PAH extraction and estimation of plasma flow in human postischemic acute renal failure

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**METHODS**

**Patient Population**

Forty-four patients undergoing renal transplantation at our institution gave informed consent to a study of allograft function. Each was studied according to a protocol approved previously by the Panel for Research in Human Subjects at Stanford University. They ranged in age from 21 to 71 yr, and 34 were male. The transplants were exclusively from “heart-beating,” cadaveric donors. Donor age ranged from 10 to 69 yr. Each subject was studied on two occasions. The first study was on the day of transplantation (day 0) between 1 and 3 h after vascular anastomosis and reperfusion of the allograft. The second study was on postoperative day 7, at which time the subjects were arbitrarily divided into two groups according to the “effective” glomerular filtration rate (GFR), determined as the clearance of inulin. Group 1 was composed of 23 subjects who were classified as exhibiting recovering ARF, by virtue of an inulin clearance $\geq 20$ ml/min. Group 2 was composed of the remaining 21 subjects, who were classified as exhibiting sustained ARF because of persistent depression of inulin clearance ($< 20$ ml/min). The latter value was selected because it represented depression of GFR by $> 75\%$ below the average value in a group of control subjects, who provided an optimal range of values for the renal allograft. These control subjects were 18 recipients of long-standing renal allografts that were donated by a living sibling or parent and had never undergone a known episode of rejection. A second control group composed of 13 cardiac transplant recipients never exposed to cyclosporine provided a value for $E_{PAH}$ in healthy controls. All had a normal GFR as measured by inulin clearance. $E_{PAH}$ in these controls was determined by sampling renal venous plasma during the course of routine right cardiac catheterization, as described in detail elsewhere (5).

**Transplantation Procedures**

The surgical management of donors and recipients at our institution has been described in detail recently (2, 19). Each cadaveric donor in this series died from a severe brain injury. In addition, each subject also received a single dose of gentamycin (100 mg) on the day of surgery. Other drugs routinely used in the first transplant week to treat or prevent infections included trimethoprim-sulfa, acyclovir, and cephalosporin, the latter being administered for the first three postoperative days only. In addition, each subject also received a single dose of gentamycin (100 mg) on the day of surgery. Serial clearances were performed in each of the 44 recipients of a cadaveric renal allograft. The initial clearance of PAH (CPAH) and the true renal plasma flow measured by phase contrast-cine-MRI technique (RPFMRI) with the use of Eq. 3

$$E_{PAH} = \frac{C_{PAH}}{RPF_{MRI}}$$

Evaluation of early allograft function. As soon as the renal allograft was removed from cold storage in preparation for transplantation, each recipient was given 0.03–0.04 ml/kg of 20% sodium PAH (Merck, West Point, PA) by intravenous injection. PAH was allowed to equilibrate between intra- and extravascular compartments during implantation of the kidney, which took an average of 45 ± 14 min (mean ± SD), followed by a subsequent period of allograft reperfusion lasting 40–60 min. Samples of blood (10 ml) were then drawn simultaneously from the renal allograft vein and the iliac artery. Samples were centrifuged, and the supernatant plasma was removed and stored at $-70°C$ until the day of assay. The $E_{PAH}$ was calculated as the arteriovenous PAH concentration difference $(\left[A_{PAH}\right] - \left[V_{PAH}\right])$ divided by the arterial PAH concentration $(\left[A_{PAH}\right])$

$$E_{PAH} = \frac{\left[A_{PAH}\right] - \left[V_{PAH}\right]}{\left[A_{PAH}\right]}$$

Thirteen of the 25 subjects undergoing determination of $E_{PAH}$ received furosemide (100 mg iv) intraoperatively 15 ± 14 min before the renal venous blood phlebotomy. No other drugs known to compete with PAH for the organic anion transporter had been administered to any subjects during the preceding 24 h. Renal blood flow was determined intraoperatively 45–60 min after reperfusion by Doppler flow probe with the use of an ultrasonic transit time flow meter (model HT 107; Transonic Systems, Ithaca, NY). A snugly fitting flow probe 12–16 mm in diameter was placed around the renal vein. The iliac fossa was then filled with saline to optimize ultrasonic determinations. Determinations were recorded on a precalibrated digital readout. Mean arterial pressure was simultaneously determined by either dynamap or transducer in those patients with a peripheral arterial line. Central venous pressure was also determined by transducer. Renal plasma flow was calculated from the product of renal blood flow and the fractional hematocrit of venous blood.

