Mechanisms for the Elevation of Blood Pressure in Human Renal Disease
Preliminary Report

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SUMMARY Detailed hemodynamic studies were carried out in 99 subjects with chronic nonuremic renal disease and 17 healthy subjects. The earliest hemodynamic abnormality found in normotensive renal patients was a raised circulating blood volume and an increased cardiac output. The blood pressure remained normal as long as the peripheral vascular bed (arteriolar and venous) adjusted to these conditions. When this adjustment ceased, hypertension developed and the blood volume normalized. It is suggested that a disturbed volume-homeostatic function of the kidney, leading to a rise of the circulating blood volume, is the proper starter of hemodynamic events leading eventually to hypertension in chronic parenchymatous renal disease. (Hypertension 4: 839–844, 1982)

INCE the discovery that renin in the kidney is elevated in renal ischemia, efforts have been made to connect this event with the pathogenesis of hypertension in chronic renal disease. These efforts have failed so far because it was found that: 1) plasma renin activities and angiotensin concentrations were not elevated to a hypertensive level in the majority of patients with nonuremic renal disease; 2) occupation of the vascular receptors by the angiotensin antagonist saralasin neither reduced the blood pressure nor influenced the hemodynamics on the arterial or venous side of the circulation in humans under basal conditions without sodium depletion; 3) in early renal hypertension (WHO I), high cardiac output and no evidence of generalized vasoconstriction in the form of a rise of total peripheral vascular resistance (TPR) was associated with blood pressure elevation; and 4) in different types of experimental hypertension in animals the same overall pattern of hemodynamics was detected. To clarify our understanding of these findings, we have carried out over the past 8 years a detailed hemodynamic investigation of a large group of nonuremic renal patients with and without an elevated blood pressure who were restudied clinically 2 to 7 years later.

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were measured by a strain-gauge attached to a percutaneous catheter introduced into the iliac artery. Cardiac output (CO) was estimated by the dye-dilution technique, cardio-green being injected into the immediate proximity of the right atrium through a venous catheter, with which the central venous pressure was also measured. Forearm blood flow was measured by occlusion plethysmography, the hand being excluded during the measurement by an inflated wrist cuff. Forearm blood volume was estimated by the method of Pferovsky et al. Indium-Transferrin (3 mC) was injected into the blood by the central venous catheter; some blood was trapped in the forearm by an inflated cuff on the arm. The increase in forearm volume measured plethysmographically was equated with the increase in counts. To calibrate the activity, some blood was injected into the blood by the central venous catheter; 30 minutes later when stable radioactivity had been achieved over the left forearm this was recorded continuously by two collimators placed on its opposite sides. To calibrate the activity, some blood was trapped in the forearm by an inflated cuff on the arm. The increase in forearm volume measured plethysmographically was equated with the increase in counts. From this, by a simple rule of three, the forearm blood volume could be calculated at any moment. The same isotope was used for estimation of circulating blood volume. The absolute values were referred to the body weight, there having been no significant difference in weight among the various subgroups and none of the patients having been edematous at the time of the study. Peripheral venous pressure was measured in a vein of the left forearm. Venous distensibility was expressed as the volume of blood in the left forearm per 1 mm Hg venous pressure. Total and forearm vascular resistances were calculated from the mean blood pressure and cardiac output or forearm blood flow.

Plasma renin activity (PRA) was measured by the usual isotope double dilution technique. At least three hemodynamic measurements were carried out in each subject, and the results were accepted only if they fell within 10% of each other. The significance of the data was calculated according to the Dunnet procedure.  

### Results

Figure 1 shows that 95% (mean + 2 δ) of the cardiac indices (CI) of the normotensive healthy controls were below 3.57 liter/min/m², and only one was slightly above this value. On the other hand, 12 of the 32 normotensive patients with renal disease (RN) and 15 of 47 patients with renal disease and hypertension stage I-II WHO (RN II) had a CI markedly above this dividing line ("hyperkinesis"). Only one of 13 patients with renal disease and hypertension stage III (RH III) had a slightly elevated CI. In three RH III patients, CO measurements failed for technical reasons. The calculated TPR was in the normotensive control range not only in the total group of RN but also in the hyperkinetic RH I-II group, demonstrating that renal hypertension can start without evidence of a generalized vasoconstriction.

