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## The Renal Arterial Resistance Index and Renal Allograft Survival

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### ABSTRACT

#### BACKGROUND

Most renal transplants fail because of chronic allograft nephropathy or because the recipient dies, but no reliable factor predicting long-term outcome has been identified. We tested whether a renal arterial resistance index of less than 80 was predictive of long-term allograft survival.

#### METHODS

The renal segmental arterial resistance index (the percentage reduction of the end-diastolic flow as compared with the systolic flow) was measured by Doppler ultrasonography in 601 patients at least three months after transplantation between August 1997 and November 1998. All patients were followed for three or more years. The combined end point was a decrease of 50 percent or more in the creatinine clearance rate, allograft failure (indicated by the need for dialysis), or death.

#### RESULTS

A total of 122 patients (20 percent) had a resistance index of 80 or higher. Eighty-four of these patients (69 percent) had a decrease of 50 percent or more in creatinine clearance, as compared with 56 of the 479 patients with a resistance index of less than 80 (12 percent); 57 patients with a higher resistance index (47 percent) required dialysis, as compared with 43 patients with a lower resistance index (9 percent); and 36 patients with a higher resistance index (30 percent) died, as compared with 33 patients with a lower resistance index (7 percent) ( $P < 0.001$  for all comparisons). A total of 107 patients with a higher resistance index (88 percent) reached the combined end point, as compared with 83 of those with a lower resistance index (17 percent,  $P < 0.001$ ). The multivariate relative risk of graft loss among patients with a higher resistance index was 9.1 (95 percent confidence interval, 6.6 to 12.7). Proteinuria (protein excretion, 1 g per day or more), symptomatic cytomegalovirus infection, and a creatinine clearance rate of less than 30 ml per minute per 1.73 m<sup>2</sup> of body-surface area after transplantation also increased the risk.

#### CONCLUSIONS

A renal arterial resistance index of 80 or higher measured at least three months after transplantation is associated with poor subsequent allograft performance and death.

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**C**HRONIC ALLOGRAFT NEPHROPATHY and death with a functioning allograft account for 80 percent of allograft failures.<sup>1,2</sup> No measure accurately identifies patients at high risk for allograft loss. We recently found that a renal arterial resistance index of 80 or higher predicts a poor outcome of treatment after correction of renal-artery stenosis<sup>3</sup> and also predicts worsening renal function or death in patients with renal diseases other than renal-artery stenosis.<sup>4,5</sup> These findings prompted us to conduct a prospective study involving recipients of renal transplants. We investigated the long-term outcome in transplant recipients in whom the resistance index was measured at least 3 months after transplantation (median, 40 months; range, 3 to 317). We chose this time point because we wanted to ensure that recovery from any acute renal failure had occurred and that possible confounding influences of any complications of surgery were avoided. We also compared the predictive value of the resistance index with that of other factors associated with renal allograft failure.

## METHODS

### STUDY DESIGN AND STUDY PATIENTS

The ethics committee of the University of Hannover approved the study, and all patients gave written informed consent. Between August 1997 and November 1998, color Doppler ultrasonography was performed by a single investigator in 776 consecutive recipients of a renal transplant who were being followed in our outpatient clinic. A total of 175 of these patients were excluded from the study because they had undergone transplantation less than three months previously or because they had factors present on the day of ultrasonography that influenced the resistance-index value. Such factors included compression of the kidney by adjacent masses, acute tubular necrosis, untreated renal-artery stenosis resulting in a 50 percent reduction in the luminal diameter, hydronephrosis of grade 2 or worse, and acute rejection.<sup>6-9</sup> The patients were prospectively stratified into two groups according to the resistance index for their transplant: those with an index of 80 or higher and those with an index of less than 80.

### PRIMARY END POINT

The combined primary end point was a reduction of 50 percent or more in the creatinine clearance rate from the value measured at the time of ultraso-

nography, development of end-stage renal failure requiring the reinstatement of dialysis, or death with a functioning graft. The creatinine clearance rate (in milliliters per minute per 1.73 m<sup>2</sup> of body-surface area) and the rate of urinary protein excretion were measured during the 24 hours preceding the ultrasonographic examination and at yearly intervals thereafter. Urine collections were judged complete on the basis of quantification of the total creatinine excretion, corrected for age and sex. If the total creatinine excretion was 25 percent or more below the expected value (as it was for 91 of 601 patients), the creatinine clearance rate was estimated according to the Gault-Cockcroft formula.<sup>10</sup> Dialysis status and vital status were ascertained from the patients or their relatives. The mean ( $\pm$ SD) duration of follow-up for patients with uncensored data (i.e., patients who did not reach the combined end point) was 4.2 $\pm$ 0.3 years (range, 3.3 to 4.9).

### ULTRASONOGRAPHIC DETERMINATION OF THE RESISTANCE INDEX

Either an Ultramark 9 HDI ultrasound machine (Advanced Technology Laboratories) with a 2-to-4-MHz curved-array multifrequency transducer with a 2.5-MHz pulsed Doppler frequency or a Sienna Sono-line ultrasound machine (Siemens) with a 3.5-MHz convex-array transducer was used. The B-mode measurements were performed at the same time as the Doppler measurement of the resistance index. The ultrasonographic procedure has been described previously.<sup>3,11</sup> Briefly, the maximal length, width, and depth of the kidney were determined, and the renal volume was calculated as one half the product of the three dimensions. The renal parenchymal width was measured from the capsule to the tip of a renal pyramid.