Once the surgical procedure was complete, a timed urine collection was begun to permit determination of the GFR by the endogenous creatinine clearance technique. Two timed urine collections, each of 30- to 60-min duration, were made via a Foley bladder catheter. Each urine collection was bracketed by a 10-ml sample of venous blood. Plasma and urine samples were then assayed for creatinine. The sodium concentration and osmolality of each urine and plasma sample were also determined so as to calculate the fractional excretion of sodium and urine-to-plasma osmolality ratios as indexes of tubular function.

**Evaluation of postoperative allograft function.** Standard urinary clearances of inulin and PAH were determined on postransplant day 7, as described previously (19). In a subset of 16 subjects, the rate of blood flow to the renal allograft was determined by phase contrast-cine-magnetic resonance imaging (MRI) on the same day as the clearance study. Renal plasma flow (RPF) was computed from renal blood flow (RBF) with the use of Eq. 2

$$RPF = RBF \times (1 - \text{hematocrit})$$

$E_{PAH}$ was then computed indirectly from the observed clearance of PAH (CPAH) and the true renal plasma flow measured by the phase contrast-cine-MRI technique (RPFMRI) with the use of Eq. 3

$$E_{PAH} = \frac{C_{PAH}}{RPF_{MRI}}$$

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Laboratory determinations. Concentrations of inulin in urine and plasma were determined by the AutoAnalyzer method of Fjeldbo and Stamey (13) with the use of resorcinol as the colorimetric reagent. PAH concentrations in urine and plasma were assayed simultaneously, employing a modification of the colorimetric assay of Bratton and Marshall (6). The concentration of creatinine in urine and plasma was determined by an automated rate-dependent picrate method with the use of a creatinine analyzer (Creatinine Analyzer 2; Beckman Instruments, Fullerton, CA). This method minimizes the influence of slow-reacting, noncreatinine chromagens and thus provides an estimate of the true creatinine concentration. Concentrations of sodium were determined by ion-selective electrode (NOVA 11; NOVA Biomedical, Waltham, MA), and osmolality was determined by a vapor pressure osmometer (model no. 5500; Wescor, Logan, UT).

MRI measurement of renal blood flow. The phase contrast-cine-MRI method used to determine blood flow in the renal allograft has been validated and described by Myers et al. (22) in detail. It depends on the use of magnetic field gradients to acquire velocity information from phase data. As the precessing protons move in the presence of a magnetic field gradient, they acquire a phase shift that is proportional to velocity. Images encoding the phase information are called phase contrast-MRI. Cine-MRI is a technique that acquires data throughout the cardiac cycle and uses a simultaneously monitored electrocardiogram to produce images at selected intervals. When the cine-MRI technique is combined with phase contrast to produce images that portray the spatial distribution of velocities during the cardiac cycle, the technique is known as phase contrast-cine-MRI. If the phase contrast acquisition is encoded for motion through the imaging plane, the product of the average velocity in a region encompassing a blood vessel and the vessel area yields the flow rate.

When phase contrast-cine-MRI data are used the flow rate at each point in the cardiac cycle can be computed. These time-dependent measurements are then averaged and scaled to yield the average flow rate through the vessel (ml/min). The plane of acquisition for the phase contrast-cine-MRI was defined with the use of gradient-recalled images of the allograft vein, with the acquisition plane set as perpendicular as possible to the vessel, near the anastomosis with the renal vein, with the acquisition plane set as perpendicular as possible to the vessel, near the anastomosis with the external iliac vein. The following conditions were employed: electrocardiogram gating, respiratory compensation, pulse repetition time of 25 ms, echo time of 12 ms, slice thickness of 4 mm, and a maximum flow encoding velocity of 50 cm/s. After acquisition of data, an analysis of renal blood flow was performed off-line. Dedicated software was used to compute and integrate renal blood flow from the product of velocity and renal venous cross-sectional area through 16 equal phases of the cardiac cycle.

