THE CAPACITY OF THE RENAL VASCULAR BED IN HYPERTENSION

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During the past 80 years there have been many reports of perfusion studies of human kidneys (1, for literature; 2; 3). As a rule the kidneys were perfused as soon as possible after death, with water, serum, saline, or acacia solution. The observed rates of flow, at 100 mm. Hg, were from 1 to 2.5 cc. per gm. per minute in normal kidneys. Correcting for differences in viscosity of the solutions used, these studies suggest a possible blood flow of less than 150 cc. (3) to as much as 400 cc. (2) per minute for the kidneys of an adult. While this seems high in relation to blood flow in the arm during intense hyperemia (about 0.6 cc. per gm. per minute) it is less than one-third the blood flow through the kidneys during life as estimated by diodrast clearance (4).

The growing interest in renal vascular disease as a possible cause of arterial hypertension makes it highly desirable for pathologists to have available direct measurements of the renal vascular bed as well as morphologic studies of the large and minute vessels. A satisfactory method must yield values comparable with those obtained in similar groups of cases by diodrast clearance. In postmortem material it is obviously impossible by perfusion to duplicate the flow during life, but by proper preparation of the specimens the maximum carrying capacity of the vessels can be measured.

Methods

To measure the maximal rate of flow it is necessary to allow rigor of the blood vessels to pass off, or to break it up by perfusion at high pressure, but such procedures hasten the rate of edema formation in the tissues and the vessel walls. To avoid the decline in flow consequent on edema formation we have used an oil rather than a watery solution. With this technique rates of flow as high as 10 cc. per gm. per minute, at 100 mm. Hg were obtained in young adults, although the fluid used, kerosene, has twice the viscosity of saline. Correcting for relative viscosity this method yields figures for possible blood flow well above those obtained by diodrast clearance in people of the same age group.

In most instances but one kidney was used, but only if the other was comparable in weight and structure. In 15 hypertensive cases both kidneys were perfused. The kidney, perirenal fat, renal vessels, and half of the aorta were removed *en bloc*, and the renal artery or arteries cannulated through the aortic ostia. The largest possible snug fitting thin walled metal cannulae were used; these ranged from 2 to 4.7 mm. inside diameter. Occasional accessory vessels were cannulated with 1 mm. cannulae. Heavy clamps were applied on the perirenal fat, and small leaks were caught with hemostats while perfusing with kerosene at 200 mm. Hg. A pneumatic pressure system was used which maintained constant pressure during perfusion, as shown by a mercury manometer. Neoprene tubing was not altered after months of exposure to the oil. The flow from the system with no organ in the circuit was 5100 cc. per minute at 100 mm. Hg with the largest, 1500 cc. per minute with the smallest cannula.

TABLE I

	Flow of kerosene at 100 mm. Hg pressure	Kidney weight total for body	Mean blood pressure $(S+D)/2$	"Possible renal blood flow"	"Corrected" blood flow
	cc./gm./min.	*gm.*	*mm. Hg*	*cc./min.*	*cc./min.*
Normal individuals, 18–32 yrs.	8.3	370	97	2080	2960
Normal individuals, 46–60 yrs.	5.7	390	99	1580	1950
Normal individuals, 61–68 yrs.	5.7	310	101	1250	1500
Hypertensives, 38–60 yrs.	5.2	350	158	2010	2440
Hypertensives, 61–84 yrs.	4.3	304	150	1370	1560

Average values for perfusibility of kidneys of non-uremic patients. The methods for calculating "possible renal blood flow" and "corrected blood flow" are given in the text. The former represents the flow of whole blood at the patient's mean blood pressure, calculated from perfusion rate with kerosene at 100 mm. Hg. The "corrected flow" is obtained similarly after the observed rate of flow is corrected by subtracting the resistance of the perfusion apparatus from the total resistance of kidney and apparatus. It is apparent that the perfusibility of normal kidneys is only slightly greater than indicated by the data reported by those who have used diodrast clearance, and that there is a distinct fall with age and with arterial hypertension.

