Serial Hemodynamics after Renal Allotransplantation in Man

By Samuel L. Kountz, M.D., Gary Truex, M.D., Laurence E. Earley, M.D., and Folkert O. Belzer, M.D.

SUMMARY
Serial measurements of glomerular filtration rate (GFR), independent and simultaneous clearances and extractions of para-aminohippurate (PAH), radiohippuran, and iopropylacet (Diodrast) were made in 11 adults and one child who received renal transplants from living donors. Measurements were made within 3 hours and repeated two to four times during the following 14 days. Immediately after transplantation, PAH clearance averaged 385 ml/min (range, 218 to 510), GFR averaged 54 ml/min (range, 22 to 87), renal plasma flow (RPF) averaged 672 ml/min (range, 309 to 1424), and marked vasodilatation was present with an average renal blood flow (RBF) of 979 ml/min (range, 435 to 2,114). As observed in other studies, immediate diuresis and natriuresis but no glycosuria occurred. Extraction ratios for PAH (EPAH) were below normal, ranging from 0.59 to 0.94, and those for $^{125}$ (or $^{131}$)I-hippuran, and $^{131}$I-Diodrast were even lower. Extraction ratio for PAH to radiohippuran averaged 1.43 in 17 simultaneous studies. However, RPF measured simultaneously with these agents was the same, indicating a true difference in transport of these substances. The low extraction ratio for PAH, $^{131}$ (or $^{125}$)I-hippuran and $^{131}$I-Diodrast was not related to depression of the maximal tubular transport of PAH and may have been a consequence of vasodilatation and increased RBF. Another observation made on these kidneys was a low filtration fraction which averaged 0.089. These hemodynamic changes did not appear to relate to circulating factors in the anephric recipients since they persisted throughout the 13-day study period in eight patients. In four patients showing transient rejection, GFR and the clearance of PAH and $^{131}$I-hippuran decreased proportionately more than RBF. It is concluded that marked vasodilatation and a low filtration fraction are characteristic of uncomplicated renal allotransplantation in man, and that early rejection is expressed by measurable decreases in the clearances of PAH and insulin despite maintenance of RBF. These changes were present prior to clinical evidence of rejection.

Additional Indexing Words: Renal hemodynamics Extraction ratios Renal vasodilatation

Although changes in renal blood flow are thought to be an early expression of the rejection reaction, which has been detected by independent changes in the renogram, a glomerular filtration rate (GFR), intrarenal distribution of blood flow, pulsatile and total blood flow, and the single-injection $^{131}$I-hippuran

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clearance, the patterns of renal hemodynamics following transplantation in man have not been reported.

The purpose of this study was to measure the renal hemodynamic changes repeatedly during the early postoperative period in a series of patients who received kidneys from living donors. This offered the opportunity to observe the course of renal hemodynamics in patients with and without the complication of transient rejection. In addition, the effect of transplantation on normal kidneys in an altered physiologic state of the recipient was observed almost immediately after operation. Although the clearance of PAH has been reported to be within the normal range immediately after transplantation, the present data demonstrate that this measurement grossly underestimates true renal plasma flow in the transplanted kidney. The extraction ratios for PAH and related substances were strikingly depressed immediately after transplantation and remained low throughout the 14-day period of observation. The data demonstrate that marked vasodilatation is characteristic of uncomplicated renal transplantation and may persist to a relative degree during transient rejection when there has been a severe depression of the clearances of inulin and PAH.

**Methods**

Twelve consecutive patients who received renal allografts from living donors (eight related and four unrelated) were studied. The kidneys were transplanted by the standard technic. At the time of transplantation, catheters were placed in the transplanted renal artery and vein and were exteriorized onto the anterior abdominal wall (fig. 1). The arterial catheter was used for intrarenal administration of immunosuppressive and pharmacologic agents. The venous catheter was used for collection of renal venous blood. The sampling tip was placed 4 to 6 cm from the iliac-renal vein anastomosis to make sure the samples of renal vein blood were not contaminated with systemic blood. At the end of each study period, the position of the renal venous catheter was confirmed radiologically (fig. 2).