Intrarenal Doppler signals were obtained from two to three representative proximal segmental arteries (the first vessels branching off the main renal artery). The peak systolic velocity ( $V_{\max}$ ) and the minimal diastolic velocity ( $V_{\min}$ ) were determined, the renal segmental arterial resistance index was calculated as  $100 \times [1 - (V_{\min} \div V_{\max})]$ , and the results from the two or three measurements were averaged. The reproducibility of resistance-index measurements was tested in 12 renal-transplant recipients by two independent investigators on two consecutive days in order to calculate the intraobserver, intrasession variability; the intraobserver, intersession variability; and the interobserver, intrasession variability. The respective values for the

coefficient of variation were 2.2 percent, 4.8 percent, and 3.7 percent.

In order to rule out renal-artery stenosis in the transplant, the course of the renal artery was determined with color-flow imaging. Stenosis was suspected if a segment of the vessel showed color-flow disturbance ("aliasing"). The maximal systolic-flow velocity was measured at the site of aliasing ( $V_{\text{sten}}$ ) and at the point most distal to the site ( $V_{\text{poststen}}$ ). The area of stenosis (as a percentage of the total area) was calculated according to the continuity equation as  $100 \times [1 - (V_{\text{poststen}} \div V_{\text{sten}})]$ . With the use of this approach, a stenosis resulting in a reduction in the area of 75 percent or more (equivalent to a reduction in the diameter of 50 percent or more) was diagnosed only when  $V_{\text{sten}}$  exceeded  $V_{\text{poststen}}$  by a factor of four or more. The sensitivity, specificity, and positive and negative predictive values of this method for detecting a reduction in the diameter of 50 percent or more, when verified against the findings on selective angiography in 70 renal-transplant recipients, were 100 percent, 88 percent, 96 percent, and 100 percent, respectively (unpublished data).

#### BIOPSY SUBSTUDY

In addition to performing this ultrasonographic procedure in the 601 patients with long-term follow-up, we also performed it in another 141 patients who, starting in December 2000, routinely underwent biopsy six months after transplantation as part of a biopsy program designed to guide routine clinical care. We compared their resistance-index values with histologic findings suggestive of chronic allograft nephropathy according to Banff 97 criteria.<sup>12</sup> The presence or absence of tubular atrophy, interstitial fibrosis, chronic allograft nephropathy (i.e., the combination of tubular atrophy and interstitial fibrosis), and chronic allograft arteriopathy (fibrous intimal thickening) was noted, and the findings were graded from 0 to 3. In addition, global glomerulosclerosis was evaluated semiquantitatively (with 0 denoting no globally scarred glomeruli, 1 denoting less than 25 percent globally scarred glomeruli, 2 denoting 25 to 50 percent, and 3 denoting more than 50 percent). The same histologic criteria were applied to a subgroup of the 601 patients for whom biopsy was indicated because of worsening renal function or proteinuria at least one year after transplantation (median, 5.2 years; range, 1.0 to 20.3). In these patients, ultrasonography was performed

a median of 1.3 years before biopsy (range, 4.2 years before biopsy to 1.7 years after biopsy).

#### STATISTICAL ANALYSIS

The SPSS statistical package (version 11.0, SPSS) and SAS software (version 8.2, SAS Institute) were used for all statistical analyses. Unpaired t-tests, chi-square analysis, or Kaplan-Meier analysis with the log-rank test was used as appropriate to assess the differences between groups. Cox proportional-hazards analysis was used to calculate univariate and multivariate hazard ratios as estimates of relative risks. The number of years of follow-up was calculated from the date of ultrasonography until the date of a first event or the last documented visit in our outpatient clinic. For multivariate analysis, the effect of multiple variables on worsening of renal function, need for dialysis, and death was evaluated in all 601 cases with stepwise forward Cox regression analysis (with  $P=0.10$  as the threshold level of significance for the removal of the variable from analysis and  $P=0.05$  as the threshold for entry into the model).

The variables investigated were the resistance index; the number of renal transplantations; the cold-ischemia time; the solution used for perfusion; the presence or absence of cytomegalovirus viremia and symptomatic infection; the age of the donor; the number of mismatches at the HLA-A, B, and DR loci; the number of acute interstitial and vascular rejections within and after the first three months after renal transplantation; the occurrence or nonoccurrence of a delay in graft function of more than six days after transplantation<sup>13</sup>; the percentage of panel-reactive antibodies; whether the graft was from a living or cadaveric donor; the type of underlying renal disease; the duration of dialysis; the sex of the patient; whether transplantation occurred before or after the introduction of cyclosporine; the age of the patient; the presence or absence of atherosclerosis in the heart, legs, or central nervous system; the presence or absence of diabetes; the presence or absence of hypertension; the mean systolic and diastolic blood pressure and pulse pressure as measured at home; the degree of proteinuria; the creatinine clearance rate; and the size, volume, and parenchymal width of the transplanted kidney. The pulse rate, the fasting serum glucose level, the C-reactive protein level, cholesterol levels, the uric acid level, height, and weight were always measured on the day of the ultrasonographic investigation, usually within two hours before ultrasonography,

**Table 1. Demographic and Clinical Characteristics of the Patients and Their Allografts at Base Line.\***

Characteristic	Resistance Index		P Value
	≥80 (N=122)	<80 (N=479)	
<b>Patient-related factors</b>			
Age — yr	57±11	48±13	<0.001
Coronary artery disease — no. (%)	36 (30)	89 (19)	0.01
Diabetes — no. (%)	34 (28)	74 (15)	0.002
Systolic blood pressure — mm Hg	144±19	137±15	<0.001
Diastolic blood pressure — mm Hg	79±10	82±10	0.01
No. of classes of antihypertensive drugs	2.9±1.3	2.5±1.4	0.01
<b>Graft-related factors</b>			
Cold-ischemia time — hr	25.0±6.7	23.2±8.4	0.03
Delayed graft function (>6 days) — no. (%)	40 (33)	94 (20)	0.002
Time since transplantation — yr	6.6±5.5	4.6±4.6	<0.001
Living kidney donor — no. (%)	2 (2)	41 (9)	0.005
Euro–Collins perfusion solution — no. (%)	49 (40)	108 (23)	<0.001
Trough level of cyclosporine — ng/ml†	108±37	122±34	<0.001
<b>Laboratory values</b>			
Creatinine clearance — ml/min/1.73 m <sup>2</sup> of body-surface area	51±29	65±28	<0.001
Proteinuria — g of protein excretion/day	1.1±1.8	0.5±1.0	<0.001
Serum C-reactive protein level >5 mg/liter — no. (%)	76 (62)	215 (45)	0.001

