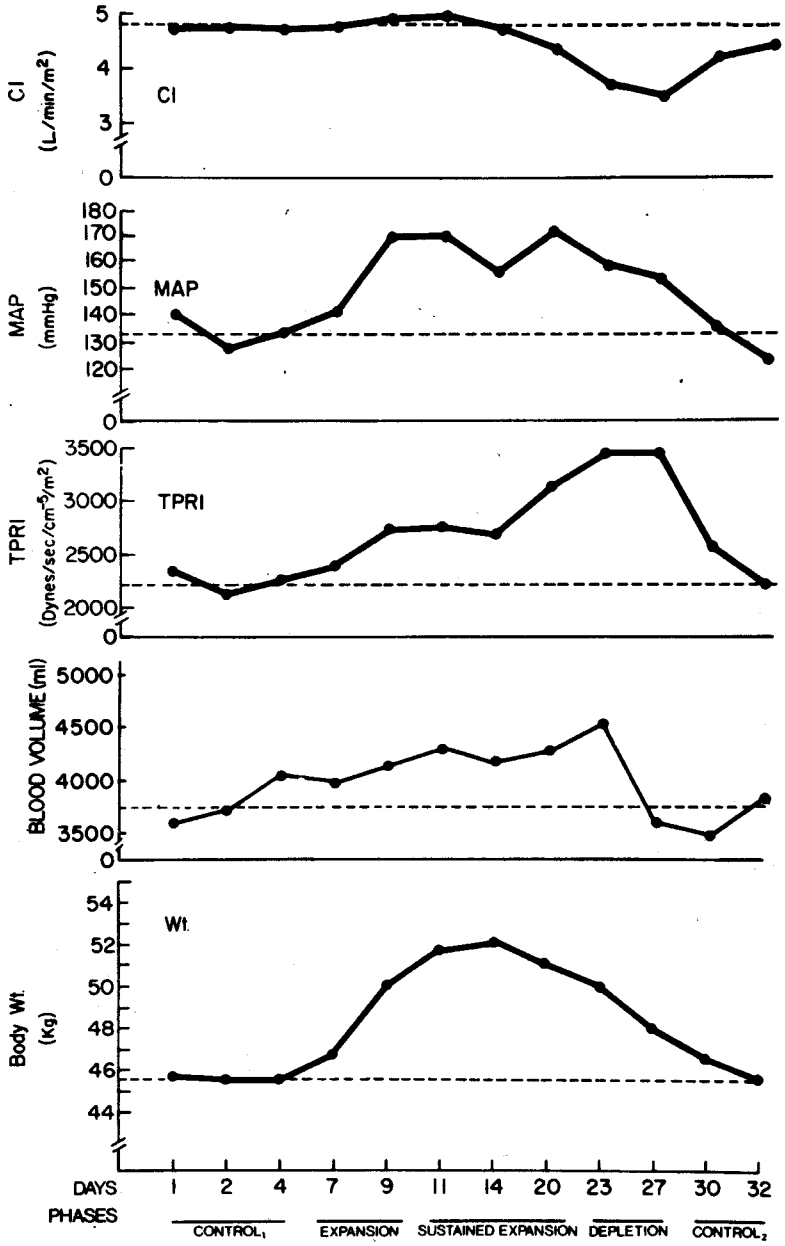

Fig. 11. Sequential hemodynamic changes during volume expansion and depletion. Increases in body weight and blood volume raised mean arterial pressure which was associated with an increase in total peripheral resistance index with no increase in cardiac index. The dashed lines indicate control, values. From Kim et al. (1980).

the blood pressure. Thus, volume expansion, per se, does not invariably increase blood pressure. In contrast to the remaining eight patients (the responders), these two non-responders did not have a prior history of hypertension. The reasons for the difference between the responders and non-responders are not clear. The following mechanisms, however, may be considered: a) a genetic predisposition may play a role in these differences (Mark *et al.*1975; Kirkendall *et al.*1972; Abboud 1974; Ganguli *et al.*1979; Knudson *et al.*1973); b) sodium chloride- and water-logging of the arteriolar wall is more conspicuous in the thickened arterioles of patients with previous hypertension (Tobian and Binion 1952); c) structural changes in the