Before timing the rate of flow the kidneys were kept for 24 hours after death at 4°C., and at 37°C. for 4 hours, in order to allow rigor to pass off, and they were perfused with one liter of kerosene at 200 mm. Hg to break up the remaining rigor and wash out the vessels thoroughly. Actually, blood remains in some glomerular loops and a few intertubular capillaries even after perfusing with several liters of kerosene. Since kerosene and blood do not mix, it seems probable that where a large plexus of vessels opens out of a single narrow inlet, as in the glomerulus, the kerosene pours through some channels and traps blood in a few. It was found that perfusion repeated at 48 hours gave no higher rate than at 24, but the lower time limit for maximal perfusion rates was not explored. The rate of flow was timed from a calibrated bottle, with a stop-watch, at 160 mm., then at 100, again at 160 and 100. Occasionally a third pair of observations was made if the second did not check with the first, which in such cases was always slower. Usually the duplicates checked within 5 per cent.

On the average the resistance (Pressure/Flow) was 6 per cent higher at 100 mm. than at 160. Individual variation was from 0 to 16 per cent, but the average in normal and hypertensive individuals and at different ages did not differ significantly.

It should be noted that the perfusion system itself was not free from resistance. This introduces little error in cases where flow is less than one liter per minute, but in the rapid flow of young normal individuals the error rises to as much as 50 per cent. Thus the fastest flow, 10.5 cc. per gm. per minute, becomes 16 when recalculated subtracting the resistance of the system. We have followed the usual custom of not correcting for this error, which tends to minimize the actual spread between the fastest and slowest rates. In Table I, however, corrected average figures are also given.

After washing out the kerosene with warm salt solution, lead carbonate in warm 6 per cent gelatin was injected, the kidney chilled with pressure at about 140 mm. Hg in the injection system, and roentgenograms were made with the kidney and vessels intact and again after splitting the kidney lengthwise. This gave a reliable check on the completeness of injection, the state of large branches, and the amount of tissue to subtract if a small accessory artery was missed. Judging by differences between injected right kidneys and non-injected left kidneys, they increased 10 to 15 per cent in weight during perfusion and injection. In this laboratory the renal pelvis and pelvic fat are not trimmed out before weighing.

Material Studied.—While recognizing the desirability of using kidneys from coroner's cases, in which death occurred quickly from violence or poison, as the normal controls, we have used the best available material—kidneys from patients dying of disease in which the kidneys were not directly involved, and only from those with normal heart weights, and several blood pressure records before premortal circulatory failure. None had systolic levels over 140 or diastolic levels over 85. In the hypertensive group all had cardiac hypertrophy, systolic levels over 170, and diastolic over 90 on all observations prior to final circulatory failure, which in many was associated with cerebral or coronary arterial accidents. None was considered uremic unless the blood urea was more than 100 mg. per cent in the last week of life. There were relatively few women among the normal controls; the flow per gram of kidney apparently was in the same range as in males of the same age.

RESULTS

Effect of Age.—The kidneys of older people, including those with low normal arterial pressure, show variable degrees of disseminated focal atrophy of the renal cortex, associated with arterial disease, chiefly atherosclerosis and reduplication of the inner elastic lamellae. Such changes are more striking in hypertensives, yet in some of these (markedly hypertensive in a few cases for many years) scarcely any gross change and only rare hyalinized glomeruli are seen. However even in normal individuals with minimal histologic renal changes and those who are senescent rather than senile, the capacity of the vascular bed of the kidney decreases strikingly with age (Table I and Fig. 1).

