Cortex Perfusion Index: A Sensitive Detector of Acute Rejection Crisis in Transplanted Kidneys

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Damage to the renal cortical microcirculation, an early event in the course of acute rejection crisis (ARC), usually precedes measurable functional derangements in the transplanted kidney. Direct assessment of cortical blood flow by radionuclide renography may provide a sensitive and reliable index to the diagnosis of ARC, with particular regard to the differential diagnosis of ARC and ATN. Computer generated time-activity curves of global, cortical, and medullary renal blood flow were analyzed in 67 instances (35 patients) of renal allograft dysfunction and correlated with needle biopsy of these kidneys. No increase in cortex perfusion index (CPI), i.e., decrease in cortical perfusion, was found when the patients were suffering from ureteral obstruction or drug and viral nephropathy (mean perfusion index (PI) increase (8%). In contrast, a marked increase in CPI of 193% was noted in ARC. Global and medullary PI increased only 116%. As a result, global and medullary PI were capable of diagnosing ARC in only 73% and 55% of the cases, respectively, whereby cortex PI correctly diagnosed ARC in 94% of the cases. Selective analysis of cortical perfusion may thus enhance the accuracy of [^{99m}Tc]DTPA scans (radionuclide renograph) for the early detection of ARC and in differentiating ARC from nonimmunological causes of kidney allograft dysfunction.

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Acute rejection crises (ARC) continue to pose a serious threat to patients receiving renal allografts, and require prompt diagnosis and treatment. The diagnosis of ARC may, however, be hampered by a paucity of definitive clinical signs or symptoms, as well as by a lack of definitive biochemical or radiological diagnostic modalities capable of detecting early ARC and differentiating ARC from the many other conditions that can adversely affect renal function (*1*). "Classic" signs and symptoms of early ARC, including decreased renal function, graft tenderness, fever, and/or hypertension are frequently absent in early rejection crises, and frequently occur in the course of graft ureteral obstruction, pyelonephritis, viral nephropathy or drug-induced renal dysfunction (*2*).

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It is generally agreed that damage to the renal cortical microcirculation is an early event in the course of allograft rejection, (*4–6*) usually preceding measurable functional derangements in the transplanted kidney (*6*). This observation raised the possibility that accurate detection of decreases in renal blood flow rates might provide a useful approach to the early diagnosis of ARC. The capacity of radionuclide methods to provide accurate noninvasive measurements of changes in renal blood flow has, in turn, led to the development of numerous new methods designed to recognize ARC on this basis (*7–13*). These techniques have included use of a variety of tracers (*7,8*) and ligands (*9–11*) and the development of computer-enhanced techniques for the identification of renal blood flow changes in the course of ARC (*12–13*). These techniques have, however, not been sufficiently reliable to accurately detect ARC (*14–16*).

Studies of the renal microcirculation (*17,18*) including work in this laboratory (*19,20*) have shown recently that damage to the renal cortical microcirculation may

not necessarily be reflected in changes in the *total* renal blood flow, as a consequence of shunting and redistribution of blood flow from the cortex to the medulla. It appeared from these studies that a direct assessment of *cortical* blood flow by radionuclide renography might provide a more sensitive and reliable index to the diagnosis of ARC, with particular regard to the differential diagnosis of ARC and ATN. The results of the present study indicate that alterations in cortical blood flow, as measured by the cortex perfusion index (CPI), may constitute a particularly sensitive and accurate guide for the early diagnosis of acute renal allograft rejection crises. The potential value and reliability of this noninvasive approach as an early warning signal for the institution of prompt and effective anti-rejection therapy is highlighted in the present study by the regularly reproducible confirmation of each radionuclide renographic diagnosis by needle biopsy histologic examination.