Initial measurements of renal hemodynamics were begun within 3 hours after transplantation. Following operation, the patients received 5% dextrose and water for 24 to 48 hours at approximately 1 ml/min and then were allowed a regular house diet.

**Hemodynamic Studies**

The glomerular filtration rate (GFR) was estimated by independent or simultaneous clearances of inulin and \textsuperscript{125}I-iothalamate. In 26 simultaneous clearance determinations of inulin and \textsuperscript{125}I-iothalamate, the GFR was 58.4 and 60.8 ml/min, re-
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respectively. Student’s t-test showed no significant difference. Independent and simultaneous clearances (C) and extraction ratios (E) of para-
aminohippurate (PAH), $^{131}$I (or $^{125}$I)-hippuran, and $^{131}$I-iodopyracet (Diodrast) were calculated
from the following formulae: $C = \frac{UV}{A}$ where $U$
is the urine concentration of these substances, $V$ is the rate of urine flow (ml/min), and $A$, the arterial concentration of the substances; and
$E = \frac{A - R}{A}$ where, in addition, $R$ is the renal
venous concentration of these substances. Renal plasma flow (RPF) was calculated by the formula
of Wolf$^{13}$ as $RPF = \frac{V (U - R)}{(A - R)}$; renal blood
flow was calculated as $RBF = \frac{1 - \text{hematocrit}}{1 - \text{hematocrit}}$; and filtration fraction was calculated as $GFR/$
RPF. Maximal tubular transport ($TmPAH$) was de-
termined during infusion of PAH sufficient to in-
crease plasma concentrations to levels greater than
53 mg/100 ml. At the beginning of each study, priming
injections of insulin or $^{125}$I-iodothalamate, or both were given; then PAH and $^{131}$I-hippuran
or PAH, I-hippuran and $^{131}$I-iodopyracet were
given, followed by constant intravenous infusion of
these substances in amounts sufficient to permit
measurements of clearance. Analyses in plasma
and urine were performed by previously described
techniques.$^{10, 16}$ After a 45 to 60-min equilibration
period, three to four consecutive 15 to 23-min
urinary collection periods were performed. At the
mid-point of each urinary collection period, peripheral arterial and renal venous blood samples
were collected. Values were expressed as an
average of the three or four collection periods.
All studies were performed in the fasting state,
and fluids were frequently given by mouth to
achieve an adequate output of urine.

Results

Clinical and hemodynamic data on all 12
patients are summarized in table 1. Eight
patients had an uncomplicated course and four
exhibited hemodynamic evidence of transient
rejection. Immediately following transplanta-
tion, GFR averaged 54 ml/min (range, 22 to
87), PAH clearance averaged 385 ml/min
(range, 218 to 510), clearance of $^{131}$I-hip-
 puran, 366 ml/min (range, 198 to 999), and
RBF, 979 ml/min (range, 435 to 2,114). Two
patients had minimal glycosuria (Clinistix)
during the initial studies. These two patients
(patients HS and BG, table 1) had the longest
warm ischemic times. In the eight patients
without complication (patients JH through
BC, table 1), marked vasodilatation, low
extraction, and low filtration fraction persisted
during repeated measurements (up to 13
days, table 1). In four patients (WH through
BP), evidence of transient rejection occurred
initially as manifested by only a decline in
GFR and the clearance of $^{131}$I-hippuran, both
changes being out of proportion to RBF. This
fall in clearance of hippuran without a
proportional fall in RBF related to a decrease
in the renal extraction of this substance. These
hemodynamic changes were the only expres-
sions of the apparent rejection process which
would not have become evident from observa-
tions of the serum creatinine alone (JD and
KC, table 1). In all four subjects, reversal of
the rejection process was evidenced by a
return of GFR and the clearance of $^{131}$I-
hippuran toward normal.

