Renal Distribution Volumes of Indocyanine Green, [^{51}Cr]EDTA, and ^{24}Na in Man during Acute Renal Failure after Shock

IMPLICATIONS FOR THE PATHOGENESIS OF ANURIA

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ABSTRACT The mechanism responsible for the anuria in acute renal failure after shock is still controversial. Suppressed glomerular filtration and/or tubular back-diffusion of the filtrate are major possible causes. In the present investigation, seven patients with acute anuria, three of these seven again in the polyuric phase, six patients with moderate renal impairment, four patients with chronic renal failure, and eight subjects with normal renal function were studied by a multiple indicator-dilution method in which the total renal blood flow and renal distribution volumes of indocyanine green, [^{51}Cr]EDTA, and ^{24}Na were determined. In normal subjects the average values for one kidney were 582 ml/min, 42 ml, 92 ml, and 139 ml, respectively. The measurements in the patients with moderate renal impairment were similar to those in the normal subjects, but were decreased in chronic renal failure. In acute anuria, the average values were 269 ml/min, 40 ml, 101 ml, and 114 ml and the kidney volume, estimated radiographically, was increased by 40%. When expressed as milliliters per milliliters kidney, the average distribution volume of ^{24}Na was decreased from 0.64 to 0.38. This decrease is consistent with the hypothesis that suppressed filtration is largely responsible for the anuria and that back-diffusion is, at most, a contributory factor. The apparent contradiction between the relatively well-preserved total blood flow and the suppressed filtration may be due to a combination of afferent vasoconstriction and efferent vasodilatation. This view is supported by the observation that low filtration fractions were found in clearance measurements performed during the polyuric phase.

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INTRODUCTION

The pathogenesis of acute renal failure after shock is still controversial. Renal ischemia, suppressed glomerular filtration, tubular obstruction, interstitial edema, and back-diffusion of tubular fluid are the alternative causative mechanisms which have been proposed most frequently. The possible importance of renal vasoconstriction was first suggested more than 20 yr ago by van Slyke and his co-workers (1, 2), Trueta, Barclay, Daniel, Franklin, and Pritchard (3), and Bull, Joekes, and Lowe (4), although at that time there was no reliable method to measure renal blood flow in anuric subjects, and thus no direct evidence to support the hypothesis. However, the subsequent development of gas diffusion (5), indicator-dilution (6, 7), and isotope washout techniques (8) made it possible to obtain satisfactory estimates of the total, and indeed, the cortical renal circulations. The total renal blood flow (RBF)¹ was found reduced in anuria to between one-fourth and one-half of normal and the cortical flow was decreased more than the total flow (5-7, 9-12). At present several investigators believe that cortical ischemia is entirely responsible for the development of anuria (9, 13, 14).

The results from more detailed investigations of acute renal failure in animals are conflicting. The data from several studies are consistent with the concept of suppressed filtration (13-15), whereas other results suggest that the urine formed by glomerular filtration is entirely reabsorbed by the tubules (16-21). Unfortunately, most of the models used to produce acute renal

¹Abbreviations used in this paper: DV, distribution volume; MTT, mean transit time; PAH, para-amino hippurate; RBF, renal blood flow; VV, vascular volume.

FIGURE 1 Renal indocyanine green-dilution curve (F) from a subject with normal renal function. Below, the recirculation wave recorded from the contralateral kidney (R). Three methods of analyzing the dilution curves and corresponding MTT's are shown: (a) exponential extrapolation, (b) subtraction of the recirculation wave, (c) oblique base line.

failure in animals bear little resemblance to the human type of shock anuria. Injections of glycerol, mercuric chloride, and uranium nitrate usually result in severe tubular necrosis and these changes are more comparable to the lesions of toxic nephropathy in man.

The purpose of the present investigation was to obtain additional knowledge about the glomerular filtration in patients with acute renal failure after shock. A multiple indicator-dilution technique was used to determine the RBF and the distribution volumes (DV) of indocyanine green, ^{51}Cr EDTA, and ^{24}Na in patients with normal renal function, acute anuria, and other types of acute and chronic renal diseases.

METHODS

Seven patients in the anuric stage of acute renal failure after shock were studied and three of them were reinvestigated in the polyuric phase. The cause of renal failure was postoperative shock in two patients, bleeding after surgery in two, severe trauma in one, intravascular coagulation in one, and peritonitis in one. No case of toxic nephropathy was included in the present series. For comparison, the same procedure was performed in eight subjects with normal renal function, in six with renal disease without severe excretory failure (serum creatinine less than 2.0 mg/100 ml), and in four with chronic renal failure (serum creatinine between 3.6 and 11.8 mg/100 ml). All 25 subjects were in reasonably good general condition and had stable blood pressures. Informed consent was obtained for the above procedures.

Catheters were introduced transfemorally and placed in one renal artery and the ipsilateral renal vein by means of the Seldinger technique. Good visualization was assured by the use of an image amplifier, and the positions of the catheters were considered satisfactory when their tips appeared to lie in the main stems of the vessels. The catheters were kept open between indicator injections by means of slow constant infusions of isotonic saline solution with added heparin.²

Renal vein blood was withdrawn at a constant rate by a Harvard pump (Harvard Apparatus Co., Millis, Mass.), usually at 25 ml/min, first through a scintillation detector³ and then immediately through a photoelectric cuvette.⁴ After starting withdrawal, and when the dye and radioactive base lines were stabilized, 2 ml of an indicator solution were injected from a calibrated syringe into the arterial catheter during 1–2 s. The two different indicator solutions contained approximately 0.1% indocyanine green (Cardio-Green) and 1.5–2.5 mCi/100 ml ^{51}Cr EDTA⁵ or 0.5–0.7 mCi/100 ml ^{24}Na ⁶ in aqueous solvent. The injectate remaining in the catheter was not rinsed into the patient, and its volume of 0.7–0.8 ml was exactly measured after each experiment and subtracted from the amount delivered from the calibrated syringe in calculating the flow.