\* Plus–minus values are means ±SD. Clinical and laboratory data were obtained on the day of Doppler ultrasonography. Variables that did not differ significantly between groups defined according to the resistance index were sex; number of transplantations; number of cytomegalovirus infections; the age of the donor; number of HLA mismatches (range, 0 to 6) for all patients and for patients who received cadaveric grafts; number of episodes of rejection; percentage of panel-reactive antibodies; duration of dialysis before transplantation; percentage of patients with hypertension; body weight; body-mass index; use or nonuse of angiotensin-converting–enzyme inhibitors, calcium-channel blockers, beta-blockers, clonidine, or other classes of antihypertensive drugs; length of the renal allograft; renal volume; and renal parenchymal width.

† A total of 98 patients with a resistance index of 80 or higher and 400 patients with a resistance index of less than 80 received cyclosporine.

and information on concomitant drug use (angiotensin-converting–enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, beta-blockers, diuretics, alpha-blockers, moxonidine, clonidine, other antihypertensive drugs, and statins) was always obtained on that day as well.

Extrapolations of median survival times were performed with regression analysis (with SAS soft-

ware), with the assumption of a gamma distribution. All data are expressed as means ±SD unless otherwise stated.

## RESULTS

### THE RESISTANCE INDEX AS A PREDICTOR

Follow-up data were available for all 601 patients (Table 1). Patients with resistance-index values of 80 or higher were significantly older, had had their transplants for a longer time, had higher blood pressure, had worse graft function, had more severe proteinuria, and were more likely to have coronary artery disease than patients with resistance-index values below 80. However, only a resistance-index value of 80 or higher accurately identified patients who subsequently had a decrease of 50 percent or more in the creatinine clearance, required dialysis, or died (sensitivity, 56 percent; specificity, 96 percent).

A total of 122 patients (20 percent) had a resistance index of 80 or higher. Eighty-four of these patients (69 percent) had a decrease of 50 percent or more in the creatinine clearance rate, as compared with 56 of the 479 patients with a resistance index of less than 80 (12 percent); 57 patients with a higher resistance index (47 percent) required dialysis, as compared with 43 patients with a lower resistance index (9 percent); and 36 patients with a higher resistance index (30 percent) died, as compared with 33 patients with a lower resistance index (7 percent) ( $P<0.001$  for all comparisons). A total of 107 patients with a higher resistance index (88 percent) reached the combined end point, as compared with 83 of those with a lower resistance index (17 percent;  $P<0.001$ ). The resistance index was the strongest predictor of the combined end point (Table 2).

This finding was not altered when the variables were considered as continuous rather than dichotomous variables or when patients were stratified according to quintiles of age, time since transplantation, creatinine clearance rate, or degree of proteinuria (data not shown). The sensitivity of the resistance index improved to 65 percent (73 of 113) when the analysis included only the 113 patients who had graft failure due to biopsy-proved chronic allograft nephropathy (83 patients) or death from cardiovascular causes (30). The other major causes of a decrease of 50 percent or more in the creatinine clearance rate were recurrent disease (in 11 patients), rejection (in 7), and acute renal failure (in 5). Six patients had allograft failure from other

**Table 2. Sensitivity, Specificity, and Positive and Negative Predictive Values of the Renal Resistance Index and Other Factors for the Prediction of the Combined End Point of a Decrease of at Least 50 Percent in the Creatinine Clearance Rate, the Need for Dialysis, or Death.**

Analysis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
	<i>percent (number/total number)</i>			
<b>Resistance index <math>\geq 80</math></b>				
As predictor of the combined end point	56 (107/190)	96 (396/411)	88 (107/122)	83 (396/479)
As predictor of the need for dialysis	57 (57/100)	87 (436/501)	47 (57/122)	91 (436/479)
As predictor of death	52 (36/69)	84 (446/532)	30 (36/122)	93 (446/479)
As predictor of decrease of $\geq 50\%$ in creatinine clearance	60 (84/140)	92 (423/461)	69 (84/122)	88 (423/479)
<b>Other risk factors as predictors of the combined end point</b>				
Cold-ischemia time $>12$ hr	97 (184/190)	9 (38/411)	33 (184/557)	86 (38/44)
Urinary protein excretion $\geq 1$ g/day	26 (49/190)	95 (390/411)	70 (49/70)	73 (390/531)
Creatinine clearance $<30$ ml/min/1.73 m <sup>2</sup>	21 (39/190)	95 (392/411)	67 (39/58)	72 (392/543)
Donor age $>65$ yr	11 (20/190)	95 (390/411)	49 (20/41)	70 (390/560)
Renal parenchymal width $<15$ mm	15 (29/190)	96 (396/411)	66 (29/44)	71 (396/557)
Pulse pressure $>70$ mm Hg	32 (60/190)	86 (354/411)	51 (60/117)	73 (354/484)

known causes, and 19 had allograft failure from unknown causes. Noncardiovascular causes of death included infection (in 10 patients), cancer (in 10), other known causes (in 6), and unknown causes (in 13).