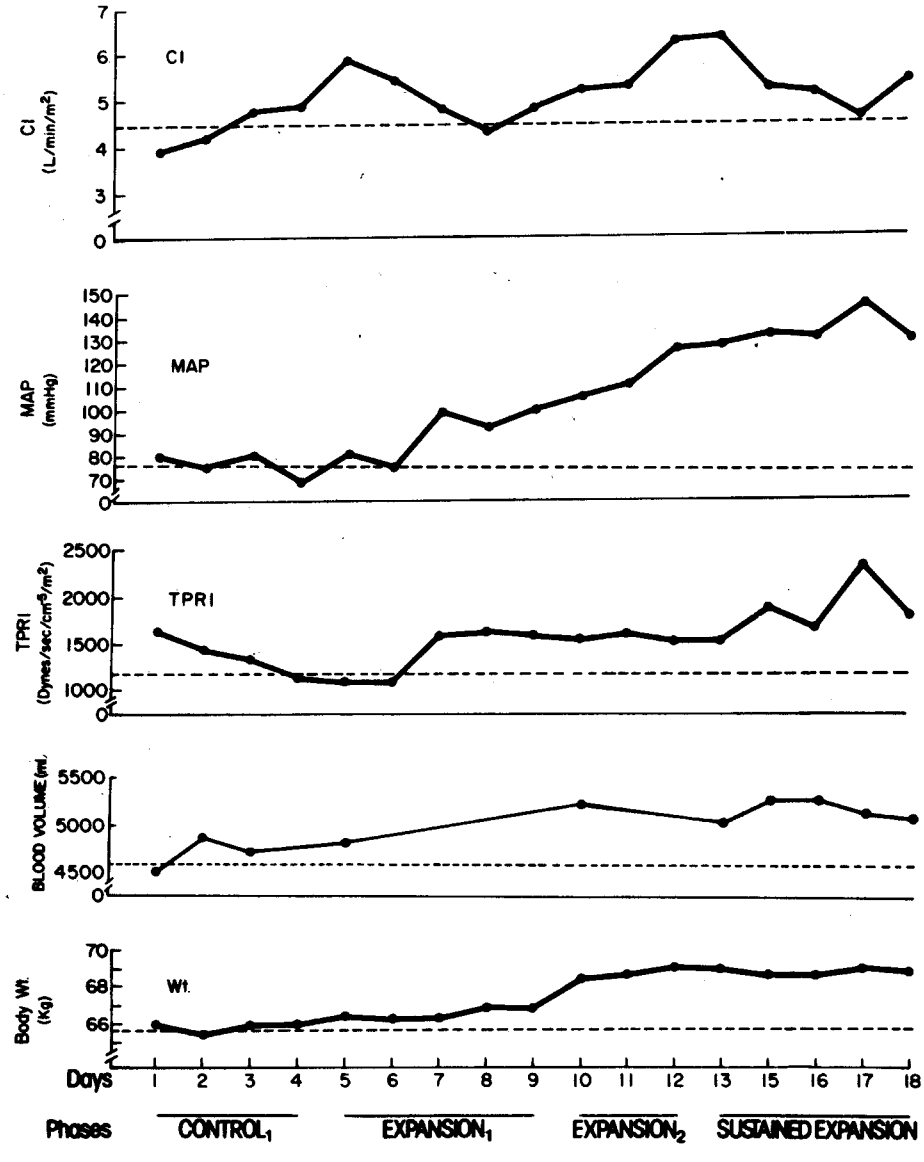

Fig. 12. *Sequential hemodynamic changes during volume expansion. This patient had two steps of volume expansion: during the first step (volume expansion$_1$), there was an initial rise in cardiac output followed by an increase in mean arterial pressure and total peripheral resistance index. During the second step (volume expansion$_2$), there was a further increase in mean arterial pressure associated with an increase in cardiac index followed later by a further increase in total peripheral resistance index. The dashed lines indicate control$_1$ values. From Kim et al. (1980).*

arterioles induced by previous hypertension, similar to those described by Folkow (1971), may determine vascular sensitivity to volume expansion in those patients with previous hypertension; d) activity of the adrenergic nervous system may be more prominent in some patients (Lilly *et al.*1976; McGrath *et al.*1977).

In the eight patients, volume expansion resulted in a significant increase in blood pressure. This increase, however, was accompanied by three different sequences of hemodynamic events.