The consistent finding of a low extraction of
PAH and $^{131}$I-hippuran suggested the possibility
of a defect in tubular transport. This was
investigated by measurements of $TmPAH$. The
results of repeated measurements in three
patients are shown in table 2. In patient BP, in
whom $TmPAH$ was determined during an
episode of apparent rejection, $TmPAH$ was
unaltered despite a significant decline in GFR
and the clearance of $^{131}$I-hippuran. Simulta-
neous extraction ratios for PAH and $^{131}$I-
hippuran in these six studies were signifi-
cantly different. $EPAH$ was greater than $E^{131}$I-
hippuran on every test in the three cases
except during an episode of transient rejection
(patient BP, table 2) when it was lower.
Furthermore, extraction ratios of hippuran
were depressed in studies employing only
isotopic tracer amounts, which could not
exceed transport maxima. It is possible that
the low extraction ratios for these transported
substances were related in some way to their
molecular sizes and the high rates of blood
flow.$^{17}$ The possibility that the differences in
extraction ratios were related to the molecular
size of the substances was investigated further
by simultaneously measuring the extraction of
PAH, $^{125}$I-hippuran, and $^{131}$I-iodopyracet in
three patients on five separate occasions. The
<table>
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<th>Day</th>
<th>Ischemic time (min)</th>
<th>BP</th>
<th>P</th>
<th>Serum creatinine (mg%)</th>
<th>GFR (ml/min)</th>
<th>RBF (ml/min)</th>
<th>C (ml/min)</th>
<th>E</th>
<th>GFR/RPF</th>
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<td>46</td>
<td>826</td>
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<td>92</td>
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<td>433*</td>
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<td>1.1</td>
<td>69*</td>
<td>448*</td>
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* 24-hour creatinine clearance.
† Determined by single injection of ^131^I-hippuran.
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Table 2
Serial Hemodynamics and PAH Transport in Renal Allotransplants

<table>
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<tr>
<th>Patient</th>
<th>Donor relationship</th>
<th>Day</th>
<th>GFR (ml/min)</th>
<th>Extraction ratio</th>
<th>Renal plasma flow (ml/min)</th>
<th>TmPAH (mg/min)</th>
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<td>EB</td>
<td>Mother</td>
<td>0</td>
<td>41</td>
<td>0.64</td>
<td>0.72</td>
<td>309</td>
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<tr>
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Table 3
Simultaneous Extraction Ratios for PAH, 125I-Hippuran, and 131I-Iodopyracet

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<th>131I-Iodopyracet</th>
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<td>0.75</td>
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<td>0.86</td>
<td>0.66</td>
<td>0.35</td>
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</table>

results of these studies are summarized in table 3. In each study, the extraction ratio for PAH was greater than that for 125I-hippuran which in turn was greater than that for 131I-Iodopyracet. These observations indicate an inverse relationship between molecular size and extraction ratio and are consistent with the view that the extent of extraction may be limited by diffusion of the species from plasma at these high rates of blood flow. However, further studies would be necessary to delineate the exact mechanism. These differences in extraction ratios were reflected by a similar difference in the clearance of the three substances (fig. 3). However, RPF calculated from the simultaneous measurements of clearances and extractions was the same for each substance (fig. 4).

Discussion
Two unexpected findings emerged from this study—the marked and persistent vasodilatation and the varying degrees of depression of the extraction ratios for PAH, radiohippuran, and iodopyracet. The extraction ratios were inversely related to molecular size of the species. In these patients, therefore, clearances of these substances grossly underestimated true RPF and during rejection when extraction ratios were further decreased, this error was even greater. Under these conditions and in the absence of a rejection episode, PAH, which has the lowest molecular weight, would most closely approximate RPF. The finding of relative maintenance of total renal blood flow during the rejection in the face of marked depression of the clearances of inulin, PAH, and radiohippuran agrees with the earlier

