Kidney International, Vol. 60 (2001), pp. 309–318

Post-transplant renal artery stenosis: The hemodynamic response to revascularization

Piero Ruggenenti, Lidia Mosconi, Simona Bruno, Andrea Remuzzi, Fabio Sangalli, Maria Serena Lepre, Roberto Agazzi, Roberto Nani, Giorgio Fasolini, and Giuseppe Remuzzi

Clinical Research Center for Rare Diseases "Aldo & Cele Daccò," Mario Negri Institute for Pharmacological Research, and Units of Nephrology and Radiology, Ospedali Riuniti, Azienda Ospedaliera, Bergamo, Italy

Post-transplant renal artery stenosis: The hemodynamic response to revascularization.

Background. Percutaneous transluminal angioplasty and stenting are relatively noninvasive approaches to treat post-transplant renal artery stenosis. However, the real impact of this procedure on renal function recovery has never been quantitated precisely to date.

Methods. In eight consecutive renal transplant patients with renal graft artery stenosis, blood pressure, body weight, and anatomical, functional, and Doppler ultrasound parameters were evaluated before and one month after renal artery transluminal angioplasty and stenting. On both occasions, glomerular filtration rate and renal plasma flow were evaluated by inulin and paraaminohippuric acid renal clearances, and glomerular size-selective function was evaluated by the fractional clearances of neutral dextran macromolecules.

Results. The correction of renal artery stenosis, by normalizing renal vascular resistances, fully restored kidney perfusion and decreased arterial blood pressure, relieved water and sodium retention, restored an almost laminar arterial blood flow, and normalized vascular shear stress without appreciable effects on glomerular barrier size-selective function and proteinuria. Pre-angioplasty and postangioplasty renal resistive indices and peak systolic blood velocity estimated by Doppler ultrasounds were significantly correlated with the effective renal plasma flow and the blood velocity calculated at the site of stenosis. All patients were discharged without sequelae one or two days after angioplasty.

Conclusions. Percutaneous transluminal angioplasty and stenting are safe and effective procedures to normalize the functional changes sustained by hemodynamically significant artery stenosis after renal transplantation. Doppler ultrasound scanning is a reliable and reproducible technique to monitor the renal functional response to vascular reperfusion.

Key words: stenosis, transplantation, vascular perfusion, Doppler ultrasound, hypertension, kidney perfusion, renal artery stenosis.

Received for publication August 31, 2000
and in revised form November 20, 2000
Accepted for publication January 26, 2001

Renal artery stenosis is a well-known cause of post-transplant hypertension that can result in renal allograft dysfunction [1, 2]. The incidence ranges from 1 to 12% depending on the definition of significant stenosis and on the indications for arteriography [3]. Arteriography is the definitive diagnostic method, but new noninvasive procedures such as Doppler ultrasonography may be useful for screening of the disease [4].

For many years, surgical correction has been the only treatment option for transplant renal artery stenosis, with reported correction rates ranging from 63 to 92% [5]. The procedure, however, carries a significant risk of graft loss, uretheral injury, reoperation, and mortality. On the other hand, medical management may allow control of arterial hypertension but fails to restore kidney perfusion. In the last few years, percutaneous transluminal revascularization has gained large popularity as a relatively noninvasive approach to improve both blood pressure control and kidney perfusion. The procedure may be successful in up to 76% of cases, but its effectiveness is strongly dependent on center experience and on the type of lesion [5]. Moreover, despite immediate success, 5 to 30% of treated renal artery stenoses show restenosis six to eight months after the procedure, which may require the use of endoprostheses, namely stents, as an adjunctive therapy to angioplasty [6, 7]. Regardless of the adopted procedure, however, the real impact of reperfusion on renal function recovery has not been quantitated precisely to date.

Actually, in addition to a decreased systemic blood pressure, the relief of renal artery stenosis is assumed to decrease prerenal resistance and to restore kidney perfusion. It is conceivable that the consequent increase in glomerular perfusion pressure and rate might alter the intrinsic properties of the glomerular barrier, thereby facilitating the passage of circulating proteins into the Bowman's space [8, 9]. On the other hand, the attendant improvement in perfusion might elevate the glomerular