MATERIALS AND METHODS

Patient Population

Thirty-four patients who underwent renal transplantation between June 1, 1982 and June 1, 1984, were studied prospectively on the Transplantation Service at Stony Brook. Each of these subjects had baseline radionuclide renographic study of the transplanted kidney with technetium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) within 48 hr after operation. There were 67 instances of renal dysfunctions in this series, for which a clinical diagnosis of acute rejection was entertained. Each patient underwent a standard comprehensive diagnostic workup, including: history and physical examination, serial hematologic analysis, renal and liver function tests. Urinalyses and urine cultures, as well as viral serology, chest x-rays, and renal ultrasonography. Transplant radionuclide renography using [^{99m}Tc]DTPA was performed in all cases within 24 hr of admission. Additional renograms were performed as indicated as well as during and after recovery of renal function. A total of 358 renograms was performed and analyzed in the course of this study.

Group A

Thirty-five instances of acute rejection crises were noted in 24 patients (168 renograms). The diagnosis of rejection was confirmed histologically by needle biopsies in all patients.

Group B

Thirteen instances of ureteral obstruction were noted in eight patients (67 renograms). Establishment of this diagnosis by ultrasonography and retrograde pyelography was followed immediately by surgical exploration and repair. Open renal biopsy to rule out the possible concurrent occurrence of obstruction and rejection was performed in each case.

Group C

Ninety-one radionuclide renograms were performed in 14 patients with a clinical diagnosis of ARC, in whom needle biopsies were consistently negative for cellular and/or humoral rejection (19 instances). Further investigation uncovered a variety of etiologies for renal dysfunction in this group, including viral infection(s) (especially herpes simplex and cytomegalovirus), pyelonephritis, drug toxicity (bactrim; captopril) and diabetic ketoacidosis.

Group D

Thirty-two renograms were performed in patients with stable graft function.

Radionuclide Studies

Technetium-99m DTPA renal imaging studies were performed within 24 hr of the clinical diagnosis of rejection crisis. Repeat studies were performed as needed during the rejection phase as well as upon recovery. A total of 358 [^{99m}Tc]DTPA studies was performed in 34 patients during this study period. The [^{99m}Tc]DTPA study was performed with a rapid i.v. bolus injection of 20 mCi (74 MBq) administered whenever possible through the dialysis access or through a large antecubital vein using a radioisotope bolus injection.* A large field-of-view gamma camera† fitted with an all-purpose, low-energy, parallel hole collimator was used. Dynamic acquisition of analog images on film and digitalization of data on a magnetic disk of a dedicated minicomputer‡ was performed at the rate of 1 frame/sec for 40 sec, followed by 1 frame/20 sec for 17 min on a 64 × 64 matrix.

Visual interpretation of the analog images were correlated with the computer generated data. A program was used for calculating the perfusion index as described by Hilson (*12*). In addition, the program calculated the iliac to transplant peak time (Delta-P), the washout on the downslope flow curve ($T_{1/2}$) and the renal peak counts to the plateau counts over the transplant, peak-to-plateau ratio (P/P), according to Preston et al. (*13*).

The global perfusion index (GPI) was calculated by flagging the whole outline of the allograft (Fig. 1). Care was taken to exclude the iliac artery when superimposed on the renal allograft image. Subtraction of background activity was performed in all cases. The cortical perfusion index (CPI) was determined by flagging the cortex on the images from 1–4 min after injection, comprising ~25% of the total kidney area, usually 2–3 pixels in width. Selection of this region of interest is based on our earlier studies (*19*), showing that the renal cortex comprises 25% of the transverse diameter of the kidney. For calculating the medullary perfusion index (MPI), an irregular region of interest (ROI) was drawn between