Statistical Analysis

Analysis of the data described above involved 30 separate but related comparisons among 18 variables. For six variables there were three groups (controls and recovering and sustained ARF); in all others there were two groups. Evaluation with the Shapiro-Wilk test revealed the distribution of data to be approximately Gaussian. However, the separate groups had different variance and in some instances different sample sizes, thereby rendering ordinary pooled t-tests inappropriate. Instead, we tested the significance of differences among the groups and paired differences between days 0 and 7 within the ARF groups by using the Behrens-Fisher-Welch t-test, which respects differences in population variances. Our implementation was with the Minitab package (28). All results are expressed as means ± SD.

RESULTS

Early Allograft Function (1–3 h Postreperfusion)

The duration of cold ischemia averaged 1,100 ± 421 min in the group with recovering ARF and 1,356 ± 503 min in the group with sustained ARF (P = not significant [NS]). The corresponding durations of subsequent rewarming times during performance of the vascular anastomosis were also similar: 35 ± 12 vs. 42 ± 21 min, respectively (P = NS, Table 1). Classification of subjects into recovering and sustained ARF groups according to inulin clearance on posttransplant day 7 also separated the two groups by creatinine clearance on day 0. The latter measure of effective GFR immediately after surgery was significantly lower in those destined to exhibit sustained ARF than in those destined to manifest recovering ARF: 5 ± 5 vs. 16 ± 10 ml·min⁻¹·1.73 m⁻², respectively (P < 0.001). However, simultaneous values for fractional sodium excretion in excess of 20% and isoosmuria in each group attest to a severe postischemic tubular injury in both groups (Table 1).

Renovascular pressures and flows, determined intraoperatively after 1 h of reperfusion, also failed to distinguish the recovering and sustained ARF groups. Mean arterial pressure averaged 94 ± 24 in recovering ARF vs. 85 ± 23 mmHg in sustained ARF subjects (P = NS). Corresponding central venous pressures averaged 12 ± 5 and 17 ± 16 mmHg, respectively (P = NS). Despite the low GFR observed in each group, the renal blood flow rate was close to the expected value for a normal single kidney in both the recovering and sustained ARF groups: 340 ± 190 vs. 427 ± 221 ml/min (P = NS). The same was true for corresponding renal plasma flow rates, which averaged 252 ± 133 and 296 ± 162 ml·min⁻¹·1.73 m⁻², respectively (P = NS). As a result, the filtration fraction was depressed to only 0.07 ± 0.05 in those destined to exhibit recovering ARF and even more profoundly to 0.02 ± 0.02 in those destined to exhibit sustained ARF (P < 0.001 vs. recovering ARF). Thus GFR depression in this postische-

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<tr>
<th>Table 1. Early allograft function and hemodynamic findings (1–3 h postreperfusion)</th>
<th>Recovering ARF</th>
<th>Sustained ARF</th>
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<tr>
<td>Cold ischemic time, min</td>
<td>1,100 ± 421</td>
<td>1,356 ± 503</td>
</tr>
<tr>
<td>Anostomosis/rewarming time, min</td>
<td>35 ± 12</td>
<td>42 ± 21</td>
</tr>
<tr>
<td>Creatinine clearance, ml·min⁻¹·1.73 m⁻²</td>
<td>16 ± 10</td>
<td>5 ± 5†</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>94 ± 24</td>
<td>85 ± 23</td>
</tr>
<tr>
<td>Central venous pressure, mmHg</td>
<td>12 ± 5</td>
<td>17 ± 16</td>
</tr>
<tr>
<td>Renal plasma flow†, ml·min⁻¹·1.73 m⁻²</td>
<td>252 ± 133</td>
<td>296 ± 162</td>
</tr>
<tr>
<td>Filtration fraction‡</td>
<td>0.07 ± 0.05</td>
<td>0.02 ± 0.02‡</td>
</tr>
<tr>
<td>Fractional sodium excretion, %</td>
<td>24 ± 12</td>
<td>40 ± 29*</td>
</tr>
<tr>
<td>Urine/plasma osmolality</td>
<td>0.97 ± 0.09</td>
<td>0.92 ± 0.22</td>
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Values are expressed as means ± SD; n = no. of subjects. ARF, acute renal failure. *P < 0.05 and †P < 0.001 vs. recovering group. ‡Recovering, n = 20; sustained, n = 15.
mic injury cannot be attributed to impairment of renal plasma flow.