It seemed desirable to interpret our results in terms of blood flow in order to compare them with reports on diodrast clearance. To correct for the difference in viscosity of blood (4 at 37°C.) and kerosene (2 at 20°C.), we per-

fused one kidney with kerosene and then with a mixture of cosmetic oil and kerosene (viscosity 4). The decrease in flow through the tortuous renal vascular bed on doubling viscosity is not 50 per cent, as would be the case in a straight tube, but only 30 per cent. Using this factor, the observed kidney weight, and mean blood pressure, $S + D/2$, of each patient, we calculated a

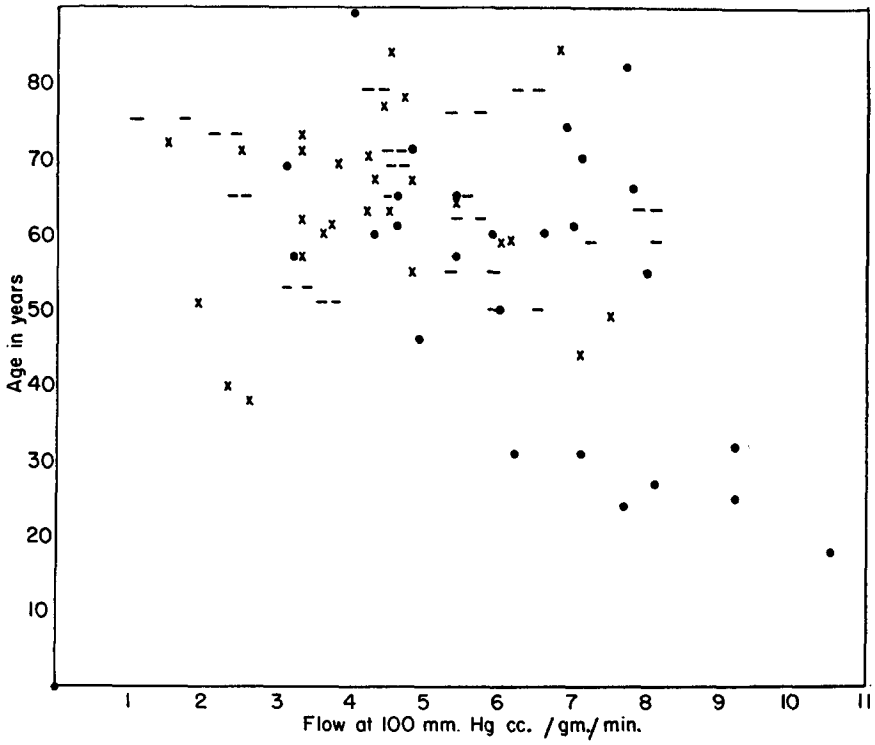

FIG. 1. Kerosene flow through kidneys postmortem. ● = normal kidney from patient without hypertension, × = kidney from hypertensive patient without uremia, – – = two kidneys from hypertensive patient without uremia.

"possible renal blood flow." These figures are not corrected for surface area, but the average for a group may be compared with figures obtained on living men with diodrast (4). We also give a further "corrected" figure, where the resistance of the perfusion system is taken into account, rather than being ignored as is the usual custom. This is given to show the absolute maximum which can be computed if all factors are considered, and also for comparison with figures obtained in the conventional way which assumes that the pressure at the entrance to the main artery is that at the surface of the fluid in the perfusion bottle.

The reported diodrast clearances (4) on fourteen men 18 to 32 years old indicate a blood flow in life of 1390 cc.; our seven kidneys in this age group yield a figure for "possible blood flow" of 2080 cc. For thirteen men, aged 45 to 60, the diodrast renal blood flow figure was 1018, 26 per cent below that of the younger group, while kerosene perfusion indicates a "possible flow," in the group 45 to 60 years old, of 1580 cc., 24 per cent lower than in the young adults.