#### OTHER POSSIBLE PREDICTORS

Univariate analysis revealed a number of variables that differed significantly between the patients who reached the combined end point and those who did not (Fig. 1). However, none of these variables had a discriminatory power equal to that of the resistance index, as evidenced by the lower relative risks associated with these variables. Multivariate analysis of the combined end point (Table 3) or the various end points separately (Table 4) did not alter these findings. Moxonidine treatment, although used in only a small number of patients, was the only factor that significantly reduced the risk of the combined end point in the multivariate analysis (Table 3).

#### PREDICTION OF DEATH

Kaplan–Meier curves for the combined end point of a reduction of 50 percent or more in the creatinine

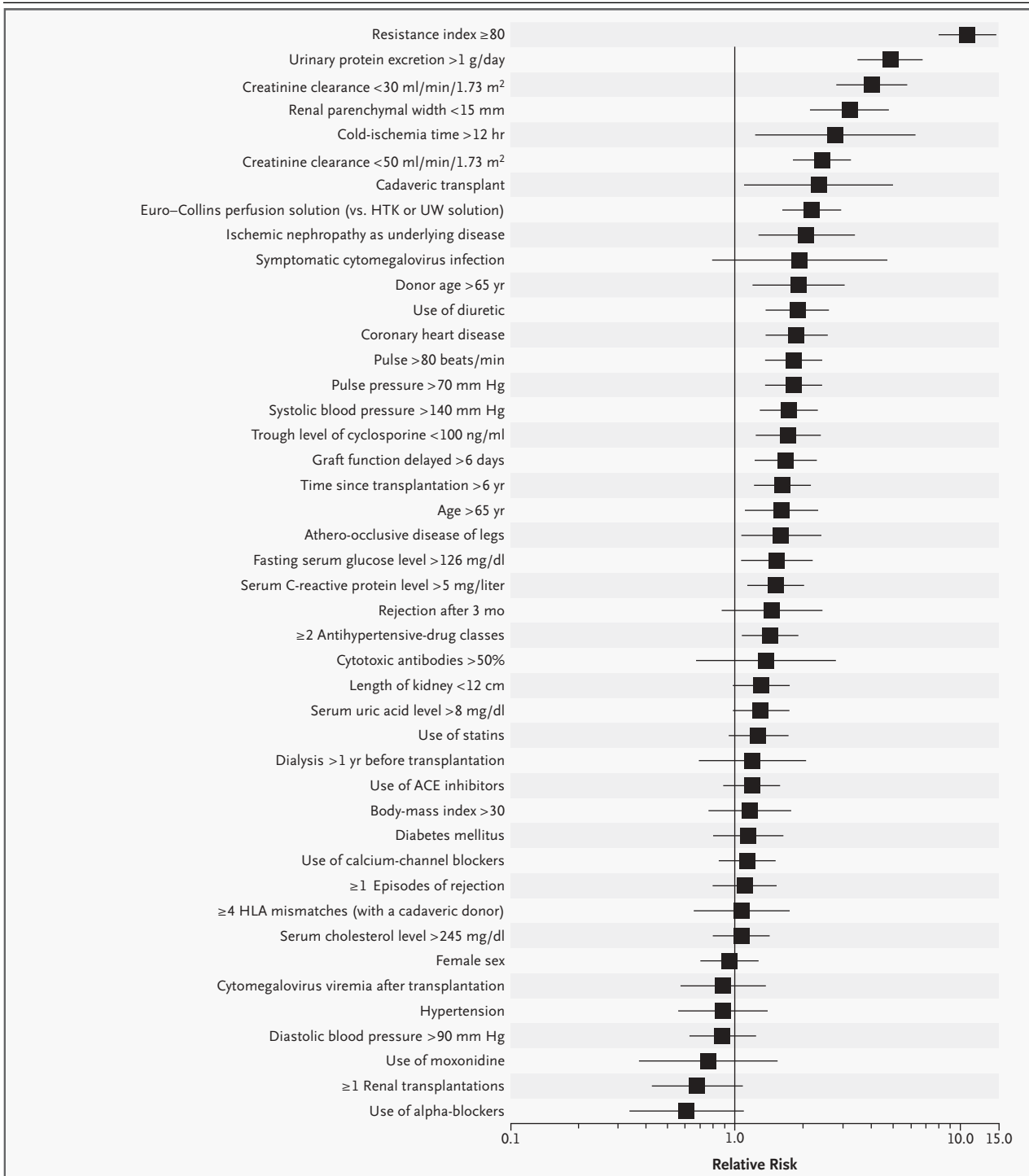
clearance rate, the need for dialysis, or death and for all end points considered separately (Fig. 2) were calculated for the group with a resistance index of 80 or higher and the group with a resistance index of less than 80. When patients who died were included in the analysis, patients with a resistance index of 80 or higher had a median allograft survival of 2.5 years (95 percent confidence interval, 2.3 to 2.6), as compared with 23.3 years (95 percent confidence interval, 5.4 to 100.5) among patients with a resistance index of less than 80.

#### VERIFICATION OF CUTOFF

In an analysis using a receiver-operating-characteristic curve, we retrospectively evaluated the accuracy of the predefined cutoff value for the resistance index. The highest sensitivity (56 percent) and specificity (96 percent) were attained at a resistance-index value of 0.795, confirming the accuracy of the predefined value of 0.80.