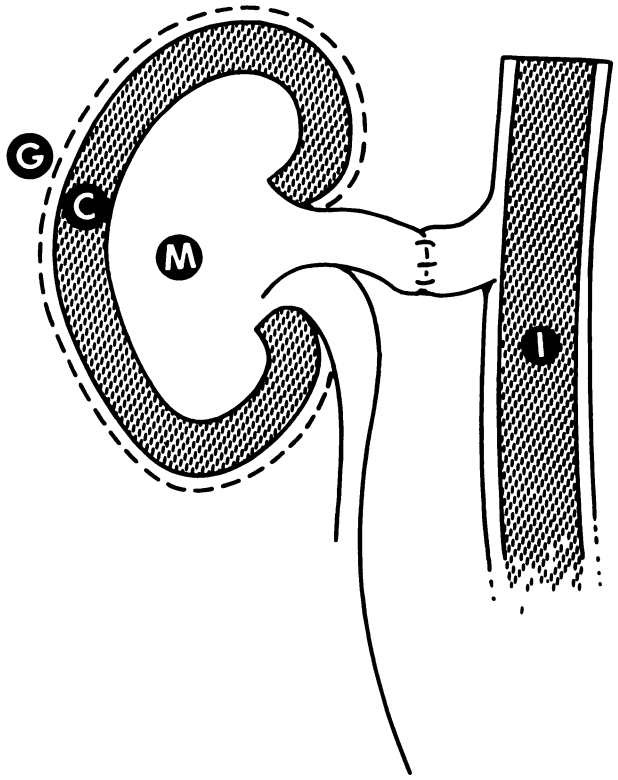

FIGURE 1
Determination of ROIs of whole kidney (G) and cortex C Medulla (M) and iliac artery (I) for calculation of global cortical and medullary perfusion indices

the cortex as described above and the renal pelvis. Statistical analysis of the global cortex and medullary perfusion indices was performed using the Student's t-test for the normally distributed data. The percent increase in the perfusion index from values obtained during stable renal function (normal) was evaluated using Student's t-test for paired data. The sensitivity and specificity for the global and cortical indices were evaluated by the chi-square analysis.

RESULTS

As shown in Table 1 there were no statistically significant differences between global, cortical, and medullary perfusion indices (GPI, CPI, and MPI) in patients suffering from ureteral obstruction or nephropathy as compared with patients with stable graft function. There was, however, a significant increase ($p < 0.001$) in GPI and CPI in patients with acute rejection crisis (mean 302 and 410, respectively).

TABLE 1
Global, Cortex, and Medullary Perfusion Indices (mean and s.e.m.) Derived from Analysis of Renograms of Transplant Recipients Performed During Periods of Normal Function, Nephropathy, Ureteral Obstruction and Acute Rejection Crises

	Normal	Nephropathy	Obstruction	Rejection
n	32	19	13	35
Global	148 ± 10	159 ± 16	165 ± 17	302 ± 25
Cortex	159 ± 11	178 ± 16	187 ± 18	410 ± 35
Medullary	128 ± 11	135 ± 14	151 ± 14	218 ± 17

TABLE 2
Percent Increase in Perfusion Indices (Mean and s.e.m.) over Previous Renograms Performed During Stable Graft Function

	Nephropathy	Obstruction	Rejection
Global	8 ± 37	7 ± 9	142 ± 24
Cortex	8 ± 11	4 ± 10	193 ± 26
Medullary	4 ± 16	12 ± 10	116 ± 21

Serial renal imaging allowed calculation of the percent increase of the perfusion indices during rejection crisis from values obtained during stable graft function. As shown in Table 2, while the cortical perfusion index of patients suffering from ARC increased dramatically (mean increase 193%), only minimal changes in the cortex perfusion index of other patients were seen (mean increase 8%, $p < 0.02$).

In contrast to the marked increase of the cortex perfusion index during ARC (mean 410) the medullary perfusion index increased only moderately (mean 218) the difference between CPI and MPI for both absolute numbers and percent increase was statistically significant ($p < 0.001$).