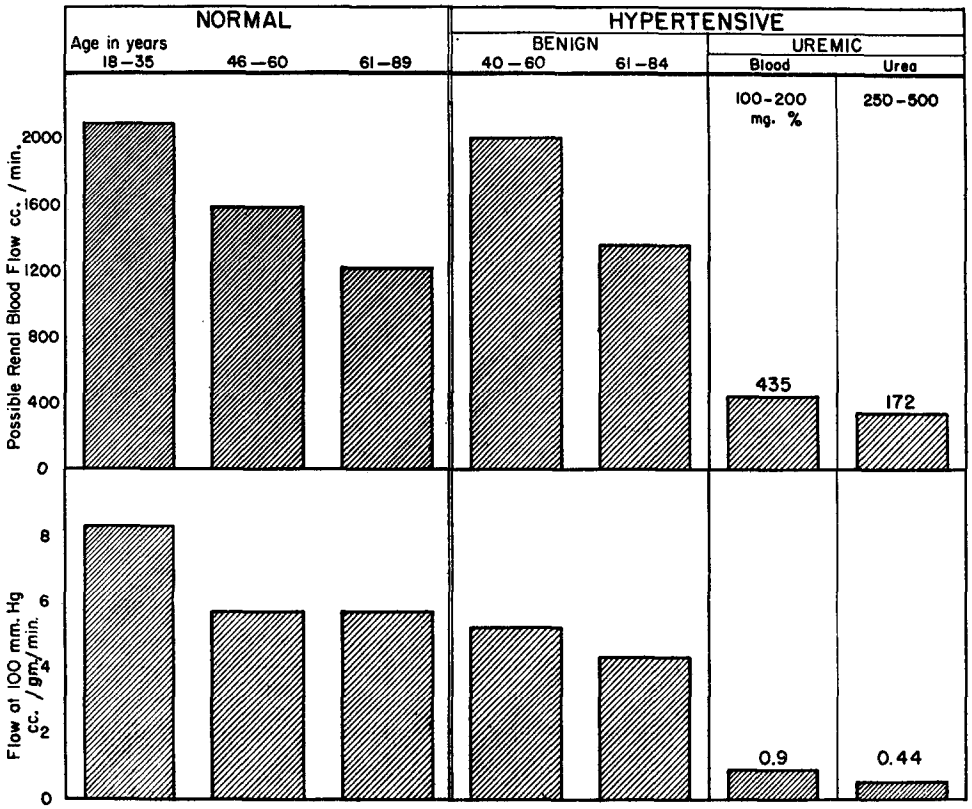

FIG. 2. Average values for kerosene flow postmortem, and "possible renal blood flow" calculated as described in Table I. Renal perfusibility decreases with age, is somewhat lower in hypertensives, is greatly diminished in most uremics.

The fact that similar changes with age are apparent in both groups, and that the kerosene method gives a figure 50 per cent higher than the diodrast flow, as contrasted with a figure 60 to 80 per cent lower in the reported aqueous perfusions gives us some confidence in the validity and value of the method we have used. The decrease in total flow, in normal kidneys, is 40 per cent between young adults and those past 60 years. In those 60 to 89 the further

decline over the rate of flow in those of 45 to 60 is associated with the decrease in renal tissue, since the flow per gram of kidney at 100 mm. Hg remains constant in the two older groups.

Hypertension with Normal Blood Urea.—The "possible renal blood flow" appears to be greater in these hypertensives as compared with normal individuals of the same age groups, but it is probable that the true mean pressure, in hypertensives, is not so high as that calculated by averaging systolic and diastolic levels. The curves showing percentile distribution of various levels of renal vascular resistance in normal and hypertensive individuals show that about 75 per cent of such hypertensives have resistance in the normal range (Fig. 3). Indeed the average kerosene flow per gram, at 100 mm.

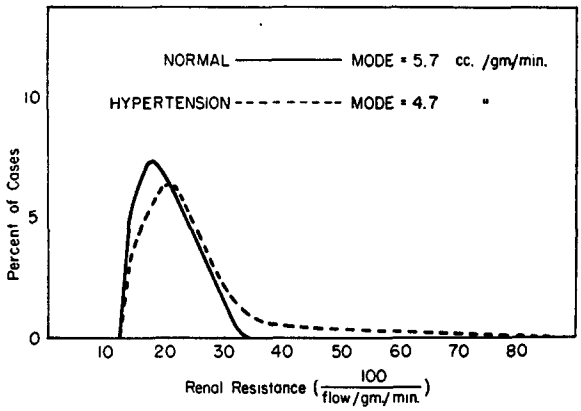

FIG. 3. Distribution of values for resistance in renal vascular bed in normal and in hypertensive patients without uremia. While most hypertensives fall in the normal range, a few have slight to marked increase in resistance to flow.