In general, three pairs of simultaneously recorded indocyanine green and ^{51}Cr EDTA curves were first obtained. Calibration was then done according to the method described by Sparling (22) for the measurement of cardiac output in which blood was withdrawn at the same rate used for determining RBF, and a calibrated amount of the indicator solution (0.02–0.08 ml) was injected into the sampling system. Four pairs of calibration curves were usually recorded. Next, three pairs of simultaneous indocyanine green and ^{24}Na dilution curves were obtained and calibrated in the same manner.

In 13 of the procedures, after the above curves were recorded, the tip of the venous catheter was subsequently placed in the contralateral renal vein. Two additional pairs of dilution curves were then obtained using the indocyanine green and ^{24}Na solution and were considered to represent recirculation of the indicators. Finally, in every anuric subject before the catheters were removed one of several vasodilating drugs was injected into the renal artery (hydralazine, phentolamine, mannitol, or procaine hydrochloride). Diuresis did not occur in any patient.

Total RBF. Total RBF was calculated by comparing the surfaces obtained by planimetry of the indocyanine green experimental curves with the calibration curves. With reference to the experimental curves the main problem was to exclude recirculating dye from the measurements. The narrow, "fast" curves from subjects with normal renal function have a characteristic shape (Fig. 1). That is, as the exponential downslope approaches the preinjection base line, a second wave becomes clearly apparent and the tracing does not return to the base line for a relatively

² Liqueimine, Hoffmann-La Roche Inc., Nutley, N. J.

³ A Packard NaI-Scintillation crystal (Packard Instrument Co., Inc., Downers Grove, Ill.) specially designed for this purpose, with a Tri-carb scintillation spectrometer model 3001.

⁴ A Waters densitometer D-400 (Waters Instruments, Inc., Rochester, Minn.) coupled with a G-2000 Varian recorder (Varian Aerograph, Walnut Creek, Calif.).

⁵ Farbwerke Hoechst AG, Frankfurt, West Germany.

⁶ Eidgenössisches Institut für Reaktorforschung, Würenlingen, Switzerland.

long time. This second wave may represent the sum of recirculating dye and that from the slow medullary blood flow. In previous studies we attempted to reduce the influence of the recirculating indicator on the surface calculation by drawing an oblique base line between the pre- and postinjection levels (6, 12). Other investigators ignored the second wave and simply extrapolated the exponential downslope to 1% of the curve's peak height (23-26). A better way is probably to subtract the recirculation wave recorded from the contralateral vein, which yields values that are between those from the two other methods. The broad, "slow" curves from subjects with reduced renal blood flow do not exhibit a clear second wave, but the last third of the downslope smoothly departs from the exponential tracing and also remains above the preinjection base line for a long time. In such cases the three methods yield comparable results (Fig. 2). In the present study the recirculation wave was subtracted whenever it was recorded, and in the remaining cases the exponential downslope was extrapolated to 1% of the curve's peak height. The total renal blood flow, in one kidney, was calculated from Sparling's equation (22):

$$F = \frac{I \cdot s \cdot f}{S \cdot i}$$

in which F = renal blood flow (ml/min), f = flow through the recording system (ml/min), I = quantity of indicator solution injected into the renal artery (ml), i = quantity of indicator solution used for calibration (ml), S = area of the corrected flow curve (cm^2), and s = area of the calibration curve (cm^2).

The ^{51}Cr EDTA and ^{24}Na curves were treated similarly, that is corrections for recirculating indicator and the patients' increasing radioactive backgrounds were estimated by one of the two methods applied to the dye curves. This was particularly important in the case of ^{24}Na , since the postinjection levels were always significantly elevated (Fig. 3). Sparling's formula (22) was also applied to these curves, but, as the isotopes were incompletely recovered, the calculated flows were necessarily virtual. If it is assumed that the recovery of indocyanine green was 100%, the recovery (R) of the other indicators is expressed in the equations:

$$R^{24}\text{Na} (\%) = \frac{100 \cdot F_{\text{Indo}}}{F^{24}\text{Na}},$$

and

$$R_{[^{51}\text{Cr}]\text{EDTA}} (\%) = \frac{100 \cdot F_{\text{Indo}}}{F_{[^{51}\text{Cr}]\text{EDTA}}}.$$

The average $R^{24}\text{Na}$ for the whole series was 93%, and the average $R_{[^{51}\text{Cr}]\text{EDTA}}$ was 83%. In the anuric patients these values were 88 and 89%, respectively. In the remaining subjects $R_{[^{51}\text{Cr}]\text{EDTA}}$ was less than $R^{24}\text{Na}$, because the fraction of $[^{51}\text{Cr}]\text{EDTA}$ filtered by the glomeruli was not reabsorbed by the tubules and did not appear in the renal venous blood.

It is noted that the plasma clearance (C) of $[^{51}\text{Cr}]\text{EDTA}$, which approximates the glomerular filtration rate (27), can be estimated from its rate of recovery:

$$C_{[^{51}\text{Cr}]\text{EDTA}} = F_{\text{Indo}} \left(1 - \frac{F_{\text{Indo}}}{F_{[^{51}\text{Cr}]\text{EDTA}}} \right) (1 - \text{Hct}).$$

FIGURE 2 Renal indocyanine green-dilution curve and recirculation wave from a patient with acute renal failure. Methods of analyzing the dilution curve and symbols as in Fig. 1.