In two patients, the blood pressure increase was associated with an increase in cardiac output only (Fig. 10). Persistently high cardiac output was observed for a three-week period during the volume-expansion phase. This was not followed by an increase in total peripheral resistance. Thus, it would appear that the increasing cardiac output was the major factor increasing blood pressure in these patients. In patients with end-stage renal disease given a high-sodium diet for 10 to 14 days, an icnrease in blood pressure associated with only an increase in cardiac output has been reported (McGrath *et al.*1977). Bravo and coworkers (1977) described a similar persistant increase in cardiac output in some dogs with hypertension induced by metyrapone. In our patients, it is evident that the secondary increase in total peripheral resistance predicted by the theory of whole-body autoregulation did not occur (Coleman *et al.*1970; Coleman *et al.*1971; Ledingham 1971).

In five patients, the increase in blood pressure was associated with an increase in total peripheral resistance from the beginning, without an initial increase in cardiac output (Fig. 11). Thus, the increase in total peripheral resistance appears to be responsible for the increase in blood pressure during the volume-expansion phase. This resistance-mediated hypertension has been reported in metyrapone-induced hypertension in dogs (Bravo *et al.*1977), in two-kidney, two wrapped hypertension in rabbits (Fletcher *et al.* 1976), in hypertension induced by stimulation of stellate ganglion in dogs treated with propranolol (Liard *et al.*1975), and in hypertension induced by deoxycorticosterone in pigs (Terris *et al.*1976). Conway (1968) also reported that in one-kidney, one clip hypertension in the dog, the blood pressure rise appears to be due entirely to an increase in peripheral resistance.

The mechanism responsible for this primary increase in total peripheral resistance remains uncertain. The renin-angiotensin system could not play a role because two of the five patients studied were anephric and plasma renin was not detectable. Control plasma remain concentrations of the two patients with end-stage kidneys were low, and no correlations between plasma renin concentration and volume changes were found. It has been demonstrated by de Champlain and co-workers (1968) that sodium-loading facilitates sympathetic transmission and the release of norepinephrine from adrenergic granules. Thus, increased sympathetic activity may play a role in increasing total peripheral resistance during the salt-loading phase in our patients. Mark and associates (1975) showed that excessive sodium intake for 10 days in patients with borderline hypertension increased blood pressure, forearm vascular resistance and neurogenic vasoconstriction. Sodium chloride- and water-logging of the arteriolar wall has also been considered a mechanism for increasing total peripheral resistance (Tobian and Binion 1952).

In one anephric patient during the volume-expansion phase, cardiac output increased initially. This was followed by a progressive increase in blood pressure and total peripheral resistance (Fig. 12). A similar sequence of hemodynamic events has been described by Coleman and co-workers (1970) in three anephric patients. It has been postulated that the initial increase in cardiac output results in perfusion of peripheral tissues above their metabolic needs. This would elicit myogenic construction of peripheral vessels with consequent increase in total peripheral resistance (Coleman *et al.*1970; Coleman *et al.*1971; Ledingham 1971).

In patients in whom salt- and water-loading elevated blood pressure, there was a significant positive correlation between blood pressure and blood volume, and between blood pressure and exchangeable sodium. This is in accord with previous reports (Onesti *et al.*1975; Dustan and Page 1964).

Despite equivalent degrees of body fluid expansion, hemodynamic responses to salt- and water-loading followed different patterns which are likely to reflect different mechanisms.

It is concluded that an initial rise in cadiac output is not necessary to increase blood pressure and total peripheral resistance during salt- and water-loading in patients deprived of renal excretory function. Furthermore, a sustained rise in cardiac output during salt- and water-loading is not allways followed by an increase in total peripheral resistance. Mechanisms other than whole-body autoregulation (Coleman *et al.*1970; Coleman *et al.*1971; Ledingham 1971) play a role.

4. Hemodynamics and Pathophysiology of Hypertension in Stable Renal Transplant Recipients

Many clinical studies on possible causes of hypertension after renal transplantation have been

reported (Popovitzer *et al.*1973; Sampson *et al.*1973; Grunefeld *et al.*1975; Bachy *et al.*1976; Jacquot *et al.*1978; Rao *et al.*1978; Pollini *et al.*1979). However, hemodynamic studies in stable renal transplant recipients are few (Tuckman *et al.*1973).

In this section, our studies on hemodynamics and pathophysiology of hypertension in stable renal transplant recipients will be discussed (Kim *et al.*1980).