#### CORRELATIONS WITH OTHER MEASURES

Among the 141 additional patients who underwent biopsy at six months, tubular atrophy occurred more frequently among patients with a resistance index



**Figure 1. Univariate Relative Risk of a Decrease of 50 Percent or More in the Creatinine Clearance, the Need for Dialysis, or Death after Doppler Ultrasonography Associated with Selected Variables.**

Horizontal lines represent the 95 percent confidence intervals. To convert value for glucose to millimoles per liter, multiply by 0.05551. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert value for uric acid to micromoles per liter, multiply by 59.48. To convert value for cholesterol to millimoles per liter, multiply by 0.02586. HTK denotes histidine–tryptophan–ketoglutarate, UW University of Wisconsin, and ACE angiotensin-converting enzyme. The relative risks are shown on a logarithmic scale.

of 80 or higher than among those with a lower resistance index (relative risk, 8.6; 95 percent confidence interval, 1.1 to 67) but the semiquantitative histologic scores were not correlated with the resistance index. However, direct correlations were observed between the resistance index and the degree of interstitial fibrosis ( $R^2=0.07$ ), the degree of tubular atrophy ( $R^2=0.07$ ), the degree of chronic allograft nephropathy ( $R^2=0.07$ ), the degree of chronic allograft arteriopathy ( $R^2=0.11$ ), and the sum of the scores for chronic allograft nephropathy and chronic allograft arteriopathy ( $R^2=0.12$ ) among the 187 patients in the main study in whom an indicated biopsy was performed at least one year after transplantation ( $P<0.001$  for all correlations). No correlation was observed between the glomerulosclerosis score and the resistance index ( $R^2=0.02$ ,  $P=0.08$ ).

Among the 601 study patients, direct correlations ( $P<0.001$ ) were also observed between the resistance index and the age of the recipient ( $R^2=0.20$ ), the pulse pressure ( $R^2=0.14$ ), the systolic blood pressure ( $R^2=0.04$ ), the degree of proteinuria ( $R^2=0.04$ ), the base-line serum creatinine concentration ( $R^2=0.04$ ), and the blood glucose concentration ( $R^2=0.03$ ). Inverse correlations were observed between the resistance index and the diastolic blood pressure ( $R^2=0.04$ ) and between the resistance index and the creatinine clearance rate ( $R^2=0.05$ ). These factors explained 34 percent of the variation in the resistance index ( $R^2=0.34$ ).

## DISCUSSION

We found that a resistance index of 80 or higher in an allograft was a strong predictor of both allograft failure and death with a functioning graft. Various risk factors — including older age of the donor or the recipient, poorer renal function at one year, the presence of proteinuria, the presence and the degree of hypertension, a greater number of HLA mismatches, delayed graft function, and longer time since transplantation — have all been proposed as means for differentiating between patients with a good chance of long-term survival of a renal allograft and those with a poor chance.<sup>13-17</sup> These factors also came into play in our study. However, none of them, alone or in combination,<sup>18</sup> had a predictive value approaching that of an increased resistance-index value.

Since the resistance index is significantly correlated with many established cardiovascular risk fac-

**Table 3. Relative Risk of Allograft Loss among the 601 Patients, According to Selected Risk Factors.\***

Risk Factor	No. of Patients	Relative Risk of the Combined End Point (95% CI)	
		Univariate Analysis	Multivariate Analysis
Renal resistance index $\geq 80$	122	10.4 (7.8–14.0)	9.1 (6.6–12.7)
Urinary protein excretion $\geq 1$ g/day	70	4.7 (3.4–6.5)	4.3 (2.9–6.2)
Symptomatic cytomegalovirus infection	11	1.9 (0.8–4.6)	3.0 (1.2–7.3)
Creatinine clearance $<30$ ml/min/ 1.73 m <sup>2</sup>	58	3.9 (2.7–5.6)	2.4 (1.6–3.5)
Ischemic nephropathy as underlying disease	36	2.0 (1.2–3.3)	2.4 (1.4–4.1)
Donor age $>65$ yr	41	1.9 (1.2–3.0)	1.8 (1.1–3.0)
Euro-Collins perfusion solution	157	2.1 (1.6–2.9)	1.6 (1.2–2.2)
Pulse $>80$ beats per min	189	1.8 (1.3–2.4)	1.4 (1.0–1.9)
Coronary heart disease	125	1.8 (1.3–2.5)	1.4 (1.0–2.0)
Moxonidine use	33	0.8 (0.4–1.5)	0.3 (0.1–0.6)

\* The combined end point was a decrease of 50 percent or more in the creatinine clearance rate, the need for dialysis, or death. CI denotes confidence interval.

tors, such as age, coronary heart disease, increased systolic and pulse pressure, and decreased renal function, it is not surprising that increased renal vascular resistance predicts not only graft failure but also death due to cardiovascular disease. Cardiovascular disease is the major cause of death in renal-transplant recipients. Several authors have found an increased resistance index particularly in patients who have signs of hypertensive end-organ damage such as microalbuminuria, left ventricular hypertrophy, increased carotid-wall thickness, and overt carotid atherosclerosis.<sup>19-21</sup> The resistance index during long-term follow-up has been used to diagnose allograft nephropathy.<sup>6,22</sup> No close association was observed between the resistance index and renal histology in these earlier studies or in our investigation.<sup>23</sup> Trillaud et al. did not find a relation between the resistance index measured 6 days after renal transplantation and the level of renal function at 12 months.<sup>24</sup> However, these investigators did not use the resistance index to predict allograft survival or death with a functioning graft.