Hg, is only 11 per cent less in the hypertensive groups, although an occasional case shows a level one-half the lower limit of the normal.

Marked Occlusion of Renal Artery and Its Main Branches.—Moderate narrowing at the ostia of the renal arteries is often encountered in patients with atherosclerotic plaques in the abdominal aorta. In some of the renal arteries from normal or hypertensive patients such plaques were present, and in two the narrowing was so marked that only a 2 mm. cannula, instead of the usual 4.0 or 4.7 mm. cannula, could be used. The rates of flow were not low; one of them had the same flow per gram as its mate with a fully patent artery. This merely confirms the observation (5) that narrowing of a short segment of an artery must be very marked before the blood flow is reduced. In addition to this we have observed, in the past 1400 autopsies, five cases with very marked narrowing of the main renal artery or occlusion of one of its large branches. All had a marked atrophy of the kidney or part of the kidney affected but in

only one did the findings seem comparable with Goldblatt hypertension in the dog; in the other four fairly recent thrombosis or hemorrhage in a plaque was present, renal sclerosis distal to this was similar to that elsewhere, and there was a history of years of hypertension. We interpret these as cases in which renal arterial accident supervened in hypertension just as a coronary or cerebral arterial occlusion might have occurred. Such accidents to renal arteries may lead to a new and more severe hypertensive mechanism, and in one case this seemed to have been the case. In three cases only one-third to one-half of a kidney was affected, and there was no evidence of a recent rise in pressure.

Uremia.—In one case of amyloid disease, with a rapid terminal rise in blood urea to 300 mg. per cent, the "possible renal blood flow" was calculated at 1400 cc. per minute, the flow of kerosene per gm., at 100 mm. was 2.5 cc. per gm. per minute. In a case of myeloma kidney, with hypertension, the "possible renal flow" was 660 cc., and in a case of polycystic kidneys (total renal weight 4.6 kilos) the possible flow was 620 cc. In the other three patients with blood urea over 250 mg. per cent, there was chronic glomerulonephritis and total "possible flow" averaged 172 cc. There were seven cases with blood urea between 100 and 250 mg. per cent. One had periarteritis, two chronic pyelonephritis, and four severe renal arteriosclerosis, with scarred and shrunken kidneys. The possible flow in these cases averaged 435 cc. per minute. The fastest flow in this group is about the same as the slowest flow in the hypertensives, but uremics with chronic renal disease obviously have much lower possible rates of blood flow, on the average, than even elderly hypertensives (Fig. 2).

DISCUSSION

Aside from Kimmelstiel's (2) mention of the fact that normal kidneys from patients under 40 years old all gave flows of 250 to 400 cc. saline per minute, while older ones ranged from 110 to 400 cc., the literature on renal perfusion does not mention an age correlation with vascularity of the kidney. Moore (8) has recorded a decline in total glomeruli per kidney of 8.5 per cent in persons of the 45 to 60 year group as contrasted with the 18 to 35 year group. But in perfusion of the kidney with kerosene it is apparent that the vascular bed decreases about one-fourth between maturity and late middle age in the average person. The same decrease also is seen in the renal blood flows of normal men, calculated from diodrast clearance (4) and in the heart, perfused with kerosene (9). Some individuals do not show any reduction in vascular bed even at 70 or 80; they are like the men who pass three score and ten with no bald spots and few grey hairs. After 60 there seems to be little decrease in blood flow per gram of kidney in normal people, although decrease in kidney weight becomes quite striking in senility.