Mean transit time (MTT). MTT of the three indicators was estimated by replotting the corrected curves on thick paper and finding their center of gravity. The apparent MTT was corrected for the delay of the indicators in the sampling system by simply calculating the volume/flow relationships in the catheter between its tip and the scintillation detector and cuvette densitometer (28). These volumes usually were about 3.0 and 3.5 ml, respectively. No additional effort was made to correct for distortions of the curves caused by other hydraulic factors in the sampling system. The frequency-response characteristics of

FIGURE 3 Renal ^{24}Na -dilution curve and recirculation wave from a subject with normal renal function. Exponential extrapolation (a) and subtraction of the recirculation wave (b) yield similar surfaces and MTT.

TABLE I
Renal Blood Flow and Distribution Volumes of Indocyanine Green, [⁵¹Cr]EDTA, and ²⁴Na
in Eight Subjects with Normal Renal Function

Patient	Renal blood flow (F _{Indo})	Indocyanine green		[⁵¹ Cr]EDTA		²⁴ Na		Volume ratios		
								[⁵¹ Cr]EDTA	²⁴ Na	²⁴ Na
		MTT	DV	MTT	DV	MTT	DV	Indo	Indo	[⁵¹ Cr]EDTA
	ml/min	s	ml	s	ml	s	ml			
1. S. B.	725	4.3	52	12.0	143	17.1	206	2.75	3.95	1.44
2. He. Wa.	756	3.9	49	7.8	98	10.9	137	2.0	2.79	1.4
3. Ha. Wu.	646	4.4	47	8.2	86	13.6	145	1.83	3.09	1.69
4. M. P.	581	5.9	57	12.6	122	17.8	172	2.14	3.03	1.41
5. M. O.	534	3.9	35	6.0	53	9.7	87	1.52	2.49	1.64
6. J. G.	510	3.8	32	8.9	76	13.8	118	2.36	3.70	1.55
7. E. A.	490	5.0	41	10.7	87	16.2	132	2.13	3.21	1.52
8. A. E.	414	3.3	23	10.7	74	16.2	112	3.21	4.87	1.51
Mean	582	4.3	42	9.6	92	14.4	139	2.2	3.35	1.51
SE	111	0.76	10.7	2.1	26.8	2.8	34.5	0.49	0.71	0.1
Coefficient of variation (%)	19		27		30		25	22	21	7

The values refer to one kidney.

MTT, mean transit time; DV, renal distribution volume.

the Waters-Varian recording system used here make it unlikely that the dye-dilution curves were distorted by these apparatus. However, to reduce the amounts of the isotopes injected, the radioactive detection equipment was operated at a high level of sensitivity. At this level, it was necessary to set the time constant of the rate meter at 3 s to obtain usable smooth curves. The effect of this damping was estimated by comparing simultaneously recorded dye and isotope calibration curves, and as a result, an average time of 2 s was subtracted from the MTT of all [⁵¹Cr]EDTA and ²⁴Na curves.

DV. The DV of the three indicators was calculated from the following equations:

$$DV_{\text{Indo}} = \frac{F_{\text{Indo}} \cdot \text{MTT}_{\text{Indo}}}{60},$$

$$DV_{[\text{Cr}]\text{EDTA}} = \frac{F_{\text{Indo}} \cdot \text{MTT}_{[\text{Cr}]\text{EDTA}}}{60},$$

$$DV_{^{24}\text{Na}} = \frac{F_{\text{Indo}} \cdot \text{MTT}_{^{24}\text{Na}}}{60}.$$

Volume of the kidney. Kidney volume was estimated radiographically in all patients with acute renal failure and in seven of the eight normal subjects. The area of the renal shadow was measured by planimetry on plain films, tomograms, urograms, or angiograms and multiplied by three-fifths of its maximal breadth. Corrections were made for the effects of projection. Despite the geometrical simplifications involved in this method it is probable that it yields a volume which closely approximates that of the kidney itself, the main renal vessels and the small amount of adjacent tissues supplied by the renal artery. This is supported by the results from the normal subjects in whom the mean was 215 ml, and thus only slightly above the value

of 180 ml estimated as the in vivo volume of the human kidney by Effros, Lowenstein, Baldwin, and Chinard (25). The DV of indocyanine green and inulin measured by these authors were less than those reported here, but when they are expressed as milliliters per milliliters of kidney, 0.19 and 0.39 ml, respectively, they are nearly identical with the normal means presented in Table V. It would seem, therefore, that the method used in the present investigation permits reliable comparison between normal and anuric subjects.

All flows, DV's, and kidney volumes reported here refer to one kidney and a body surface area of 1.73 m².

Reproducibility. The reproducibility of the indicator-dilution curves was satisfactory. Although the areas of consecutive curves from a patient varied somewhat, presumably reflecting rapid changes in renal circulation (25), when the means of the two sets of indocyanine green curves recorded in each patient were compared the coefficient of variation was low. In a series of 18 pairs of determinations of RBF (normal subjects and patients with acute renal failure), the SE of the differences was 29.8 ml/min, the mean RBF was 428 ml/min, and the coefficient of variation was 7%. The variation of the isotope tracings was not greater than that of the dye curves. Consecutive dye and isotope calibration curves agreed within 5%.

RESULTS

The eight subjects with normal renal function had renal blood flows (RBF, F_{Indo}) between 414–756 ml/min, with an average of 582 ml/min (Table I). The vascular volume (VV) was 23–57 ml, and averaged 42 ml (Fig. 4). The average and range of the distribution volumes of [⁵¹Cr]EDTA and ²⁴Na were 92 ml, 53–143 ml, and 139 ml, 87–206 ml, respectively. The average DV ratio ²⁴Na/[⁵¹Cr]EDTA was 1.51 and varied between

1.14 and 1.69 (Fig. 5). The MTT's of the three indicators are shown in Table I.