Figure 3
Seven simultaneous clearances of PAH and 131I-hippuran and five simultaneous clearances for PAH, 125I-hippuran and 131I-Diodrast are compared. The ratio of PAH/C131 (or 131I-hippuran) is 1.43. The two instances in which PAH clearance was lower than the hippuran clearances occurred during episodes of transient rejection.
observation of Dempster, who found an adequate total blood flow up to the oliguric stage of rejecting canine renal allografts. This suggests that during the rejection reaction, blood flows more rapidly through the graft, that is, increased transient time, which could be the result of intrarenal vascular lesions known to occur during allograft rejection. This phenomenon may be enhanced by vasoconstriction, which is also believed to be associated with the rejection reaction. The rapid flow of blood accompanied by the intrarenal vascular reaction during rejection could further limit tubular contact with transported substances in the plasma. Therefore, declines in the clearances of inulin and PAH, rather than a decrease in total renal blood flow, are the earliest expressions of the rejection reaction and provide a sensitive guide for the effectiveness of immunosuppressive drug therapy.

Ogden and co-workers observed an average clearance of PAH of 207 and 357 ml/min 6 and 18 hours, respectively, after transplantation in five patients. The clearance of PAH averaged 385 ml/min in six of our patients studied immediately after transplantation, which is in close agreement with their findings. However, true renal plasma flow (RPF) in our studies averaged 672 ml/min. This striking degree of vasodilatation would be overlooked without measurements of extraction ratios. However, the etiology of the vasodilatation is obscure. Although we, like others, observed marked initial diuresis and natriuresis, the persistence of vasodilatation after this phase makes it unlikely that this was responsible. The possibility that a humoral factor in end-stage renal failure may be responsible is also unlikely, since it would be unusual for such a substance to persist for 13 days after correction of the azotemic state. However, it is possible that the diuresis and natriuresis were the result of allograft vasodilatation. Henderson and associates postulated proximal tubular malfunction as the etiology of the post-transplant diuresis and natriuresis. Support for their hypothesis was the finding of glycosuria in their patients. Our data are in contradistinction to theirs, as minimal glycosuria was observed initially in only two of our patients. This difference may be related to the length of the warm ischemic time, which was longer in their cases. It is also possible that in our studies the degree of initial renal ischemia was minimized and vasodilatation was maximized from the initial intrarenal injection of immunosuppressive drugs. However, we believe this to be unlikely because vasodilatation was repeatedly observed when these substances were not being intrarenally infused. In our studies, further evidence against tubular malfunction was the finding of a normal TmPAH which remained normal during a transient rejection episode.

Arteriovenous fistulae have been observed during the rejection reaction in dogs by Almgard and associates. They observed a greater decline in GFR and TmPAH than in RBF in allografts, but not in autografts. Also, they demonstrated arteriovenous shunts by microangiograms and suggested that these shunts explained the observed hemodynamic abnormalities. However, such a mechanism would predict a shunting of more than 50% of RBF in some cases, which appears unlikely.
The low extraction ratios for PAH, radiohippuran, and iodopyracet, which were inversely related to their molecular sizes, seem best explained by the hypothesis that their diffusion from plasma to the tubules is limited by their molecular size during high rates of blood flow. The possibility that anemia or protein binding is responsible appears unlikely since the difference in extraction ratios was less pronounced in the same subject as the vasodilatation decreased and the GFR increased. It is interesting that marked increases in the GFR were not observed. The proposed hypothesis may explain the occasional failure to obtain identical clearance values of transported substances, especially when the single injection technic is simultaneously compared with the constant infusion technic, for example, PAH and radiohippuran. Therefore, simultaneous measurements of extraction ratios of transported substances having different molecular sizes are important in comparing their clearance rates. This should allow differentiation of clearance differences due to defects in tubular transport from those due to a diffusion limit at high rates of blood flow. It is theoretically possible for this to occur to some degree in the absence of vasodilatation, that is, when RBF is out of proportion to GFR.

This unique hemodynamic phenomenon of the singly transplanted human kidney (vasodilatation, varying degrees of depression of the extraction ratios of PAH, radiohippuran, and iodopyracet, and low filtration fraction) may well be the same as the response of a normal kidney either to (1) lack of renal mass in relation to body surface area, (2) severance of the renal nerves, or (3) the responsibility to regulate the internal milieu and perform the total excretory work. A similar phenomenon has been observed in the normal intact kidney under pharmacologic vasodilatation.17

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