In keeping with a severe tubule injury, suggested by the presence of isothenuria and marked elevation of the fractional sodium excretion (Table 1), E\textsubscript{PAH} was severely depressed in each group (Fig. 1). Arterial PAH concentration exceeded 3 mg/dl in three members of the recovering ARF group and two members of the sustained ARF group. Because the PAH transporter begins to become saturated at concentrations of this magnitude, these five individuals were excluded from the assessment of E\textsubscript{PAH}. In the remaining subjects, the arterial PAH concentrations averaged 1.5 ± 0.4 and 1.9 ± 0.5 mg/dl in recovering (n = 10) and sustained (n = 10) ARF groups, respectively. The corresponding values for the E\textsubscript{PAH} (×100) were profoundly depressed, averaging only 18 ± 14 and 10 ± 7%, respectively. These group ratios did not differ from each other but were profoundly and significantly lower than the control value for our laboratory of 87 ± 10% (P < 0.0001, Fig. 1). Mean E\textsubscript{PAH} in subjects who received furosemide before renal venous blood sampling did not differ from that in subjects who did not receive furosemide. Among the subjects who received furosemide, the E\textsubscript{PAH} averaged 14 ± 12%. The corresponding value among those patients who did not receive furosemide was 13 ± 12% (P = NS).

Late Allograft Function (Day 7)

Judged by inulin clearance, the effective GFR remained depressed below the normal allograft “control” level even in those subjects assigned to the recovering ARF group: 37 ± 21 vs. 77 ± 15 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2}, respectively (P < 0.001). The former day 7 value nevertheless exceeded the corresponding day 0 value of 16 ± 10 ml/min significantly (P < 0.05). In contrast, in those assigned to the sustained ARF group, the GFR remained depressed to a level (6 ± 5 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2}) similar to that observed on day 0 (Table 2). Of the 21 members of this group, no fewer than 18 required hemodialytic treatment for the ARF during the first posttransplant week. Fractional sodium excretion, albeit considerably less than on day 0, continued to exceed physiological levels on day 7, averaging 4 ± 4 and 10 ± 15% (P < 0.05) in the recovering and sustained ARF groups, respectively (Table 2). Inability to effectively concentrate or dilute the urine also pointed to persisting day 7 tubular dysfunction in each group.

Arterial pressure was similar in each ARF group and controls (Table 2). In contrast, the clearance of PAH was lower in those with recovering ARF than in our long-standing allograft controls: 200 ± 126 vs. 340 ± 66 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2}, respectively (P < 0.001). PAH clearance was even more depressed in the sustained ARF group, averaging only 50 ± 48 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2} (P < 0.001 vs. controls and recovering ARF). That the low PAH clearance does not result from depression of the renal plasma flow rate is suggested by determination of the latter quantity by phase contrast-cine-magnetic resonance imaging. For true renal plasma flow values: controls, n = 16; recovering, n = 11; sustained, n = 5. *P < 0.05 vs. controls, †P < 0.05 between ARF groups, ‡P < 0.01 vs. controls, §P < 0.001 between ARF groups.

The disparity between PAH clearance and true renal plasma flow was used to compute a value for the E\textsubscript{PAH} in those subjects studied by both clearance and MRI techniques. The E\textsubscript{PAH} for the allograft control group (n = 13) averaged 87 ± 10%. As shown in Fig. 2, the true renal plasma flow exceeded the PAH clearance in all but one of the 16 subjects with postischemic allograft injury who underwent the MRI determinations of renal plasma flow. From the disparity between the two, we estimate that the E\textsubscript{PAH} averaged 66% (range: 42–100%) in subjects with recovering ARF (Fig. 3). Of the five subjects with sustained ARF studied by MRI on day 7, three were anuric, with the result that the E\textsubscript{PAH} is computed to be zero. In the remaining two subjects with