filtration rate (GFR), thereby making it possible for the filtered protein load to increase without an accompanying change in filtration barrier charge or size selectivity. To distinguish these possibilities, we studied patients with renal artery stenosis before and after angioplasty and stenting, and compared the urinary protein excretion to the clearance of a broad-size distribution of neutral dextrans. Because the test dextran preparation was uncharged and because dextran was excreted solely by glomerular filtration and neither secreted into nor reabsorbed from the tubule lumen [10, 11], any changes in its urinary clearance relative to that of freely permeable inulin should reflect the alterations in the size-selective properties of the glomerular filter uniquely. Thus, the present study was primarily aimed at comparing renal hemodynamics and glomerular size-selective function before and after angioplasty by ad hoc renal clearance protocols. Moreover, the measured changes in renal plasma flow (RPF) and vascular resistances were compared with the changes in blood flow velocity profiles recorded from the renal artery and parenchyma by Doppler ultrasound scanning. This served to evaluate whether Doppler ultrasonography was a reliable and reproducible technique to monitor the renal functional response to vascular reperfusion.

METHODS

Patient selection and baseline evaluation

All renal transplant patients referred to the Outpatient Clinic of the Unit of Nephrology of the Ospedali Riuniti, Azienda Ospedaliera of Bergamo, because of suspected renal artery stenosis were asked to enter the study. Only those providing written informed consent according to the declaration of Helsinki were selected for study participation. All selected cases were referred to the Clinical Research Center for Rare Diseases "Aldo & Cele Daccò" Villa Camozzi, Ranica, where an ultrasound evaluation was carried out with an Ultramark 9 HDI device (Advanced Technology Laboratories, Bothell, WA, USA), employing a 7-4 MHz convex probe. Color flow Doppler was performed according to a predefined diagnostic protocol aimed to detect blood flow turbulences and increased peak systolic velocity in the renal graft artery, and to quantitate intrarenal vascular resistance by calculating the resistive index (RI) using this formula:

$$RI = (PSF - LDF)/PSF \qquad \text{(Eq. 1)}$$

where PSF is the peak systolic frequency shift and LDF is the lowest diastolic frequency shift. At least three different measures were performed on each graft. In all patients with clinical and instrumental (Doppler) suspicion of a hemodynamically significant renal graft artery stenosis, GFR and RPF were measured by inulin and para-aminohippuric acid (PAH) clearances, respectively, and the glomerular barrier size selectivity was assessed by the fractional clearances of neutral dextran test molecules (**Methods** section). Then a selective renal artery angiography was performed. One additional patient with severe (Leriche class III-IV) peripheral artery disease was studied during an angiographic evaluation of both iliac and femoral arteries, despite no echo-Doppler evidence of renal artery stenosis.

Angioplasty and stent deployment

A transluminal angioplasty combined to a stent deployment was performed whenever a >50% renal artery stenosis—that is, a stenosis considered hemodynamically relevant [7, 12]—was detected. The degree of stenosis was measured before and immediately after the procedure by use of a millimetric ruler. The percentage of stenosis (S%) was determined using this formula:

$$S\% = (D_o - D_s)/D_o \qquad \text{(Eq. 2)}$$

where D_o is the reference diameter, and D_s is the diameter at the site of stenosis. D_o was measured at a segment of an uninvolved renal artery.

Ipsilateral femoral artery puncture was performed, and a 7F introducer sheath was inserted. Standard balloon angioplasty was performed before stent deployment. The selected balloon diameter was equal to the diameter of the transplant renal artery. Then a balloon-expandable stent (Palmaz Cardis Stent; Johnson & Johnson, Princeton, NJ, USA) was implanted. The stent diameter was the same as the largest percutaneous transluminal angioplasty balloon used. After stent deployment, an intrastent angioplasty was performed when the diameter within the stent was less than the reference diameter of the artery. The selective renal artery angiography was repeated immediately after the completion of the procedure to verify and quantitate the achieved dilation of the stenotic tract. The procedure was considered successful when residual stenosis was 0%. A 24-hour heparinization and antiplatelet treatment (aspirin 100 mg/day) was given to all patients. The patients were discharged one to two days after the procedure.

Follow-up

A second ultrasound evaluation was repeated one month later to verify and quantitate the changes in peak systolic velocities and intrarenal resistive indices as compared with baseline. On the same occasion, the renal clearances were repeated according to the same protocol described for baseline evaluations (see next section).

The primary clinical and laboratory parameters—including systolic, diastolic, and mean arterial blood pressure, body weight, serum creatinine and creatinine clearance, 24-hour urine protein excretion rate, routine hematochemistry, and immunosuppressive and antihypertensive therapy—were recorded at each of the two clearance

study time points. Any serious or nonserious adverse event was carefully monitored up to resolution and was recorded in the patient case record form.