The measurements from the six patients with renal disease, who did not have severe impairment of the renal function, are presented in Table II. In patient 1, who had acute glomerulonephritis, the RBF and the three DV's were increased. In patients 2 and 3 the RBF was normal, and it was slightly decreased in patients 4, 5, and 6. The DV's were within the normal range in patients 2-6. The volume ratio $^{24}\text{Na}/[^{51}\text{Cr}]\text{EDTA}$, in this group, varied between 1.34 and 1.82.

In the four patients with chronic renal failure (Table III), the RBF was reduced to 110-261 ml/min, and averaged 197 ml/min (Fig. 4). The MTT of the three indicators were increased, but the average DV of each was reduced. The average decrease in DV ^{24}Na was greater than in DV $^{51}\text{Cr}]\text{EDTA}$, so that the average volume ratio $^{24}\text{Na}/[^{51}\text{Cr}]\text{EDTA}$ was reduced to 1.29 (Fig. 5).

The data for the seven anuric patients with acute renal failure after shock are presented in Table IV and Figs. 4 and 5. The average RBF was reduced to 269 ml/min, and varied between 79 and 530 ml/min. The averages and ranges of the DV's were for indocyanine green 40 ml, 23.5-57 ml, for $^{51}\text{Cr}]\text{EDTA}$ 101 ml, 60-178 ml, and for ^{24}Na 114 ml, 78-185 ml. The MTT of the three indicators were markedly prolonged. The volume ratio $^{24}\text{Na}/[^{51}\text{Cr}]\text{EDTA}$ was below the lower limit of the normal range in all patients, and varied between 1.04 and 1.3, with an average of 1.13.

Patients X. R., E. S., and C. T. were studied again during the polyuric phase, when the blood urea nitrogen was almost normal (Table IV). At this time, the RBF and the three DV's especially the DV ^{24}Na , were greater compared with the initial investigations. The volume

FIGURE 4 RBF and VV in eight normal subjects (N), four patients with chronic renal failure (CN), seven patients with acute renal failure in the anuric phase (ARF, A), and three of them in the polyuric phase (ARF, P).

ratio $^{24}\text{Na}/[^{51}\text{Cr}]\text{EDTA}$ also increased from 1.08 to 1.3, from 1.1 to 1.46, and from 1.05 to 1.44, respectively.

The average and range of the estimated renal volumes were in seven normal subjects 215 ml, 158-262 ml, in the anuric patients 302 ml, 223-360 ml, and in the polyuric patients 308 ml, 225-415 ml. Because of the marked increase of the renal volume in patients with acute renal failure the DV's were expressed as milliliters per milliliters kidney in these patients and in the normal subjects, and are presented in Table V and Fig. 6. Compared with normal values, the DV's in anuria of indocyanine green decreased from 0.19 to 0.13 ml/ml kidney, of $^{51}\text{Cr}]\text{EDTA}$ from 0.42 to 0.34 ml/ml kidney, and of ^{24}Na from 0.64 to 0.38 ml/ml kidney.

The scatter of the DV's in Tables I and IV, and of the RBF in anuric patients is considerable, so that the coefficients of variation are large. The differences be-

FIGURE 5 Renal DV's of $^{51}\text{Cr}]\text{EDTA}$ and ^{24}Na , and $^{24}\text{Na}/[^{51}\text{Cr}]\text{EDTA}$ volume ratios in normal subjects and patients with chronic and acute renal failure. Symbols as in Fig. 4.

TABLE II
Renal Blood Flow and Distribution Volumes in Six Cases of Renal Disease without Excretory Failure

Patient	Diagnosis	Renal blood flow (F_{Indo})	Indocyanine green		[^{51}Cr]EDTA		^{24}Na		Volume ratios		
									$\frac{[\text{Cr}] \text{EDTA}}{\text{Indo}}$	$\frac{^{24}\text{Na}}{\text{Indo}}$	$\frac{^{24}\text{Na}}{[\text{Cr}] \text{EDTA}}$
			MTT	DV	MTT	DV	MTT	DV			
		<i>ml/min</i>	<i>s</i>	<i>ml</i>	<i>s</i>	<i>ml</i>	<i>s</i>	<i>ml</i>			
1. R. C.	Acute glomerulonephritis with nephrotic syndrome	1100	3.2	58	9.9	181	13.7	250	3.1	4.32	1.38
2. H. E.	Acute glomerulonephritis	598	3.8	38	7.3	73	10.3	103	1.92	2.7	1.41
3. M. F.	Chronic glomerulonephritis	558	5.9	55	13.3	123	20.0	185	2.24	3.36	1.5
4. N. Z.	Chronic glomerulonephritis	392	5.2	34	10.4	68	16.5	107	2.0	3.14	1.58
5. M. S.	Chronic glomerulonephritis	381	4.9	31	10.9	69	14.5	92	2.23	2.97	1.34
6. P. M.	Essential hypertension	442	5.2	39	12.1	89	22.1	162	2.28	4.16	1.82

tween the anuric and normal groups, by the t test, are statistically significant only for the RBF, $P < 0.001$, and for the $^{24}\text{Na}/[\text{Cr}] \text{EDTA}$ DV ratio, $P < 0.001$. The polyuric and normal groups differ significantly only with respect to the RBF, $P < 0.025$. The Wilcoxon test disclosed no more significant differences than the t test. In contrast, in Table V, despite the large coefficients of variation, there are more instances of statistically significant differences between the anuric and normal subjects. In the former group the estimated renal volume is increased, $P < 0.0025$, and the VV and DV ^{24}Na are decreased, $P < 0.025$ and $P < 0.005$, respectively. In polyuria, only the estimated renal volume differs significantly from the normal value, $P < 0.025$.