Figure 2 analyzes the hemodynamic and other parameters studied simultaneously in subjects with a high CI (hyperkinetic) and those with a CI below 3.57 liter/min/m² ("normokinetic"). Obviously, the high CI was due, in the first instance, to a faster heart rate. In the hyperkinetic RNs, the TPR was reduced compared to the normokinetic RNs and was also below the control mean. This was also reflected in the forearm where vascular resistance was significantly reduced com-
FIGURE 1. Cardiac index (CI) and total peripheral vascular resistance (TPR) in normotensive and hypertensive renal patients. The open circles of the TPR indicate hyperkinetic subjects. Asterisks indicate statistical significance. Each dot is the mean of at least three measurements in each patient. The horizontal heavy lines in the panels of TPR indicate the mean of the whole group (irrespective of the level of the CI), the thin lines indicate ± SEM. It is obvious that at least two-thirds of the TPRs of the hyperkinetic renal hypertensive subjects (WHO stage I-II) are within the range of the mean ± 1 SEM of the controls. The elevation of blood pressure in these subjects is due entirely to an increased cardiac output.

pared to the normokinetic RNs and the controls. The consequence of this was a hyperperfusion of the forearm in the hyperkinetic RNs. Venous distensibility of the forearm was slightly higher than in the controls and normokinetic RNs, suggesting that the capacitance vessels were in a relaxed state. A significant difference was found in the hyperkinetic RNs compared to controls and normokinetic RNs with regard to the circulating blood volume, which was raised to 93.4 ± 11.5 ml/kg body weight vs that of controls (73.4 ± 17.9 ml/kg) and normokinetic RNs (78.9 ± 22.3 ml/kg). In spite of this, the central venous pressure of the hyperkinetic RNs was slightly but consistently reduced. The PRA, although completely in the accepted normotensive range, had a higher mean both in normokinetic and hyperkinetic RNs compared to controls, but the difference was statistically not significant. The increase in blood pressure in the hyperkinetic RH I-II was due to a high CI while the TPR was within the normal range. The same applied to the forearm vascular resistance. Consequently, the forearm blood flow was normal. Venous distensibility was significantly lower compared to that of the hyperkinetic RNs, and so was the blood volume which did not differ from the control range. All this happened without any change of PRA.

Discussion

The data from this investigation of a series of patients with chronic parenchymatous kidney disease whose renal function was still adequate confirm our previously published data that, early in its development, the blood pressure rise could be due to a high cardiac output. This was confirmed by Onesti et al. However, a high CO was detected in one third of our subjects with chronic renal disease who were still normotensive. Our so far unpublished data on their oxygen consumption do not point to increased metabolic requirements; the high CO cannot be accounted for on this basis. An emotional tension with sympathetic overaction produced by the stress of the investigation could not explain why the high CO should be restricted to the renal normotensive and early hypertensive subjects. In addition, it could hardly be responsible for the changed blood volume, the relaxed capacitance bed in the hyperkinetic RNs, and the normal forearm blood flow and vascular resistance in the hyperkinetic RH I-II. With the exception of the raised plasma volume, all other objections can also be raised against an increased sympathetic activity produced by the central nervous action of the slightly higher (though normotensive) plasma concentration of renin (and possibly angiotensin).
Figure 2. Comparison of data (mean ± se) from normotensive controls (CON) and patients with chronic renal disease (RN = renal normotensives; RH = renal hypertensives stage I-II, and stage III WHO). The data of RN and RH I-II are split between normokinetic (left column) and hyperkinetic (right adjacent column) subjects. Asterisks indicate statistical significance.