Functional studies

All patients underwent solute clearance studies shortly after Doppler ultrasound evaluation and one month after the renal artery angiography and transluminal angioplasty. The time lag between angioplasty and the clearance studies was aimed at eliminating any potential and transient confounding effect of radiocontrast toxicity on the renal function parameters. Exactly the same procedure was used for each patient in all functional evaluations. After overnight fasting, on the morning of the clearance studies, patients were admitted to a Metabolic Ward and submitted a 24-hour urine collection for the evaluation of creatinine clearance and urinary urea, sodium, and total protein excretion. They were given their usual immunosuppressive therapy except for cyclosporine, which was administered only after completion of the clearance studies in order to avoid the confounding effect of acute cyclosporine-induced changes in renal hemodynamics [13]. Antihypertensive therapy and diuretics were withdrawn until the end of the study, and only sublingual nifedipine was allowed in selected cases to control severe or symptomatic hypertension throughout the clearance studies. A constant diuresis was induced by oral water loading. As soon as a steady-state diuresis was achieved, inulin, PAH, and neutral dextran clearances were performed, as described in detail previously (in one patient with previous history of allergy, neutral dextrans were not injected) [14, 15]. Briefly, primed infusion of inulin and PAH was immediately followed by a slow intravenous administration (about 15 min) of Dextran-40 (130 mg/kg, Rheomacrodex; Pharmacia, Uppsala, Sweden). A sustained infusion of inulin and PAH was continued throughout the study to maintain constant plasma concentrations. After an equilibration period of approximately 60 minutes, three exactly timed urine collections of 30 minutes each were made by spontaneous voiding. Blood samples were collected at the beginning and the end of each clearance period. Urine and plasma samples obtained during the first clearance period were used to determine fractional clearance of dextran molecules of graded size (effective molecular radius ranging from 26 to 66 Å).

Analytical methods

Inulin and PAH concentrations in plasma and urine samples were determined using previously described methods [14, 15]. GFR was calculated as the average inulin clearance. Effective RPF (ERPF) was calculated from the average PAH clearance, assuming, as reported previously [16], a renal extraction coefficient for PAH of 0.9. Methods for calculating the other functional parameters are given in the **Appendix**. Separation of graded-size dextran molecules and inulin in plasma and urine samples was performed by gel permeation chromatography on a Sephacryl S-300 column (1.6 × 95 cm), as previously described [14, 15]. Column calibration was performed using dextran standards of known molecular weight (Pharmacosmos, Viby Sj., Denmark).

The molecular radius of individual dextran fractions was calculated according to direct measurements of dextran standards as reported by Oliver et al, which relate to effective molecular radii and mean molecular weight of these macromolecules [17]. Dextran and inulin concentrations were assayed in eluted fractions using colorimetric methods as previously described [14, 15, 18]. The urine-to-plasma concentration ratio for inulin was calculated from inulin concentrations in eluted fractions. The fractional clearance of dextran macromolecules was then computed as follows:

$$\vartheta_D = (U/P)_D/(U/P)_{IN} \qquad \text{(Eq. 3)}$$

where $(U/P)_D$ and $(U/P)_{IN}$ are the urine-to-plasma concentration ratios of dextran and inulin, respectively. Other laboratory measurements were performed using routine laboratory techniques.

Statistical analysis

Data were expressed as mean ± SD or median and range as specified. Statistical analysis was performed using the analysis of variance (ANOVA), and specific comparisons between different group means were performed using the two-tailed Student *t* test for paired data. Correlation analyses were done using Pearson *r* coefficients. Statistical analysis was performed using the software package Statwiew (Abacus Concepts Inc., Berkeley, CA, USA). The statistical significance level was defined as $P < 0.05$.

RESULTS

Eight consecutive renal transplant patients (6 men and 2 women) referred to the Clinical Research Center from October 1994 to October 1999 completed the study. They were 37 (range of 20 to 61) years old and had received a cadaveric kidney graft a mean of 26 (range of 3 to 94) months before. They were on chronic, oral immunosuppressive therapy with a mean dose of cyclosporine A microemulsion (Sandimmun Neoral) of 3.9 (range of 1.9 to 6.7) mg/kg/day and prednisone (5 to 12 mg/day). Four patients also were receiving mofetil micophenolate (1 or 2 g/day) and four azathioprine (50 to 200 mg/day). All patients were on chronic antihypertensive therapy with one drug ($N = 2$), two drugs ($N = 2$), two drugs plus a diuretic ($N = 3$), or three drugs ($N = 1$). Seven patients were on atenolol (50 to 100 mg/day) and five on nifedipine (30 to 60 mg/day). No patient was receiving angio-

Table 1. Main clinical parameters before and after angioplasty (AP)

	Before AP	After AP	*P* value
Body weight *kg*	71.7 ± 15.4	69.1 ± 14.8	<0.01
SBP *mm Hg*	150 ± 5	143 ± 7	<0.05
DBP *mm Hg*	94 ± 9	92 ± 11	NS
MBP *mm Hg*	113 ± 7	109 ± 9	NS
HR *beats/min*	61.5 ± 5	57 ± 4	NS

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; NS, not significant.