Twenty-four stable renal transplant recipients were studied. There were 14 males and 10 females. The age ranged from 17 to 55 years with a mean of 35 years. Of the 24 patients studied, 16 were normotensive and eight were hypertensive. The groups of hypertensive and normotensive patients were of comparable age and sex. Thirteen of the 16 normotensive patients and six of the eight hypertensive renal transplant recipients had bilateral nephrectomy before renal transplantation. All patients studied were on less than 10 mg of prednisone daily and had serum creatinine concentrations of less than 2 mg/dl. and hematocrit greater than 30%. None of the patients had renal artery stenosis. All antihypertensive medication was discontinued at least two weeks before the studies. Studies were performed after an average of 13 months of successful renal transplantation. The control group included 25 normal subjects. Fourteen were male and 11 were females. The mean age was 37 years.

a. Comparison of cardiac index in renal transplant recipients and normotensive subjects: In the 24 renal transplant recipients, the mean cardiac index was 3.59±0.14 liters/min/m² (mean±S.E.). In the 25 normal subjects, the mean cardiac index was 3.40±0.09 liters/min/m² (Fig. 13). The difference is not significant. After a successful renal transplantation, the hematocrit of all 24 transplant recipients increased from a mean of 21% to a mean of 35%. The mean hematocrit of the 25 normal subjects was 43%.
b. Cardiac index before and after renal transplantation: Eleven of the 24 patients had hemodynamic studies performed before and after successful renal transplantation. As described previously in section IIC, these studies showed that hematocrit in all 11 patients increased (Fig. 6A) whereas the cardiac index decreased in 10 of the 11 patients (Fig. 6B).

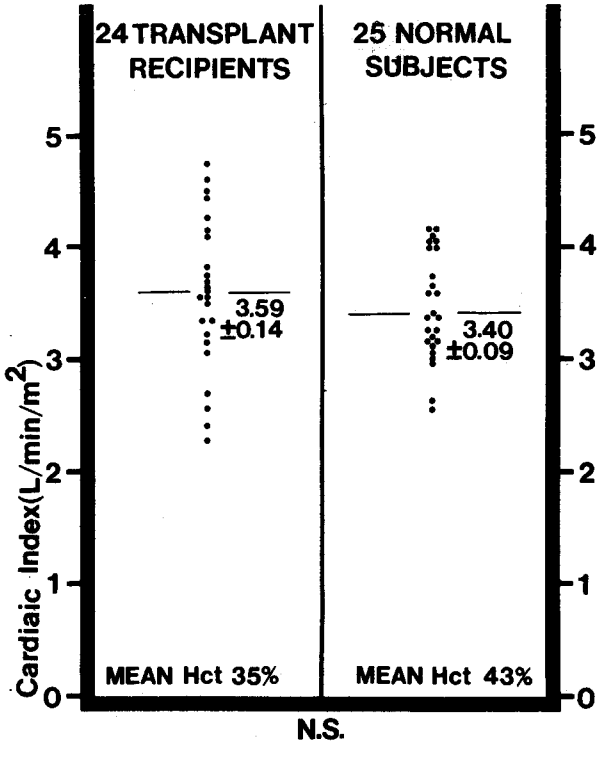

Fig. 13. Cardiac index of 24 transplant recipients compared with 25 normal subjects. Hemodynamic values are expressed as mean±S.E. From Kim et al. (1980).

c. Hemodynamic comparison between hypertensive and normotensive renal transplant recipients: Of 24 renal transplant recipients, eight patients were hypertensive and 16 patients were normotensive. The average mean arterial pressure of the hypertensive patients was 124±5 mmHg (mean±S.E.) and the average mean arterial pressure of the normotensive patients was 88±2 mmHg (Fig. 14A).

Mean cardiac index was 3.68±0.24 liters/min/m² in the hypertensive patients and 3.54±0.18 liters/min/m² in the normotensive patients (Fig. 14B). The difference is not significant. The mean hematocrit was 34.1±1.4% in the hypertensive patients and 35.6±0.9% in the normotensive patients. The mean heart rate was 70±3 beats/min in both groups. The mean stroke index was 53±3 ml/stroke/m² in the hypertensive patients and 50±2