As in previous studies in which the large renal arteries were studied by roent-

genograms and histologic study after an injection mass had set at arterial pressure, significant atherosclerotic narrowing of large renal arteries was uncommon in this series of cases. In a fairly large proportion significant narrowing probably occurs late in hypertension as a result of atherosclerosis and hemorrhage in plaques, the latter accident perhaps being related to the hypertension. Observations based on renal arteries constricted by rigor or fixation have led to wholly erroneous estimates of the frequency of significant narrowing (6). In vessels not fixed while distended at arterial pressure even a small plaque seems to obstruct the lumen.

So far as the relation of renal arteriosclerosis and reduced vascular bed to arterial hypertension is concerned, our results agree essentially with the classical studies of Kimmelstiel (2), whose careful histological correlations we have not repeated. Uremic patients with hypertension have very much slower rates of flow, on perfusion after the kidney has passed out of rigor, than do non-uremic hypertensives. In Kimmelstiel's work the average normal flow, at 140 mm. Hg, was 231 cc. per minute, the average in hypertensives ranged from 199 in the group with no arteriolar sclerosis to 175 in those with marked arteriolar sclerosis but none of the pathological stigmata of "malignant sclerosis." In those with such stigmata, the flow, as in those with the clinical features of "malignant sclerosis," averaged just over 50 cc., those with chronic glomerulonephritis just below 50 cc. While our absolute values are very different, the trend is similar, and contrary to the findings of Christian, Schlesinger, and Myers (3), who apparently perfused kidneys immediately post-mortem, probably before rigor had passed off, and found little difference between uremic and non-uremic hypertensives.

On the whole the results of renal perfusion indicate that hypertension frequently occurs without any significant reduction in the vascular bed, and not infrequently with a vascular bed potentially as capacious as that of a young adult. The average resistance to flow through the renal tissue of such hypertensives is only 20 per cent greater than in normal individuals, but this is due to the fact that old hypertensives have more renal vascular disease than comparable controls (producing in our material a perfusibility 32 per cent lower in the hypertensives over 60), and even at early ages a few hypertensives have kidneys with marked vascular change and reduced capacity for flow. We interpret the evidence, in the light of other observations and particularly the phenomena encountered in experimental renal hypertension, as indicating that hypertension may accelerate and initiate degenerative changes in the retinal and renal arterioles, and to lesser degree changes in larger vessels and other organs. Therefore much more severe vascular changes and greater reduction in vascular bed will be observed in some hypertensives than in any normal individuals. Of particular interest were two pedigreed hypertensives, always showing levels of 200/120 or higher over more than 10 years, who had prac-

tically normal kidneys and renal vessels, and capacity for flow in the upper normal range. In other words hypertension is usually not associated with renal arterial disease at its onset, and is usually not accompanied by significant reduction in renal vascular bed. It can, and often does cause renal arteriosclerosis to progress to the point where the vascular bed is narrow and uremia begins, but it may exist for years without affecting these vessels. While the kidneys may play a part in all cases of hypertension, it is only in a small group that renal disease, usually inflammatory, is the primary process.

SUMMARY

By using kerosene and avoiding postmortem rigor one can obtain perfusion rates in kidneys nearly five times faster than those reported by observers who perfused kidneys immediately post mortem with saline solution, only half as viscous as kerosene.

The results obtained by kerosene perfusion indicate possible renal blood flow 50 to 100 per cent greater than that measured by Smith and his coworkers (7) in living men by diodrast clearance under normal conditions, and about as high as those observed in febrile subjects. Like the diodrast method, kerosene perfusion shows a striking decrease in renal vascular bed between early maturity (age 18 to 35) and senescence (45 to 60). This decrease is about 25 per cent.

Most kidneys from patients with hypertension without uremia have vascular beds in the normal range, but a few show great decreases in capacity for blood flow. This evidence is interpreted as another indication that renal arteriosclerosis is often a result, rarely a cause of hypertension. Significant occlusion of large renal arteries is rare.

Uremia due to amyloid may occur with no significant decrease in renal vascular bed, but the uremia of renal sclerosis, glomerulo- or pyelonephritis is associated with reduction of vascular bed to very low levels.

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