However, most of these changes could be reproduced by a rapid infusion of isotonic saline in healthy men and in normotensive renal patients, which invariably raised the cardiac output. In some subjects the blood pressure remained unchanged, suggesting a full adaptation of the arteriolar bed to the high CO; in these subjects the venous distensibility rose markedly. In the others, this vascular adjustment failed to occur and the blood pressure increased. Similar effects were observed during the initial phase of a continuous isotonic saline expansion in dogs. The only difference was in the behavior of the central venous pressure, which rose in the course of the acute infusion whereas, in the hyperkinetic RNs under the steady-state condition, it was below the mean of all the other subjects including the controls, by about 1 mm Hg.

The venous return to the heart and the CO are determined by the pressure gradient for venous return, which is defined by the difference between the mean circulatory pressure (measure of the filling of the circulatory system with blood) and the right atrial pressure. The mean circulatory filling pressure, estimated in animals during acute cardiac arrest, cannot be measured in humans. However, in the hyperkinetic RNs, the blood volume was markedly elevated while the rise of the venous distensibility (of the forearm) was slight and irregular. It is therefore probable that the mean circulatory filling pressure was increased. The central venous pressure was slightly lower in these subjects, thus increasing the pressure gradient for venous return. This could also be the case in the hyperkinetic RHs, whose blood volume was normal but whose venous compliance (of the forearm) was significantly decreased.

From this background and in the light of our hemodynamic data, we believe we can justify the conclusion...
that the earliest hemodynamic abnormality in chronic renal disease at a time when the patient is still normotensive is a rise of the cardiac output in response to a rise of the circulating blood volume. The latter is a probable consequence of the reduced renal volume homeostatic efficiency. As long as the peripheral arteriolar bed adjusts to the increased CO and the capacitance bed to the elevated circulating blood volume, the blood pressure remains unaffected, so that no pressure diuresis can correct the hypervolemia. When this adjustment ceases, the pressure rises. Perfusion of the kidney under this increased pressure reestablishes its volume homeostatic efficiency, and the blood volume normalizes. This is not related to any corresponding changes of the PRA, this being the same or even slightly lower in the subjects whose vessels did not adjust. In many respects this is similar to the hemodynamic findings in dogs with perinephritic hypertension, where the CO rises before hypertension appears.2

At this early stage of hypertension the total and forearm vascular resistances are not higher than in the controls. Instead of pointing to a vasoconstriction, this recalls the Bayliss effect from lasting tissue hyperperfusion or the thickening of the vessel wall found by Folkow21 in spontaneously hypertensive rats. Folkow claimed that the enhanced autoregulatory smooth muscle activity is the basis of the vascular hyperplasia and eventual narrowing of the vascular lumen. It is probable that the same is true in renal hypertension. Both in experimental Goldblatt hypertension and in hypertension produced by a reduction in renal mass and salt overload,4,22 high blood pressure develops over an initial rise of the blood volume and CO to a later stage where blood volume and CO fall and the hypertension is sustained by a higher TPR. Our data provide for the first time a confirmation of this pathogenetic chain of events in humans, which starts with the inability of the kidney to keep an adequate fluid balance at a normal blood pressure level.

The question remains: Do hyperkinetic and normokinetic patients represent two different types of hemodynamic abnormalities? This is not supported by our data: the normokinetic subjects do not differ from the hyperkinetic ones by age, sex, type of renal disease, or extent of reduction of renal function (table 1). In addition, our recent (unpublished) studies on the fate of these patients show that 11 of the originally 12 hyperkinetic subjects became definitely hypertensive 2 to 6 years later; of the reexamined 17 normotensive normokinetic patients, only eight developed hypertension after the same time interval. We have tested the one-side (H_1) hypothesis that the hyperkinetics do not develop hypertension more frequently than the normokinetics. This H_1 hypothesis can be rejected, p being smaller than 0.05 (fig. 3). Eventually, the development of hemodynamic abnormalities found in our study corresponds fully to the pattern observed in the types of experimental hypertension quoted, and possibly explains the conflicting hemodynamic findings reported by others21 in renovascular (stage I-II) and renovascular (stage III) hypertension.

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