Table 2. Main functional and anatomical parameters before and after angioplasty (AP)

	Before AP	After AP	*P* value
GFR *mL/min/1.73 m²*	44.9 ± 13.0	50.9 ± 9.7	NS
ERPF *mL/min/1.73 m²*	319 ± 122	456 ± 179	<0.05
FF %	15 ± 5	12 ± 4	<0.01
RVR *mm Hg/mL/min/1.73 m²*	23.1 ± 9.7	15.9 ± 6.0	<0.05
RI	0.52 ± 0.12	0.63 ± 0.06	<0.01
SPV *cm/s*	384 ± 195	155 ± 38	<0.01
Area *mm²*	3.6 ± 2.4	27.4 ± 5.9	<0.01
Reynolds' number	1892 ± 396	888 ± 227	<0.01
Wall shear stress *dynes/cm²*	551 ± 342	21 ± 7	<0.01

Abbreviations are: GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction; RVR, renal vascular resistances; RI, resistive index; SPV, systolic peak velocity; NS, not significant.

tensin-converting enzyme inhibitors or angiotensin II receptor antagonists. The main clinical and laboratory parameters at study entry are summarized in Tables 1 and 2.

Renal artery stenosis presented with newly onset or worsening hypertension in all patients combined to increasing serum creatinine concentration in six cases. At study entry, color-flow Doppler ultrasonography showed decreased resistive indices and increased peak systolic artery velocities (Table 2). All patients had depressed GFR and ERPF and increased renal vascular resistances and filtration fraction (Table 2). The selective renal artery angiography detected a stenosis at the anastomotic site in seven patients, whereas a postanastomotic stenosis was seen in one patient. The degree of stenosis ranged from 55 to 90%, and the residual cross-sectional area, calculated at the stenotic site, ranged from 1.2 to 7.0 mm^2 (Table 2).

Standard balloon angioplasty was performed before stent deployment in all patients. The procedure was a technical success with no residual stenosis in all patients. Representative angiograms taken from two patients before (left panel) and after (right panel) stenting are shown in Figure 1. In the study group as a whole, correction of the stenosis was associated with a significant reduction in systolic (but not in mean or diastolic) blood pressure (Table 1), despite the concomitant reduction in the number and dose of antihypertensive drugs in five patients. After the procedure, the number of patients on one antihypertensive drug (including a diuretic in one case) increased from two to five. Two patients were still on two drugs and one patient on three drugs. The number of patients on atenolol decreased from seven to four (unchanged doses), and of those on nifedipine from five to four (halved doses in 2 cases). Only one patient (the one on 3 drugs) remained on the same prestenting antihypertensive therapy. Also, the body weight significantly decreased by approximately 2.5 kg (Table 1) in parallel with a trend to higher sodium and free water clearances (Table 3).

As expected, after the procedure, the mean intraparenchymal-resistive indices increased in parallel with a significant reduction in mean peak renal artery systolic velocities (Table 2 and Fig. 2). The RI did not increase in one patient (of note, the one with the highest prestenting values), and the peak systolic velocity did not change in another one. Thus, after the procedure, all patients showed a change in at least one of the Doppler ultrasound parameters considered.

These echographic changes most likely reflected the significant increase in ERPF and the parallel decrease in RVR that were uniformly observed in all functional studies after the procedure (Table 2 and Figs. 3 and 4). This interpretation is consistent with findings of a significant negative correlation between resistive indices and ERPF ($r = 0.54$, $P = 0.03$) and between peak systolic blood velocity and effective blood velocity calculated at the site of stenosis or stenting ($r = 0.77$, $P = 0.0005$). Improved kidney perfusion was sustained by a remarkable and highly significant increase in the artery cross-sectional surface area (Table 3). Mean wall shear stress and mean Reynolds' number, calculated at the site of renal artery stenosis, were remarkably elevated above normal values in all patients. After stent deployment, both indices decreased within the normal ranges in the study group as a whole and in each individual patient (Table 2 and Fig. 5). However, despite a full correction of the stenosis, GFR did not change significantly after the procedure (Fig. 3). This, in parallel with the remarkable increase in ERPF, accounted for a significant decrease in filtration faction (Fig. 4). Of note, prestenting and poststenting filtration fraction and ERPF were negatively correlated ($r = 0.79$, $P = 0.0003$). Serum creatinine concentration and creatinine clearance did not change significantly (Table 3). Sodium and free-water clearances increased, albeit nonsignificantly, after stent deployment (Table 3).