The renal resistance index is nonspecific and is influenced by many factors. Some are unrelated to disease. For example, the site at which renal resist-

**Table 4. Relative Risk of a Decrease of 50 Percent or More in the Creatinine Clearance Rate, the Need for Dialysis, or Death, According to Selected Variables.**

Variable	Relative Risk (95% CI)	
	Univariate Analysis	Multivariate Analysis
<b>Decrease of <math>\geq 50\%</math> in the creatinine clearance rate</b>		
Renal resistance index $\geq 80$	12.1 (8.5–17.1)	12.2 (8.2–18.2)
Symptomatic cytomegalovirus infection	2.9 (0.9–9.7)	5.3 (2.1–13.0)
Urinary protein excretion $\geq 1$ g/day	5.7 (4.0–8.3)	4.7 (3.1–7.1)
Ischemic nephropathy as underlying disease	2.3 (1.3–3.9)	3.5 (1.9–6.1)
Creatinine clearance $< 30$ ml/min/1.73 m <sup>2</sup>	4.4 (3.0–6.6)	2.6 (1.6–4.0)
Rejection after 3 mo	2.0 (0.7–5.7)	2.2 (1.3–3.9)
Pulse rate $> 80$ beats per min	2.0 (1.4–2.7)	1.5 (1.1–2.2)
<b>Need for dialysis</b>		
Renal resistance index $\geq 80$	9.4 (6.2–14.0)	8.8 (5.5–14.1)
Symptomatic cytomegalovirus infection	3.4 (1.4–8.4)	6.9 (2.7–17.5)
Urinary protein excretion $\geq 1$ g/day	6.8 (4.5–10.3)	5.3 (3.3–8.4)
Ischemic nephropathy as underlying disease	2.8 (1.6–5.1)	2.8 (1.5–5.2)
Creatinine clearance $< 30$ ml/min/1.73 m <sup>2</sup>	5.0 (3.2–7.8)	2.8 (1.7–4.6)
Rejection after 3 mo	1.9 (1.0–3.5)	2.6 (1.4–4.9)
Pulse rate $> 80$ beats per min	2.0 (1.4–3.0)	2.2 (1.4–3.5)
<b>Death</b>		
Renal resistance index $\geq 80$	8.9 (5.5–14.4)	7.2 (4.3–12.0)
Coronary heart disease	3.1 (1.9–5.0)	3.0 (1.8–4.9)
Creatinine clearance $< 30$ ml/min/1.73 m <sup>2</sup>	2.9 (1.5–5.6)	2.5 (1.3–5.0)
Urinary protein excretion $\geq 1$ g/day	2.3 (1.2–4.5)	2.5 (1.2–5.2)
Fasting serum glucose level $> 126$ mg/dl*	2.8 (1.6–4.6)	2.2 (1.3–3.7)

\* To convert values for glucose to millimoles per liter, multiply by 0.05551.

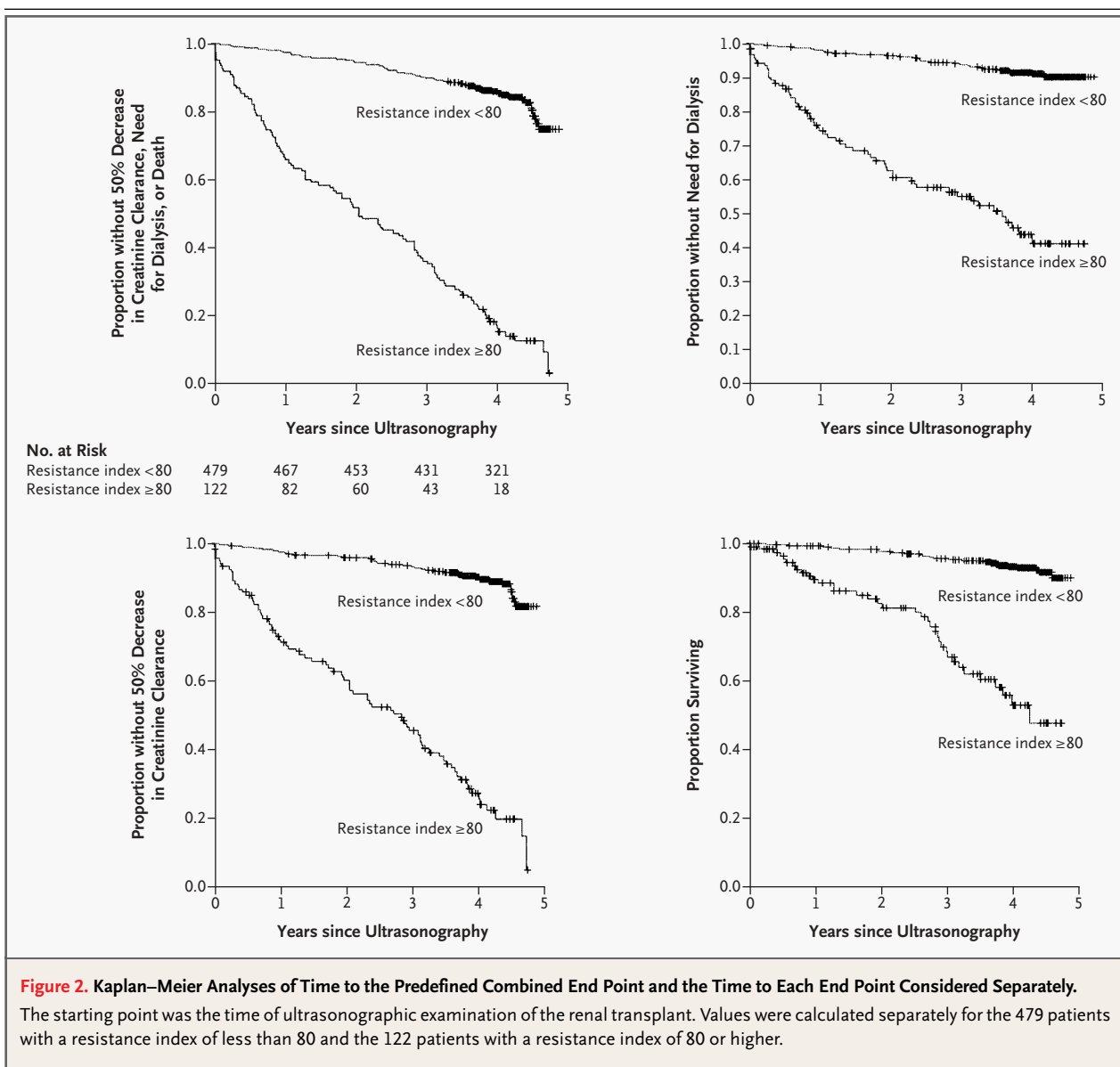
ance is measured<sup>25</sup> and the increased intraabdominal pressure during forced inspiration (the Valsalva maneuver) influence the index.<sup>26</sup> A pulse rate of less than 50 beats per minute may increase the resistance index, and a pulse rate of more than 70 beats per minute may lower it.<sup>27</sup> Finally, increasing age is also associated with an increased resistance index, particularly in hypertensive patients.<sup>28</sup> Two common renal diseases that are associated with an increased renal resistance index are diabetic and hypertensive nephrosclerosis.<sup>29</sup> Other diseases that