DISCUSSION

The reliability of the indicator-dilution technique for the measurements of total RBF and renal transit time has been discussed in detail elsewhere (12, 23–25, 29). In the present study, since relatively high RBF's were found in some patients with acute anuria, it would seem relevant to consider whether this was the result of an overestimation due to errors of the dye-dilution method. It has been observed that indocyanine green does not strictly obey Beer's law (30), and that the rate at

which it increases its optical density in blood to a stable level is considerably slowed at room temperature (31). These limitations would not seem to explain the relatively high flows found in some anuric patients. The use of Sparling's method with calibration and patient's renal curves of approximately the same height strongly minimizes errors due to deviations from Beer's law. Also, any temperature effect which might possibly have produced erroneous low optical densities in the calibration curves would have, indeed, led to an underestimation of the renal flows. Finally, in anuria, flows calculated from the dye were somewhat lower than the values obtained with the other two indicators.

Another possible cause of overestimation of flow could be the regurgitation of indicators into the aorta, especially when large volumes were delivered rapidly into patients with markedly reduced RBF. In the present study an attempt was made to avoid this possibility by injecting a small amount of indicator during a relatively long period of 1–2 s. Since low flows were found in all the patients with chronic renal failure (Table III), it is unlikely that regurgitation was a significant factor in the patients with acute anuria. Still another cause of error might be trapping of indicators within the kidney. In the case of indocyanine green it is known that the

TABLE III
Renal Blood Flow and Distribution Volumes in Four Patients with Chronic Renal Failure

Patient	Serum creatinine	Renal blood flow (F_{Indo})	Indocyanine green		[^{51}Cr]EDTA		^{24}Na		Volume ratios		
									$\frac{[\text{Cr}] \text{EDTA}}{\text{Indo}}$	$\frac{^{24}\text{Na}}{\text{Indo}}$	$\frac{^{24}\text{Na}}{[\text{Cr}] \text{EDTA}}$
			MTT	DV	MTT	DV	MTT	DV			
	<i>mg/100 ml</i>	<i>ml/min</i>	<i>s</i>	<i>ml</i>	<i>s</i>	<i>ml</i>	<i>s</i>	<i>ml</i>			
1. J. M.	11.8	261	12.6	55	26.0	113	31.7	138	2.07	2.52	1.22
2. H. Z.	3.6	232	8.7	34	23.3	90	30.5	118	2.65	3.5	1.27
3. P. J.	4.8	184	7.4	23	19.4	59	28.7	87	2.55	3.88	1.48
4. B. V.	11.0	110	8.0	15	30.3	55	34.0	63	3.66	4.25	1.13
Mean	—	197	9.2	32	24.8	79	31.2	102	2.46	3.18	1.29

TABLE IV
*Renal Blood Flow and Distribution Volumes in Seven Patients with Acute Renal Failure after Shock,
and in Three of them during the Polyuric Phase*

Patient	Cause of renal failure	Stage of disease*	Days after onset	Blood pressure	Renal blood flow (F _{Indo})	Indocyanine green			["Cr]EDTA			Volume ratios		
						MTT	DV	ml	MTT	DV	ml	["Cr]EDTA Indo	²² Na Indo	²² Na ["Cr]EDTA
1. B. B.	Hemorrhage	A	4	142/65	530	6.5	57	ml	15.5	137	ml	2.4	2.9	1.2
2. P. F.	Intravascular coagulation	A	7	150/110	314	10.7	56		34.0	178		3.17	3.3	1.04
3. M. B.	Hemorrhage	A	6	150/80	273	6.0	27		13.2	60		2.22	2.88	1.3
4. X. R.	Trauma	A	5	174/110	250	10.9	45		22.8	95		2.1	2.28	1.08
X. R.		P†	38	127/70	505	7.8	65		19.5	163		2.5	3.25	1.3
5. E. S.	Abdominal surgery	A	6	120/75	250	5.6	23.5		17.1	72		3.05	3.37	1.1
E. S.		P§	28	120/80	362	4.7	29		16.2	97		3.35	4.9	1.46
6. I. G.	Abdominal surgery	A	8	125/72	180	10.3	31		28.0	84		2.72	3.15	1.16
7. C. T.	Peritonitis	A	9	130/82	79	31.2	41		65.9	86		2.1	2.2	1.05
C. T.		P	44	120/80	378	8.4	53		21.0	131		2.5	3.6	1.44
Mean (anuria)					269	11.6	40		28.1	101		2.52	2.78	1.13
SE					122	8.3	12.5		16.6	38.5		70.415	0.44	0.08
Coefficient of variation (%)					48	31	38		35	16		16	16	7
Significance of differences from normal values					P < 0.001	P > 0.3			P > 0.3			P > 0.1		
Mean (polyuria)					415	7.0	49		18.9	130		2.66	3.7	1.38
SE					78	1.6	18.3		2.1	33		0.51	0.9	0.09
Coefficient of variation (%)					19	37	25		20	19		19	24	6
Significance of differences from normal values					P < 0.025	P > 0.2			P > 0.05			P > 0.15		

* A, anuria; P, polyuria.

† Inulin clearance on the 40th day, 37 ml/min.

§ Inulin clearance on the 30th day, 68 ml/min.

|| Inulin clearance on the 46th day, 46 ml/min.