On the other hand, the prestenting and poststenting 24-hour urinary protein excretion rates (Table 3) and neutral dextran sieving profiles (Fig. 6) were almost identical.

Finally, the procedure was well tolerated, and no patient experienced serious complications (including traumatic lesions, bleeding, or thrombosis) or recurrence of the stenosis over a mean follow-up of 25 (5 to 62) months.

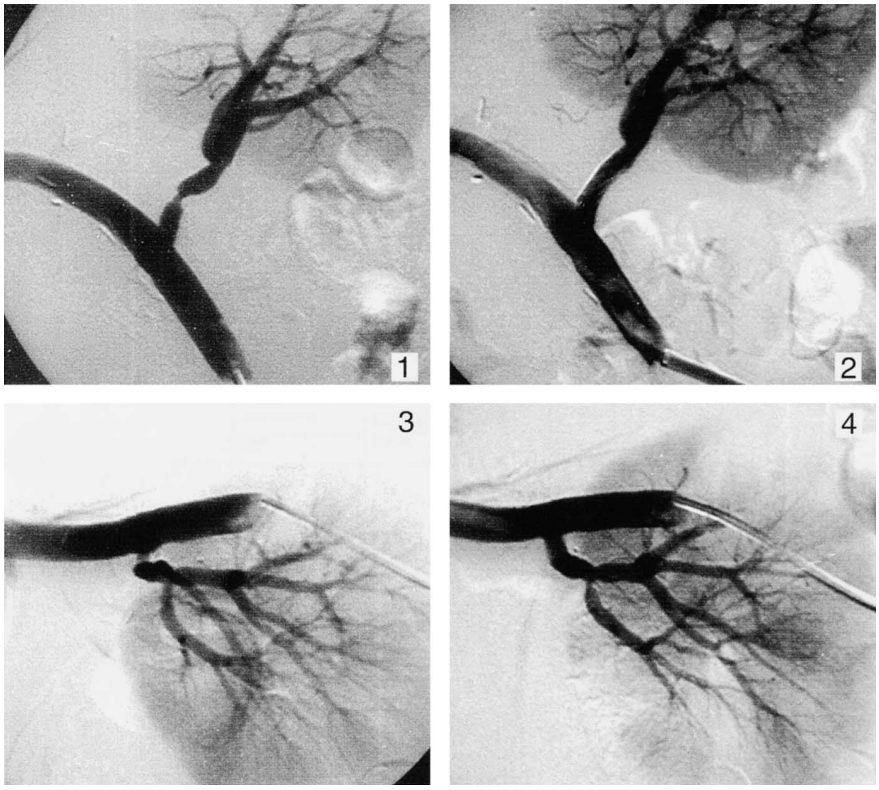

Fig. 1. Representative angiograms taken from two patients before (left panel) and after (right panel) stenting.

Table 3. Main laboratory parameters before and after angioplasty (AP)

	Before AP	After AP
Serum creatinine *mg/dL*	1.75 ± 0.5	1.53 ± 0.43
Total plasma proteins *g/dL*	6.3 ± 0.4	6.2 ± 0.6
Hematocrit %	40.4 ± 4.2	38.9 ± 4.2
Creatinine clearance *mL/min/1.73 m²*	63.1 ± 27.8	63.2 ± 21.8
Na^+ clearance *mL/min/1.73 m²*	2.8 ± 1.5	4.0 ± 2.4
Free water clearance *mL/min/1.73 m²*	3.4 ± 2.9	4.5 ± 2.6
Urinary protein excretion *g/24 h*	0.30 ± 0.25	0.37 ± 0.49

All patients were discharged without sequelae within two days after the interventional procedure.