also increase the index are acute renal failure and urinary tract obstruction with hydronephrosis. We attempted to exclude all extrarenal variables. We carefully excluded patients with potentially reversible renal disease states such as urinary tract obstruction and acute rejection.

The resistance index was correlated not with the histologic features of the allograft at six months, as was seen in the 141 patients in the biopsy study but, rather, with histologic findings obtained at least one year after transplantation. However, the latter results are confounded by the fact that only 31 percent of the 601 renal-transplant recipients underwent a renal biopsy. Thus, we are not able to rule out sampling errors entirely.<sup>12</sup> Moreover, the resistance index was correlated more closely with characteristics of the recipients, such as age and arterial pulse pressure, suggesting that extrarenal factors have a major effect on the resistance index in the allograft.<sup>9,30</sup> The factors influencing the resistance index explained only 34 percent of the variation we found in the resistance index. Thus, there are other operative variables that we were unable to define.

We observed a possible favorable effect exerted by moxonidine treatment for hypertension in cyclosporine-treated patients. This observation may be spurious, since the numbers were small. Nevertheless, cyclosporine has been shown to increase sympathetic-nerve activity<sup>31</sup> and to decrease brachial-artery distensibility.<sup>32</sup> Since an increased resistance index was correlated most closely with the pulse pressure, a crude marker of vascular stiffness, a substance such as moxonidine that inhibits sympathetic-nerve activity could positively influence vascular stiffness in renal-transplant recipients. Other drugs that could be tested for their effect on the resistance index are lisinopril,<sup>33</sup> the prostacyclin analogue iloprost,<sup>34</sup> and tacrolimus.<sup>35</sup> The use of the Euro-Collins solution for perfusion of the allograft has been associated with higher resistance and poorer outcomes than the University of Wisconsin solution not only in our study, but also in another study.<sup>36</sup>

Our study has several limitations. We did not perform renal histologic analyses in all 601 patients, nor did we routinely perform parallel duplex ultrasonographic studies in these patients. However, our more recent patients are undergoing repeated biopsies and parallel duplex ultrasonographic studies on a regular basis. The histologic findings will have to be graded quantitatively in order to permit better correlation with the results on ultrasonography. The data we obtained at six months from the biopsies



**Figure 2.** Kaplan–Meier Analyses of Time to the Predefined Combined End Point and the Time to Each End Point Considered Separately.

The starting point was the time of ultrasonographic examination of the renal transplant. Values were calculated separately for the 479 patients with a resistance index of less than 80 and the 122 patients with a resistance index of 80 or higher.

specified in the protocol probably did not represent sufficiently long-term follow-up to permit a highly sensitive comparison between histologic features and the resistance index.

We suggest that a Doppler ultrasonographic study performed three or more months after transplantation can predict long-term allograft outcomes. Our data also suggest that longitudinal Doppler studies may be useful in monitoring interventions such as different immunosuppressive protocols or in comparing the capability of various anti-

hypertensive drugs to improve allograft outcomes. Such studies may reduce the need for sequential renal biopsies, with their associated risks. However, an increased resistance index could mean acute vascular rejection with endarteritis, chronic allograft nephropathy, or both. Only a renal biopsy can distinguish among these conditions.