<table>
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<th>Table 2. Late allograft function (postoperative day 7)</th>
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<tr>
<td>Controls</td>
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<tr>
<td>Inulin clearance, ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2}</td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
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<tr>
<td>PAH clearance, ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2}</td>
</tr>
<tr>
<td>True renal plasma flow, ml·min\textsuperscript{-1}·1.73 m\textsuperscript{2}</td>
</tr>
<tr>
<td>Fractional sodium excretion, %</td>
</tr>
<tr>
<td>Urine/plasma osmolality</td>
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Values are expressed as means ± SD; n = no. of subjects. PAH, p-aminohippurate; ND, not done. True renal plasma flow determined by phase contrast-cine-magnetic resonance imaging. For true renal plasma flow values: controls, n = 16; recovering, n = 11; sustained, n = 5. *P < 0.05 vs. controls, †P < 0.05 between ARF groups, ‡P < 0.01 vs. controls, §P < 0.001 between ARF groups.
sustained ARF, the computed $E_{PAH}$ values were 7 and 50%, despite a high urinary flow rate (Fig. 3). Persistently profound depression of extraction in the sustained ARF group indicates that PAH transport remains severely depressed in recipients whose ARF fails to enter the recovery stage in the first postoperative week.

DISCUSSION

We have demonstrated that postischemic injury to the cadaveric renal allograft is associated with profound impairment of $E_{PAH}$. This abnormality is particularly marked in the immediate wake of reperfusion, independent of whether the transplanted kidney is destined to have a protracted episode of or recover rapidly from postischemic ARF (Fig. 1). We have also provided indirect evidence that impairment of $E_{PAH}$ persists for at least 7 days and remains evident even after the injury has entered the recovery stage (Figs. 2 and 3). Our findings confirm earlier reports of impaired PAH transport during postischemic injury, both in experimental animal ARF (10, 11, 14, 24) and in humans with ARF (7, 21).

The mechanism whereby PAH transport in the reperfused renal allograft becomes depressed is likely related to the fact that such transport is an active process. One possible mechanism is the presence in high concentrations within the circulation of organic anions that compete with PAH for the proximal tubule transporter. Such inhibitors could be endogenous solutes that are retained because of renal failure. An important role for endogenous inhibitors seems unlikely in the present study, however. This is because, in keeping with our routine practice, 42 of the 44 recipients were hemodialyzed immediately before transplantation surgery. As a result, our finding of a uniform and marked depression of $E_{PAH}$ during surgery on day 0 appears to coincide precisely with what might be expected to be the postdialysis nadir levels of any retained solutes that serve as endogenous inhibitors of PAH transport.

Several drugs that are organic anions have been shown to serve as exogenous inhibitors of PAH transport. However, no member of this class of drugs can be clearly identified among the immunosuppressive and antimicrobial agents that were administered on the seventh postoperative day in the present study (see METHODS). It has been suggested that active secretion by the organic anion transporter of mycophenolic acid glucuronide, the stable metabolic product in which form mycophenolate mofetil is eliminated, accounts for its urinary excretion (8). In this event, it could compete with PAH for transport and contribute to the impaired $E_{PAH}$ observed on day 7 (but not during the day 0 study, which preceded therapy). Two factors suggest that such a contribution is unlikely to be quantitatively important, however. First, $E_{PAH}$ on day 7 was far more impaired in subjects with sustained than recovering ARF, although members of both groups were being treated with mycophenolate at this time. Second, the renal clearance of mycophenolic acid glucuronide has been estimated in healthy volunteers, patients with autoimmune disorders, and renal transplant recipients to average 36% of the corresponding creatinine clearance (8). Mycophenolic acid glucuronide seems likely therefore to be eliminated either exclusively by glomerular filtration or by a combination of glomerular filtration and minor tubular secretion. Given the low clearance, the rate of tubular secretion would appear to be too low to lead to a measurable reduction of PAH transport by competitive inhibition of the organic anion transporter.
As stated in the introduction, PAH transport is vectorial, from peritubular capillaries to tubule lumen, and occurs along the entire length of the proximal tubule; the highest rate of transport per millimeter of tubule length is normally found in the proximal straight segment (31). We have shown that the proximal tubule in general and the straight segment in particular bear the brunt of postschismic injury in the reperfused renal allograft (1, 18, 19). Using lithium as a surrogate, we have also shown that proximal sodium reabsorption is markedly diminished under these circumstances (18). Structural disruption of the cell membranes of the proximal tubule is also evident during postischemic allograft ARF. This is manifest by redistribution of Na\(^{+}\)-K\(^{+}\)-ATPase and various adhesion molecules from the basolateral to either the apical membrane or to the cytosol in the interior of the cell (1, 18, 19). The ensuing loss of cell polarity and dislocation of Na\(^{+}\)-K\(^{+}\)-ATPase from the basolateral cell membrane could play a major role in limiting the extent of proximal sodium reabsorption (20).