TABLE V
Estimated Renal Volume, and Distribution Volumes Expressed as ml/ml Kidney in Seven Normal Subjects
and in Seven Patients with Acute Renal Failure

Diagnosis	Patient	Estimated kidney volume ml	Distribution volumes (ml/ml kidney)		
			Indocyanine green	[⁵¹ Cr]EDTA	²⁴ Na
Normal subjects	1. S. B.	226	0.23	0.63	0.91
	2. Ha. Wu.	262	0.18	0.33	0.55
	3. M. P.	212	0.27	0.57	0.81
	4. M. O.	158	0.22	0.34	0.55
	5. J. G.	190	0.17	0.4	0.62
	6. E. A.	240	0.17	0.36	0.55
	7. A. E.	220	0.11	0.34	0.51
	Mean	215	0.19	0.42	0.64
	SE	31	0.048	0.114	0.143
	Coeff. of var.*	14	31	27	23
Patients with acute renal failure.	1. B. B.	321	0.18	0.43	0.51
	2. P. F.	300	0.19	0.59	0.62
	3. M. B.	223	0.12	0.27	0.35
	4. X. R.	295	0.15	0.32	0.35
Anuria	5. E. S.	305	0.08	0.23	0.26
	6. I. G.	312	0.1	0.27	0.31
	7. C. T.	360	0.11	0.24	0.25
	Mean	302	0.13	0.34	0.38
	SE	38	0.039	0.121	0.127
	Coeff. of var.*	13	30	35	33
	Significance†	$P < 0.0025$	$P < 0.025$	$P > 0.05$	$P < 0.005$
Patients with acute renal failure.	4a. X. R.	285	0.23	0.57	0.74
	5a. E. S.	225	0.13	0.43	0.63
	7a. C. T.	415	0.13	0.32	0.45
Polyuria	Mean	308	0.16	0.44	0.61
	SE	97	0.057	0.125	0.146
	Coeff. of var.*	31	35	28	24
	Significance†	$P < 0.025$	$P > 0.2$	$P > 0.35$	$P > 0.35$

* Coefficient of variation (%).

† Significance of differences from normal values.

renal parenchyma retains some of the dye, but the fraction is small and would not lead to a significant overestimation of the flow (12). Finally, there is no obvious reason to assume that in anuria after shock more indocyanine green circulates extravascularly than normally. If this occurred and impaired recovery of the dye, it would result in comparable overestimations of RBF, DV [⁵¹Cr]EDTA, and DV ²⁴Na. If the extravascular dye returned to the renal vein during the recording period, only VV would be overestimated.

The accurate measurement of RBF and MTT assumes that the method of excluding recirculating indicator is correct. It was previously indicated, in Methods, that this was not a serious problem with the broad [⁵¹Cr]-

EDTA and ²⁴Na curves from all the patients, or with the indocyanine green curves from patients with anuria or chronic renal failure. Under these circumstances all three of the methods used to exclude the recirculating indicators yielded comparable results, which may well represent the total RBF. However, in the narrower dye-dilution curves from normal subjects it is often difficult to define clearly the different components of the last part of the downslope. In the present study, the exponential extrapolation method was used, whenever the recirculation wave had not been recorded separately. It is clear that, if the later parts of the curves are excluded from the surface calculations, the total flow is overestimated by 5-10%. But this method also reduces

FIGURE 6 Renal DV's of indocyanine green, ^{51}Cr EDTA, and ^{24}Na expressed as milliliters per milliliters kidney in normal subjects and in patients with acute renal failure. Symbols as in Fig. 4.

MTT to an even greater extent, so that the calculated VV is less than the true total VV and somewhat larger than the cortical VV. It is for this reason that the values reported here for normal subjects are less than those which we reported previously (12) and more comparable with those found by others (25, 32).

Accurate measurement of fluid spaces by the indicator-dilution method requires that various conditions are fulfilled: flow has to be constant, with no stagnant pools and no recirculation, and the traversal time for the indicator particles must be the same as for fluid particles (23, 33, 35). In the case of indocyanine green it is probable that these requirements are met, but in the case of extravascular tracers this is far from certain. Let us first consider what the DV's of the three indicators used here may represent in normal subjects.

Indocyanine green is bound to plasma proteins. Therefore, although a small fraction of the proteins may leave the vessels in the renal medulla, the distribution volume of the dye can be accepted as the renal VV. Since the tips of the two catheters lay in the main renal vessels, the VV reported here includes volumes from parts of the renal vein and artery in addition to that from the intrarenal vessels.

^{51}Cr EDTA is assumed to have similar characteristics to inulin as its clearance is 94% of the glomerular filtration rate (27). We chose it because it is more stable than the radioactive iodine-labeled inulins presently available. Thus, the DV of ^{51}Cr EDTA includes the VV and probably a large part of the interstitial spaces. The fraction which is filtered by the glomeruli escapes tubular reabsorption and is excreted with the urine. As this fraction does not reappear in the renal vein, the tubular system does not participate in the DV of the indicator.

^{24}Na circulates intravascularly, is distributed in the interstitial spaces, and a fraction is filtered by the glomeruli. However, in contrast to ^{51}Cr EDTA, most of the filtered sodium is reabsorbed, and this takes place rapidly: 90% of the filtered sodium load is reabsorbed in less than 1 min in dogs (34). It would seem reasonable to assume that 90% or more of the filtered sodium is returned to the renal vein within 1 min, and that the DV of ^{24}Na includes a large part of the tubular lumina and intracellular structures concerned with the transport of the ion.

The differences in the rates of diffusion across the capillaries and in the adjacent tissues, as well as inhomogeneity of distribution, probably limit the validity of the measurements of fluid spaces with extravascular indicators. Thus, the DV's ^{51}Cr EDTA and ^{24}Na do not strictly represent anatomical compartments. Nevertheless, there would appear to be adequate justification for using these measurements, since, in normal subjects, the DV's of the three indicators used here have reasonable quantitative relationships to each other, particularly in the instance of the $^{24}\text{Na}/^{51}\text{Cr}$ EDTA ratio.