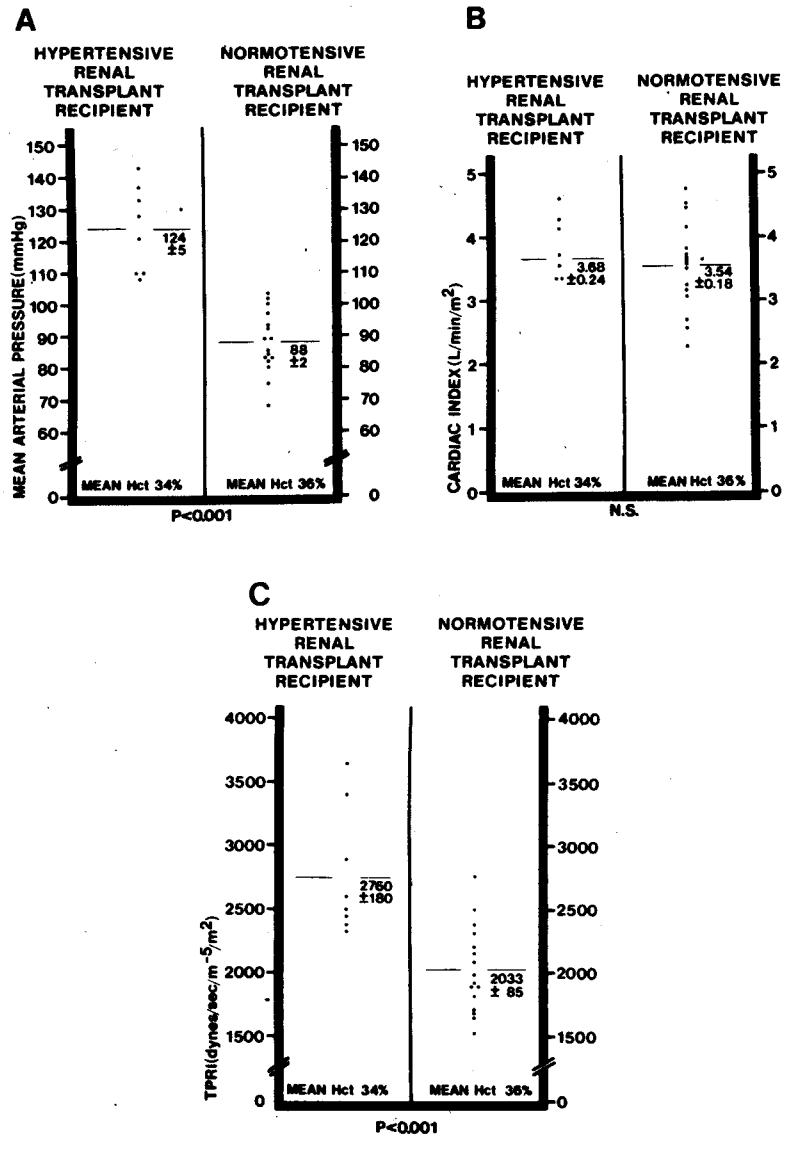

Fig. 14. *Comparison of mean arterial pressure (A), cardiac index (B) and total peripheral resistance index (C) of eight hypertensive and 16 normotensive renal transplant recipients. Hemodynamic values are expressed as mean±S.E. From Kim et al. (1980).*

ml/stroke/m^2 in the normotensive subjects. The mean total peripheral resistance index was 2760±180 dynes/sec/cm^{-5}/m^2 in the hypertensive renal transplant recipients and 2033±85 dynes/sec/cm^{-5}/m^2 in the normotensive renal transplant recipients (Fig. 14C). The difference is highly significant ($p<.001$).

d. Comparison of blood volume, plasma renin concentration and creatinine clearance in hypertensive and normotensive transplant recipients: The mean blood volume was 76±4 ml/kg body weight (mean±S.E.) in the hypertensive patients and 80±4 ml/kg body weight in the normotensive patients. The difference is not significant.

The mean plasma renin concentration was $0.26\pm0.06\times10^{-4}$ Goldblatt unit in hypertensive patients and $0.29\pm0.07\times10^{-4}$ Goldblatt unit in the normotensive patients. The mean 24-hour urinary sodium excretion at the time of sampling plasma renin concentration was 127 mEq in the hypertensive and 119 mEq in the normotensive patients.

There were no significant differences in creatinine clearance between the two groups. The mean creatinine clearance was 81±10 ml/min ranging from 57 to 130 ml/min in the hypertensive patients and 78±7 ml/min ranging from 42 to 134 ml/min in the normotensive patients.