It seems likely that a loss of cell polarity could also impair the active proximal secretion of PAH by the organic anion transporter. Such impairment could result from disruption of the cell membrane proteins that constitute the basolateral PAH transport system. The recent cloning of a human organic anion transporter (17) should allow this hypothesis to be tested. It is noteworthy, however, that the aforementioned redistribution of Na\(^{+}\)-K\(^{+}\)-ATPase could limit PAH transport, even in the event that the organic anion transporter should prove to be normally retained in the basolateral membranes of proximal tubule cells in postischemic ARF. The third step in the tertiary active process of transport by which PAH is secreted is one in which PAH enters the cell in exchange for a dicarboxylate ion (\(\alpha\)-ketoglutarate) moving out of the cell down an electrochemical gradient. The outward dicarboxylate gradient is maintained, in part, by Na\(^{+}\)-coupled transport that depends on energy derived from ATP through the activity of the basolateral Na\(^{+}\)-K\(^{+}\)-ATPase (25). In the absence of such activity, PAH entry into the cell and subsequent active transport across the apical membrane into the tubular lumen would not eventuate. We submit that altered composition of cell membranes with an ensuing loss of proximal tubule cell polarity is likely the predominant cause of the impaired PAH transport observed in the present study.

In contrast to the striking impairment of PAH transport, our study has demonstrated that there is little or no reduction in renal plasma flow in either the initiation, maintenance, or recovery stages of postischemic ARF in the cadaveric renal allograft (Tables 1 and 2). A disproportionately profound depression of GFR with preservation of relatively normal or only modestly depressed rates of renal plasma flow in the freshly transplanted kidney has also been reported by others (3, 15). The same is true for postischemic ARF of the native human kidney, during both initiation (21) and maintenance stages of the injury (16, 26). In each of the aforementioned studies, invasive techniques were required to demonstrate that renal plasma flow is not an important determinant of GFR depression in this setting. Such invasive techniques involved either direct application of an electromagnetic flow meter to the renal artery (3, 21) or cannulation of the latter vessel to measure flow by the washout of radioactive xenon (15, 16, 26). Whereas PAH clearance is a relatively noninvasive technique, it is clearly an invalid measure of renal plasma flow in this circumstance, and its use would give the artificial impression that renal plasma flow is profoundly depressed in this disorder (Table 2, Fig. 2).

In this respect it is important to emphasize that in routine clinical practice, isotopic renal scanning is frequently used in the differential diagnosis of prolonged depression of renal allograft function in the days and weeks after transplantation (9, 23, 33). Commonly used radiopharmaceuticals are \([\text{\textsuperscript{131}}\text{I}]\)orthoiodohippurate and \([\text{\textsuperscript{99}}\text{Tc}]\)-labeled mercaptoacetyltriglycerine (known as MAG-3), both of which share the same transport system as PAH. Minimal uptake of these isotopes during postischemic ARF is frequently misinterpreted as representing renal underperfusion. In fact, our findings suggest that it is impaired transtubular transport (and an ensuing absence of concentration of the isotope in the tubule fluid) that is responsible for diminished isotope uptake by the kidney. We submit that the current diagnostic use of isotope renography either to distinguish postischemic ARF from acute rejection and cyclosporine toxicity or to estimate effective renal plasma flow is likely to be of limited use. Certainly, the malfunction of the organic anion transporter that we have demonstrated during postischemic allograft injury should be taken into account in the attempt to interpret isotope renographic findings.

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