In addition to the perfusion indices the following parameters were also evaluated: the iliac artery to transplant peak-to-peak time (ΔP), renal peak to plateau ratio (P/P) and renal washout time ($T_{1/2}$). As seen in Table 3, the ability of the delta-P, $T_{1/2}$, and P/P indices to detect ARC was rather poor (sensitivity of 71%, 48%, and 17%, and specificity of 79%, 79%, 78%, respec-

TABLE 3
Sensitivity and Specificity of Indices Derived from Computer Generated Time-activity Blood Flow Curves*

	Sensitivity		Specificity	
Index	(n)	(%)	(n)	(%)
P-P	6/35	17	50/64	78
ΔP	25/35	71	52/64	80
$t_{1/2}$	17/35	48	51/64	80
GPI	22/35	63	57/64	90
CPI	28/35	80	56/64	87
MPI	23/35	66	61/64	95
% GPI	24/33	73	61/64	95
% CPI	31/33	94	60/64	94
% MPI	18/33	55	62/64	97

*Indices studied included renal transit time (P-P) renal washout of radionuclide ($t_{1/2}$) interval between curve peaks (ΔP), global, cortex, and medullary perfusion indices (GPI, CPI, MPI) and increase in those indices over previous renograms (% PI).

tively). When the perfusion index was 250 or higher, GPI correctly predicted acute rejection crises in 22 of the 35 studies (sensitivity 63%). Cortex perfusion index in contrast correctly predicted ARC in 28 of the 35 patients (sensitivity 80%). The sensitivity and specificity of the cortical perfusion index was further enhanced when the percent increase of the perfusion index over the previous studies done during stable graft functions was analyzed. When the perfusion index increased 70%, global and perfusion index predicted rejection accurately in 24 of 33 patients (sensitivity 73%) and medullary PI in only 18 of 33 patients (55%). In contrast, the cortical perfusion index predicted rejection accurately in 31 of 33 patients (sensitivity 94%, $p < 0.03$).

DISCUSSION

It is generally agreed that damage to the microcirculation of the kidney occurs early in the course of acute rejection crises (*5*). Porter et al. (*4*) have studied the progression of acute rejection crises in untreated dogs using serial renal biopsies. These studies have shown that obstruction and disruption of peritubular capillaries and venules occur in association with infiltration of the allograft by lymphoblasts, and are one of the earliest manifestations of ARC. Further progression of ARC produces fibrinoid necrosis of the walls of arterioles and small arteries. The deposition of fibrin and platelets on the damaged intima leads in turn to further obstruction of the cortical microcirculation and renal ischemia and necrosis. The observation that microcirculatory changes precede functional derangement during acute rejection crisis is the basis for the usefulness of radionuclide renal studies in the evaluation of graft dysfunction after renal transplantation (*12,13*).

These studies were found, however, to be unreliable in predicting early ARC (*14–16*). Visual interpretation of renograms is a rather subjective examination and is dependent to a large extent on the photographic quality of the scintigram. In order to enhance the reliability of radionuclide scintigraphy, computer enhanced techniques were developed analyzing time-activity curves generated from a bolus of the tracer as it passes through the kidney and the iliac vessels (*12,13*). Computer enhanced techniques offer several distinct advantages over the visual interpretation of radionuclide studies, among them enhanced objectivity, less reliance on photographic quality of a scintigram, and the ability to measure changes in renal blood flow in shorter time intervals. Numerous indices were thus analyzed and many attempts were made to predict ARC from changes in these indices. Preston et al. (*13*) reported the usefulness of analyzing the difference in time between the peaks of the iliac- and renal-activity curve (Delta-P), the ratio of maximal count at the peak of the renal curve to the average count in the plateau (P/P), and the time needed to reach from the peak to its half value ($T_{1/2}$), and have shown changes in these indices early in the development of ARC. These indices, however, did not always provide a reliable method of predicting ARC and failed to differentiate ARC from nonrejection nephropathy. In our own study, these indices (Delta-P, P/P, $T_{1/2}$) accurately diagnosed ARC in only 71%, 17%, and 48% of 35 patients suffering from ARC and incorrectly diagnosed ARC in 20% of patients suffering from obstruction, nephropathy, and patients with stable graft function.