Mean hematocrit in the 24 patients increased from 21% to 35% after a successful renal transplantation. The mean cardiac index of the 24 transplant recipients was similar (Fig. 13) when compared with that of the 25 normal subjects matched by age and sex. After a successful renal transplantation, cardiac index decreased in 10 of the 11 patients studied, whereas the hematocrit of all 11 patients increased (Fig. 6). This finding indicates that an increase in hematocrit after a successful renal transplantation normalizes cardiac index. The comparative evaluation of the hemodynamic pattern of the hypertensive transplant recipients vs the normotensive transplant recipients shows that the cardiac index, heart rate and stroke index were entirely similar in the two groups. Thus the hypertension of the stable renal transplant recipients is sustained by a high total peripheral resistance.

Hypertension after renal transplantation has been ascribed to graft rejection (Popovitzer *et al.* 1973; Grunefeld 1975; Bachy *et al.*1976), high dose of glucocorticoids (Popovitzer *et al.*1973), arterial stenosis of the transplanted kidney (Grunefeld *et al.*1975; Bachy *et al.*1976; Pollini *et al.*1979) and the presence of the patient's own kidneys (Grunefeld 1975). All these causal factors were excluded in our study by patient selection.

The data obtained in this study do not allow for identification of the mechanism of hypertension in stable renal transplant recipients. However blood volume was similar in the hypertensive and normotensive groups in our study. A high plasma renin activity has been implicated in hypertension after renal transplantation (Pollini *et al.*1979; West *et al.*1969). Plasma renin concentration was similar in the hypertensive and normotensive patients in our study. Our findings are in agreement with Sampson and coworkers (1973). The influence of renal function of post-transplant hypertension cannot be precisely identified by our study because we deliberately selected patients with good renal function. However, the mean and range of creatinine clearance were similar in the hypertensive and normotensive groups.

In summary, the hypertension of stable renal transplant recipients is sustained by a high total peripheral resistance which is not related to blood volume expansion, elevated peripheral renin or low creatinine clearance. The cause of this elevated peripheral resistance remains to be elucidated.

5. Serial Hemodynamic Studies of Hypertension in Chronic Renal Parenchymal Disease

In the previous sections we have shown that the hemodynamics of hypertension in chronic renal parenchymal disease varies in different stages. Hemodynamic studies of individual patients as they progress from early in the disease through each stage would help to define their evolution. No such serial study has yet been published.

To determine the hemodynamic evolution of hypertension in different stages of chronic renal parenchymal disease, four patients were studied serially: a) in the early-stage; b) in the end-stage; c) after bilateral nephrectomy and d) after successful renal transplantation. Serial hemodynamic changes in one representative patient are shown in Figure 15. In the first study, creatinine clearance was 105 ml/min and hematocrit was 42%. The patient was mildly hypertensive with mean arterial pressure of 112 mmHg. Cardiac index was normal (3.16 liters/min/m^2) and total peripheral resistance index was high (2835 dynes/sec/cm^{-5}/m^2). In the second study, one year later, creatinine clearance decreased to 55 ml/min and hematocrit also decreased to 37%. His blood pressure increased further with mean arterial pressure of 129 mmHg. Cardiac index did not change (3.10 liters/min/m^2). Therefore, total peripheral resistance index increased further to 3326 dynes/sec/cm^{-5}/m^2. One year after the second study, the patient became uremic and maintenance hemodialysis was started.

Hemodynamic study was not done in this end-stage because he could not be taken off antihypertensive drugs due to severe hypertension. However, we could assume from our previous study on this stage that the hemodynamics would show a high blood pressure, a high cardiac output from uremic anemia and a high total peripheral resistance. In the third study, bilateral nephrectomy reduced blood pressure to the normal value (85 mmHg of mean artrial pressure). Hematocrit was 19%, cardiac index was high (4.64 liters/min/m^2) and total peripheral resistance decreased markedly to 1464 dynes/sec/cm^{-5}/m^2. In the forurth study, nine months after renal transplantation, creatinine clearance increased to 114 ml/min, hematocrit increased to 37% and cardiac index decreased to the control level (3.21 liters/min./m^2). Blood pressure remained normal (89 mmHg) and total peripheral resistance index increased to the normal value (2216 dynes/sec/m^2).

These four patients with serial studies showed a hemodynamic evolution which is the same as would be expected from our cross-sectional studies.