In the diseased kidney, structural and functional changes are likely to modify the size of the compartments. In chronic renal failure, the most conspicuous alterations are atrophy and replacement of nephrons by connective tissue. Accordingly, in the four patients with chronic renal failure (Table III) there were marked decreases in RBF and DV ^{24}Na and moderate reductions in VV and DV ^{51}Cr EDTA. The DV ratio $^{24}\text{Na}/^{51}\text{Cr}$ EDTA was reduced. These results would be expected, since on the one hand parenchymatous atrophy should lead to reductions of both the ^{24}Na and ^{51}Cr EDTA compartments, and on the other hand replacement of the tubules by connective tissue should permit diffusion of ^{51}Cr -

EDTA into these areas. In contrast to these findings, the DV's of the indicators were not significantly altered in the patients with nephropathies unassociated with marked renal impairment (Table II).

It would seem useful to predict how the two main mechanisms which might be concerned with the development of acute shock anuria, could modify the distribution of the indicators. In the case of ischemia with abolished glomerular filtration, the ^{24}Na should not be filtered, and as it no longer had access to the tubules, its DV would be decreased. On the contrary, if glomerular filtration was preserved and was followed by total reabsorption of tubular fluid, the DV of ^{51}Cr EDTA should increase and approach that of ^{24}Na . Additional factors might be some reductions in all three compartments due to severe vasoconstriction and a parallel increase in DV's ^{51}Cr EDTA and ^{24}Na because of interstitial edema.

In the anuric patients (Table IV), the RBF varied between 79 and 530 ml/min, and the average was 269 ml/min. This was 46% of the value found in normal subjects and the difference was highly significant ($P < 0.001$). These values are in good agreement with those which were reported in a previous study (12). As the MTT of indocyanine green was markedly prolonged, the VV was normal. The average DV ^{51}Cr EDTA was within normal limits, and the individual values ranged between 60 and 178 ml. The average DV ^{24}Na was 18% less than in normal subjects, but as there was a large dispersion of the results, the difference was not statistically significant ($P > 0.1$). The DV ratio $^{24}\text{Na}/^{51}\text{Cr}$ EDTA was markedly decreased to 1.13, compared with 1.51 in normal subjects. Also, the individual values in the anuric patients were all below the lower limit of the normal range of 1.4 to 1.69 (Fig. 5). The difference between the normal and anuric subjects was highly significant ($P < 0.001$).

The obvious reduction in the $^{24}\text{Na}/^{51}\text{Cr}$ EDTA DV ratio could be caused by abolished glomerular filtration, total back-diffusion of tubular fluid, or a combination of both mechanisms, and, therefore, in order to answer this question, it is necessary to consider the "actual size" of the compartments. Unfortunately, although the average DV ^{24}Na was decreased and DV ^{51}Cr EDTA slightly increased, compared with measurements in normal subjects, the changes were not statistically significant. Furthermore, when the individual data are analyzed, five patients had low values of DV ^{24}Na and two (B. B. and P. F.) had values of DV ^{24}Na at the upper range of normal. In the latter two subjects the DV's ^{51}Cr EDTA were well above the mean. This might indicate that in five patients the glomerular filtration was suppressed, and in two subjects tubular lesions permitted some back-diffusion of the filtrate. Both mechanisms might also have occurred in the same subject, since

observations suggesting functional inhomogeneity have been made in anuric rats (36). Nonetheless, the scatter of the DV data is almost as great in normal subjects, so that it does not seem justified to separate two pathogenic subgroups within the anuric patients.

A more promising approach would seem to compare the DV's referred to the kidney size (Table V and Fig. 6). In acute anuria the weight of the kidney is known to increase by at least 30% (37) because of swelling of the proximal tubules and interstitial edema (14, 37-39). In the present study, the estimated renal volumes of the anuric patients were significantly increased and averaged 302 ml. When the DV's are expressed as milliliters per milliliters kidney, they show a definite ($P < 0.005$) reduction of the average DV ^{24}Na , 0.38 ml/ml kidney, compared with the normal value of 0.64 ml/ml kidney. The VV of 0.13 ml/ml kidney is also significantly reduced ($P < 0.025$) from the normal measurement of 0.19 ml/ml kidney, while the DV ^{51}Cr EDTA remains statistically unchanged ($P > 0.05$). Therefore, it would seem that the best explanation for the decrease in the average DV ^{24}Na is that the glomerular filtration was suppressed and ^{24}Na had no access to the tubules. The observation that the average DV ^{51}Cr EDTA is not increased is consistent with this interpretation, and indicates that total reabsorption of the filtrate was not a major factor in these patients. In contrast, in cases of acute toxic nephropathy back-diffusion of the filtrate may play an important role, as suggested by the results obtained by Eisner, Slotkoff, and Lilienfield (19) in dogs intoxicated by uranium nitrate.

The determinations were repeated in three of the patients, when they were in the polyuric phase. These results, compared with those found during anuria, showed that RBF and the three DV's increased in every patient. The striking augmentations of DV ^{24}Na and of the $^{24}\text{Na}/^{51}\text{Cr}$ EDTA DV ratio are consistent with the interpretation that at this stage ^{24}Na was again filtered and reabsorbed. The moderate increase in DV ^{51}Cr EDTA may reflect a similar trend in VV, and increased diffusion into areas with improved blood flow or interstitial edema. At this stage the kidney is still enlarged, so that the DV's expressed as milliliters per milliliters kidney, enter the normal range as does also the $^{24}\text{Na}/^{51}\text{Cr}$ EDTA DV ratio.