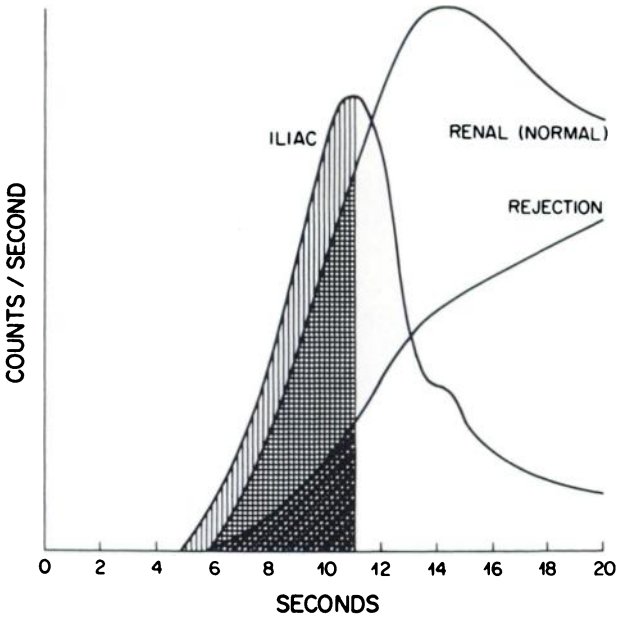

FIGURE 2
Cortex perfusion index is calculated by dividing areas under arterial (a) and renal curves (b) from time of injection to the peak of arterial time-activity curve. During rejection, area under renal curve is smaller (c) resulting in increased perfusion index. ■ a; ▤ b; ▨ c

In further studies of this question Hilson, Maisey and Brown (*12*) have analyzed time-activity curves obtained from patients with renal dysfunction after transplantation. They have calculated the kidney perfusion index by dividing the area under the curve determined by a ROI over the iliac artery from the time of injection to the peak of the arterial time-activity curve by the area under the renal curve following a rapid bolus of the tracer (Fig. 2). In a similar study Kaepfer et al. (*21*) calculated the kidney aorta index by dividing the ascending slope of the kidney perfusion histogram by the ascending slope of the aortic curve. These methods, however, did not always predict acute rejection crisis correctly, and in our study predicted ARC in only 63% of the cases.

It is generally agreed that studies of the renal blood flow do not adequately reflect the complexity of the microcirculation of the kidney with its inherent autoregulation and redistribution of blood from the cortex

to the medulla (*17,18*). Studies in our own lab (*19,20*) have recently confirmed this observation in the hypothermic ischemic kidney model. Data presented in this study reveal that the medullary perfusion index has changed only slightly during acute rejection crisis whereas the cortex perfusion index was markedly increased. As the global renal perfusion index measures changes in blood flow in both compartments the marked decrease in cortical perfusion may be masked by the relative preservation of medullary flow which is relatively unaffected early in the course of ARC. These data may explain the poor sensitivity of the renal perfusion index in predicting ARC, noted in our study. The cortex perfusion index correctly predicted ARC in 31 of 33 patients (94%) while the global and medullary perfusion indices predicted ARC correctly in only 24 and 18 of 33 patients (73%, 55%). Taken together these data suggest that evaluation of cortical perfusion as derived from the cortex perfusion index may allow early prediction of acute rejection crisis and may accurately differentiate it from nonimmunological reasons for kidney dysfunction. We hope that the improved accuracy of the radioisotope flow study to predict ARC may reduce the need for invasive diagnostic techniques with their inherent high rate of complications (*22*), and may permit timely institution of therapy thus leading to enhanced survival of renal allograft.

FOOTNOTES

* International Medical Industries, Watertown, MA.

† Maxicamera, General Electric Medical Systems, Milwaukee, WI.

‡ Gamma-11, Picker Int'l, Highland Hgts., OH.

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