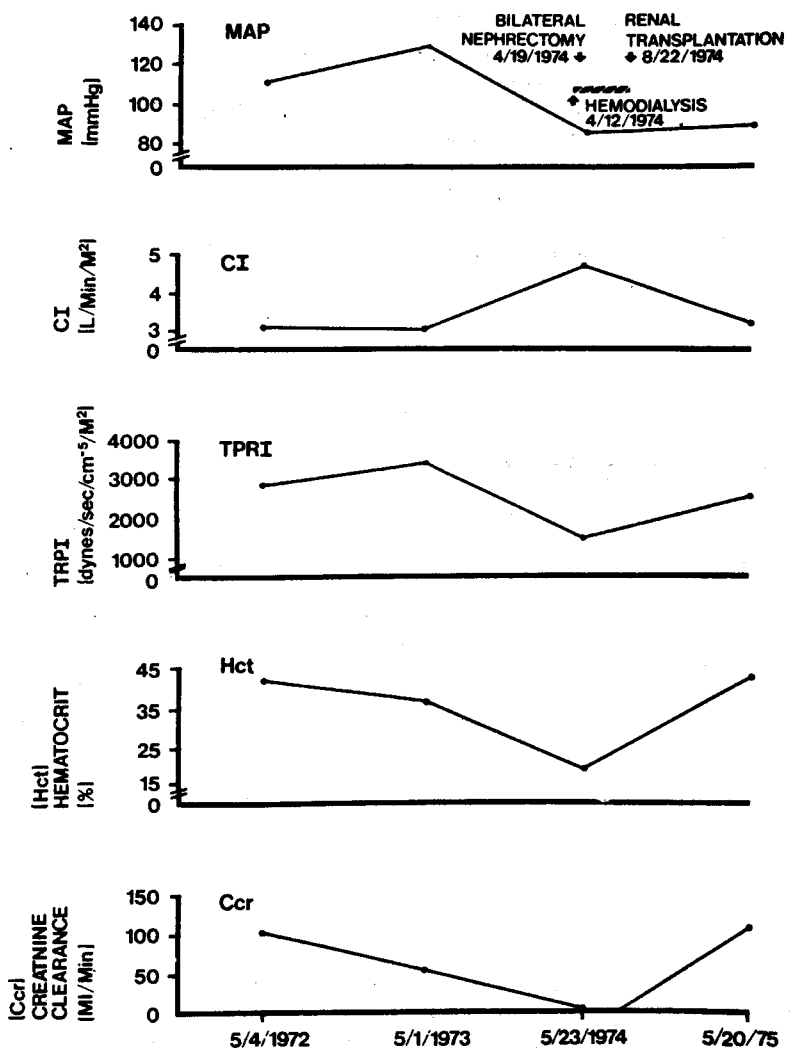

Fig. 15. Serial hemodynamic studies in different stages of chronic renal parenchymal disease in one representative patient.

SUMMARY

The present report summarizes our studies on the hemodynamics and pathophysiology of hypertension in four different stages of chronic renal parenchymal disease: a) in early-stage renal disease; b) in end-stage renal disease; c) after bilateral nephrectomy and d) after successful renal transplantation.

In early-stage renal parenchymal disease, the overall cardiac index and heart rate of hypertensive patients were higher than those of normotensive patients. Studies of ours and others suggest that with progression of hypertension, the cardiac output decreases, while the total peripheral resistance increases. There was no significant difference in blood volume, renin concentration and glomerular filtration rate between the hypertensive and the normotensive patients with early-stage renal disease.

Patients with end-stage renal disease had significantly higher cardiac indices than did normal controls. The higher cardiac indices of uremic patients were accounted for by increased heart rates with normal stroke volumes. Cardiac index was the same in the hypertensive and normotensive uremic patients, while mean total peripheral resistance index of the hypertensive uremics was higher than in the normotensive uremics. Therefore, the hypertension in end-stage renal disease is sustained by a high total peripheral resistance. The serial hemodynamic studies during the correction of anemia, and hemodynamic studies before and after a successful renal transplantation, indicate that the major factor responsible for high cardiac output in uremic patients is anemia itself.

Bilateral nephrectomy in uremic patients with severe or malignant hypertension resulted in a significant reduction in blood pressure associated with a decrease in total peripheral resistance. These findings imply that a vasopressor substance or substances of renal origin which act to increase total peripheral resistance are major factors in the pathophysiology of severe and malignant hypertension in end-stage renal disease. Bilateral nephrectomy in normotensive uremic patients resulted in no significant change in blood pressure, cardiac index and total peripheral resistance index. Therefore, the end-stage kidneys of normotensive patients without a prior history of hypertension do not exert either a pressor or a depressor effect.

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