The apparent contradiction between the suppressed filtration and the relatively well-preserved RBF in many cases with anuria of shock remains to be explained. Some investigators using the ^{86}Kr washout method found a disproportionate reduction of cortical blood flow and proposed that this might be sufficient to suppress filtration within the renal cortex (9-11). Angiographic studies also revealed a pattern consistent with cortical ischemia (9). However, in anuric patients, whose total

RBF is still one-half or more of normal (cases B. B. and P. F.), it is not certain whether this mechanism entirely accounts for the functional break down. Even if it is assumed that the bulk of flow is diverted to the juxta-medullary glomeruli, these over-perfused glomeruli should form enough urine to prevent anuria.

In this regard it should be mentioned that a diversion of the RBF from the superficial to the deep glomeruli is found not only in shock anuria but also in hypertensive patients receiving a low salt diet (40), in animals with congestive heart failure (41) or with ureteral occlusion (42), and during angiotensin infusions (43). A further difficulty is that in acute renal failure the individual values of RBF during the anuric phase show considerable differences from one patient to another (Table IV), may overlap the figures obtained during the polyuric phase (9-12) and do not correlate with the creatinine clearance (11). Finally, it should be recalled, that so far renal vasodilators have not proved capable of restoring diuresis in established anuria (44 and F. C. Reubi, unpublished observation), although they may increase markedly the RBF in this condition.

We formerly hoped that the dye-dilution method might provide information concerning the intrarenal distribution of blood flow (12). But the reliability of estimations made on this basis is questionable, even when the curves are analyzed by relatively stringent mathematical methods (45). The dye curves from anuric patients are broader than those from normal subjects, and the MTT of the indicator is prolonged. The shape of these curves is similar to the curves from patients with chronic renal failure, but the calculated VV in anuria is not reduced. The above data thus indicate that in anuria total RBF is slow, 'arteriolar' resistance is increased, the capacitance vessels are not constricted, and the intrarenal blood volume is not, or only slightly diminished.

An adequate discussion of the relationship between glomerular blood flow and filtration rate would necessarily assume that the effective filtration pressure in the normal human kidney is known. Unfortunately, estimates of this value vary widely. In the rat direct and indirect measurements have yielded conflicting results (46-48). In man, values between 11 (49) and 25 mm Hg (50) have been proposed. If the filtration pressure is normally low a moderate degree of generalized afferent vasoconstriction could be sufficient to stop filtration (9). If the filtration pressure is normally high, additional efferent vasodilatation would seem necessary to suppress filtration. The combination of afferent vasoconstriction and efferent vasodilatation would be extremely unusual, as it has not been produced by any of the endogenous vasoactive substances so far tested. For instance, administration of catecholamines, angiotensin, and histamine are known to reduce renal flow more than glo-

FIGURE 7 Filtration fractions calculated from 37 simultaneous determinations of the inulin and PAH clearances in 18 patients during the recovery phase of acute renal failure.

merular filtration (51-53). However, in animals subjected to hemorrhagic shock and in which clearance determinations were combined with direct flow measurements, it was shown that after retransfusion of the previously removed blood the inulin clearance remained relatively lower than the para-amino hippurate (PAH) clearance, observations which suggest that efferent vasodilatation occurred (54).

The hypothesis that efferent vasodilatation is concerned with the development of anuria in man has been advanced by others (55, 54), but so far adequate data to support this concept is lacking. The results reported here are consistent with this view. Additional evidence is provided by the results from clearance studies done during the recovery stage of the shock anuria. In the beginning of this period the inulin and the PAH clearances are still very low, and the filtration fraction may sometimes be extremely high, presumably because of impaired tubular secretion, intrarenal storage, or back-diffusion of PAH (4, 55, 57, 58). Obviously, at this stage the clearance results are unreliable (55). However, after the onset of polyuria, clearance studies permit reasonably valid estimation of the renal function, since the PAH extraction ratio is no longer significantly impaired (58). Interestingly, the filtration fraction may be reduced at this time (58-60). 37 measurements of filtration fraction obtained from simultaneous inulin and PAH clearances in 18 patients during recovery from acute renal failure are plotted in Fig. 7, where they are compared with the normal range (mean 0.195, SE 0.019) calculated from a series of 203 subjects without renal disease (58). For statistical analysis, the data from the patients recovering from acute renal failure have been divided into four subgroups: (a) 11 determinations up to the 20th day from onset, (b) 15 between the 21st and the 40th day, (c) 5 between the 41st and the 60th day, and (d) 6 after the 61st day. The means and SE are: (a) 0.144 ± 0.033 , (b) 0.167 ± 0.038 , (c) 0.182 ± 0.025 , and (d) 0.194 ± 0.036 . The *P* values expressing the significance of the differences from the normal are for (a) and (b), $P < 0.001$, for (c), $P > 0.05$ and for (d), $P > 0.4$. Thus, there is

on the average a significant decrease of the filtration fraction during the polyuric phase of acute renal failure with a subsequent trend toward normalization.

A reduced filtration fraction is usually indicative of acute or subacute glomerular nephritis and less frequently of hydronephrosis (58). In the shock kidney, since there are no obvious glomerular changes (38, 39) and tubular obstruction is not believed to play a role, the low filtration fraction probably indicates that the filtration pressure is decreased. It would seem reasonable to assume that the filtration pressure is even lower in the anuric phase.

The hypothesis of afferent vasoconstriction associated with efferent vasodilatation would also account for the failure of renal vasodilators to promote diuresis in anuria, as these substances predominantly cause efferent relaxation (53, 61). This would also be consistent with the rapid reversal of anuria seen in severe hypotension treated with norepinephrine or angiotensin, since these drugs not only restore the blood pressure by means of peripheral vasoconstriction but also cause efferent vasoconstriction and thus increase the filtration pressure (51, 53).

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