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## REFERENCES

- Kreis HA, Ponticelli C. Causes of late renal allograft loss: chronic allograft dysfunction, death, and other factors. *Transplantation* 2001;71:Suppl:SS5-SS9.
- Howard RJ, Patton PR, Reed AI, et al. The changing causes of graft loss and death after kidney transplantation. *Transplantation* 2002;73:1923-8.
- Radermacher J, Chavan A, Bleck J, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med* 2001;344:410-7.
- Radermacher J, Ellis S, Haller H. Renal resistance index and progression of renal disease. *Hypertension* 2002;39:699-703.
- Petersen LJ, Petersen JR, Talleruphuus U, Ladefoged SD, Mehlsen J, Jensen HA. The pulsatility index and the resistive index in renal arteries: associations with long-term progression in chronic renal failure. *Nephrol Dial Transplant* 1997;12:1376-80.
- Don S, Kopecky KK, Filo RS, et al. Duplex Doppler US of renal allografts: causes of elevated resistive index. *Radiology* 1989;171:709-12.
- Skotnicki SH, van Asten WN, Beijneveld WJ, van Roosmalen R, Hoitsma AJ, Wijn PF. Evaluation of renal allograft function by Doppler spectrum analysis: a preliminary study. *Transpl Int* 1989;2:16-22.
- Pozniak MA, Kelcz F, Stratta RJ, Oberley TD. Extraneous factors affecting resistive index. *Invest Radiol* 1988;23:899-904.
- Restrepo-Schafer IK, Schwerek WB, Muller TF, Prinz H, Gorg C, Arnold R. Intrarenal Doppler flow analysis in patients with kidney transplantation and stable transplant function. *Ultraschall Med* 1999;20:87-92. (In German.)
- Gault MH, Longerich LL, Harnett JD, Wesolowski C. Predicting glomerular function from adjusted serum creatinine. *Nephron* 1992;62:249-56.
- Radermacher J, Chavan A, Schäffer J, et al. Detection of significant renal artery stenosis with color Doppler sonography: combining extrarenal and intrarenal approaches to minimize technical failure. *Clin Nephrol* 2000;53:333-43.
- Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. *Kidney Int* 1999;55:713-23.
- Giral-Classe M, Hourmant M, Cantarovich D, et al. Delayed graft function of more than six days strongly decreases long-term survival of transplanted kidneys. *Kidney Int* 1998;54:972-8.
- Opelz G, Sasaki N, Terasaki PI. Prediction of long-term kidney transplant survival rates by monitoring early graft function and clinical grades. *Transplantation* 1978;25:212-5.
- Takemoto SK, Terasaki PI, Gjertson DW, Cecka JM. Twelve years' experience with national sharing of HLA-matched cadaveric kidneys for transplantation. *N Engl J Med* 2000;343:1078-84.
- Ponticelli C, Villa M, Cesana B, Montagnino G, Tarantino A. Risk factors for late kidney allograft failure. *Kidney Int* 2002;62:1848-54.
- Mange KC, Cizman B, Joffe M, Feldman HI. Arterial hypertension and renal allograft survival. *JAMA* 2000;283:633-8.
- Hennige M, Kohler CO, Opelz G. Multivariate prediction model of kidney transplant success rates. *Transplantation* 1986;42:491-3.
- Pontremoli R, Viazzi F, Martinoli C, et al. Increased renal resistive index in patients with essential hypertension: a marker of target organ damage. *Nephrol Dial Transplant* 1999;14:360-5.
- Shimizu Y, Itoh T, Hougaku H, et al. Clinical usefulness of duplex ultrasonography for the assessment of renal arteriosclerosis in essential hypertensive patients. *Hypertens Res* 2001;24:13-7.
- Alterini B, Mori F, Terzani E, et al. Renal resistive index and left ventricular hypertrophy in essential hypertension: a close link. *Ann Ital Med Int* 1996;11:107-13.
- Drudi FM, Cascone F, Pretagostini R, et al. Role of color Doppler US in the evaluation of renal transplant. *Radiol Med (Torino)* 2001;101:243-50. (In Italian.)
- Breitenseher M, Helbich T, Kainberger F, et al. Color Doppler ultrasound of kidney transplants: does the resistance index facilitate diagnosis of chronic kidney failure? *Ultraschall Med* 1994;15:24-8. (In German.)
- Trillaud H, Merville P, Tran Le Linh P, Palussiere J, Potaux L, Grenier N. Color Doppler sonography in early renal transplantation follow-up: resistive index measurements versus power Doppler sonography. *AJR Am J Roentgenol* 1998;171:1611-5.
- Martinoli C, Bertolotto M, Crespi G, Pretolesi F, Valle M, Derchi LE. Duplex Doppler analysis of interlobular arteries in transplanted kidneys. *Eur Radiol* 1998;8:765-9.
- Takano R, Ando Y, Taniguchi N, Itoh K, Asano Y. Power Doppler sonography of the kidney: effect of Valsalva's maneuver. *J Clin Ultrasound* 2001;29:384-8.
- Schwerek WB, Restrepo IK, Prinz H. Semiquantitative analysis of intrarenal arterial Doppler flow spectra in healthy adults. *Ultraschall Med* 1993;14:117-22. (In German.)
- Boddi M, Sacchi S, Lammel RM, Mohseni R, Sernerri GG. Age-related and vasomotor stimuli-induced changes in renal vascular resistance detected by Doppler ultrasound. *Am J Hypertens* 1996;9:461-6.
- Radermacher J. Ultrasonography in the diagnosis of renovascular disease. *Imaging Decis* 2002;6(2):15-22.
- Krumme B, Grotz W, Kirste G, Schollmeyer P, Rump LC. Determinants of intrarenal Doppler indices in stable renal allografts. *J Am Soc Nephrol* 1997;8:813-6.
- Gerhardt U, Riedasch M, Hohage H. Cyclosporine A modulates baroreceptor function in kidney transplant recipients. *Int J Cardiol* 1999;68:203-8.
- Kosch M, Barenbrock M, Kisters K, Rahn KH, Hausberg M. Relationship between muscle sympathetic nerve activity and large artery mechanical vessel wall properties in renal transplant patients. *J Hypertens* 2002;20:501-8.
- Leoncini G, Martinoli C, Viazzi F, et al. Changes in renal resistive index and urinary albumin excretion in hypertensive patients under long-term treatment with lisinopril or nifedipine GITS. *Nephron* 2002;90:169-73.
- Scorza R, Rivolta R, Mascagni B, et al. Effect of iloprost infusion on the resistance index of renal vessels of patients with systemic sclerosis. *J Rheumatol* 1997;24:1944-8.
- Radermacher J, Meiners M, Bramlage C, et al. Pronounced renal vasoconstriction and systemic hypertension in renal transplant patients treated with cyclosporin A versus FK 506. *Transpl Int* 1998;11:3-10.
- Bittard H, Benoit G, Moukarzel M, et al. Decrease in renal vascular resistance in University of Wisconsin solution preserved kidney transplants. *J Urol* 1991;146:1-4.

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