At one year, systolic blood pressure was 132 ± 15 mm Hg ($P < 0.05$ vs. preangioplasty and stenting values). Diastolic blood pressure was 89 ± 12 mm Hg, and serum creatinine concentration was 1.7 ± 0.7 mg/dL (P = NS, vs. one-month parameters). Over a median (range) follow-up of 32 (12 to 70) months, blood pressure and serum creatinine were stable, and no change in antihypertensive therapy was introduced in any of the patients except one. This patient was admitted on November 2000 (exactly one year after angioplasty and stenting) because of increasing arterial blood pressure and worsening renal function. A selective renal artery angiography detected a restenosis at the site of stent deployment, inducing a >50% reduction in the vascular cross-sectional area. The stenosis was effectively corrected by transluminal angioplasty with a prompt decrease in arterial blood pressure and progressive improvement of renal function.

DISCUSSION

To our knowledge, this is the first study of kidney transplant patients designed to investigate renal hemodynamics before and after intraluminal correction of a functionally significant artery stenosis. Results show that angioplasty and stent deployment effectively and safely corrected hemodynamically significant stenoses and ameliorated kidney perfusion, besides improving blood pressure control. Moreover, the renal hemodynamic response to reperfusion could be reliably monitored by Doppler ultrasound scanning.

Diagnosis of hemodynamically significant renal artery stenosis rests on a radiological demonstration of ≥50% reduction in renal artery diameter [7, 12]. The rationale for this assumption is derived from experimental evidence that the stenosis needs to occlude at least 50% of the lumen before renal blood flow and perfusion pressure start to decrease and systemic blood pressure to increase [12]. Thus, the finding that a radiologically documented ≥50% renal artery stenosis in all of our patients was associated with remarkably increased renal vascular resistances and decreased ERPF provides direct evidence, to our knowledge for the first time, that this assumption

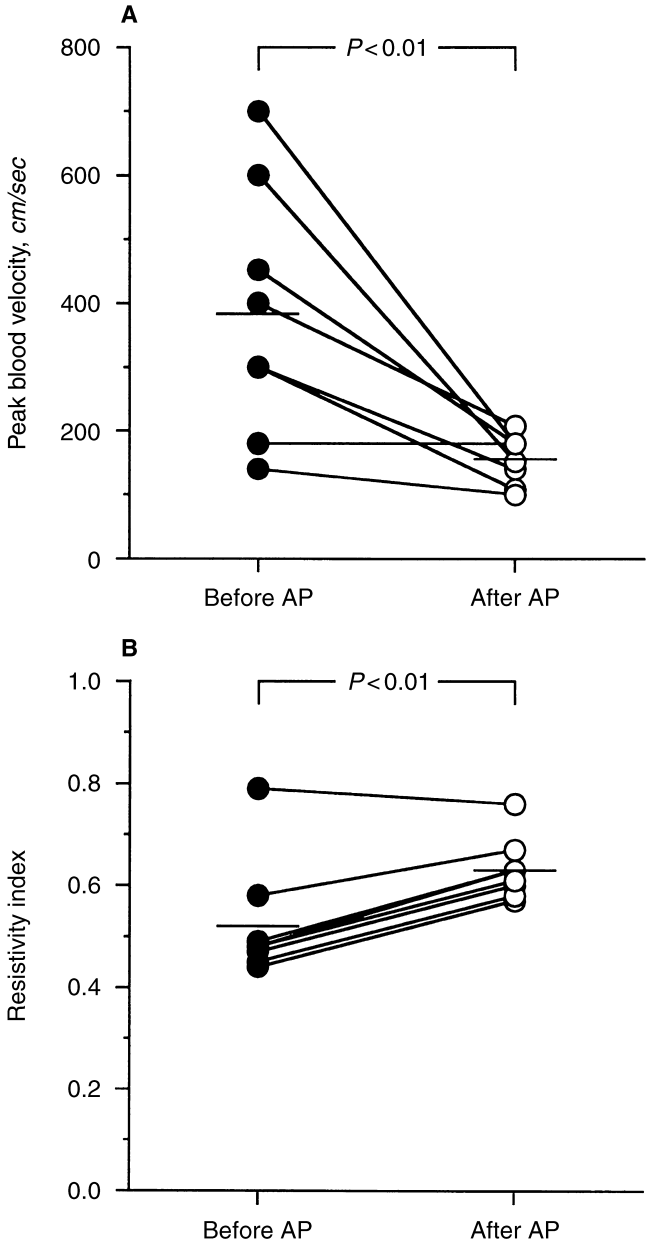

Fig. 2. Prestenting and poststenting peak blood velocity (*A*) and resistive indices (*B*) measured by echo-color Doppler in each patient.

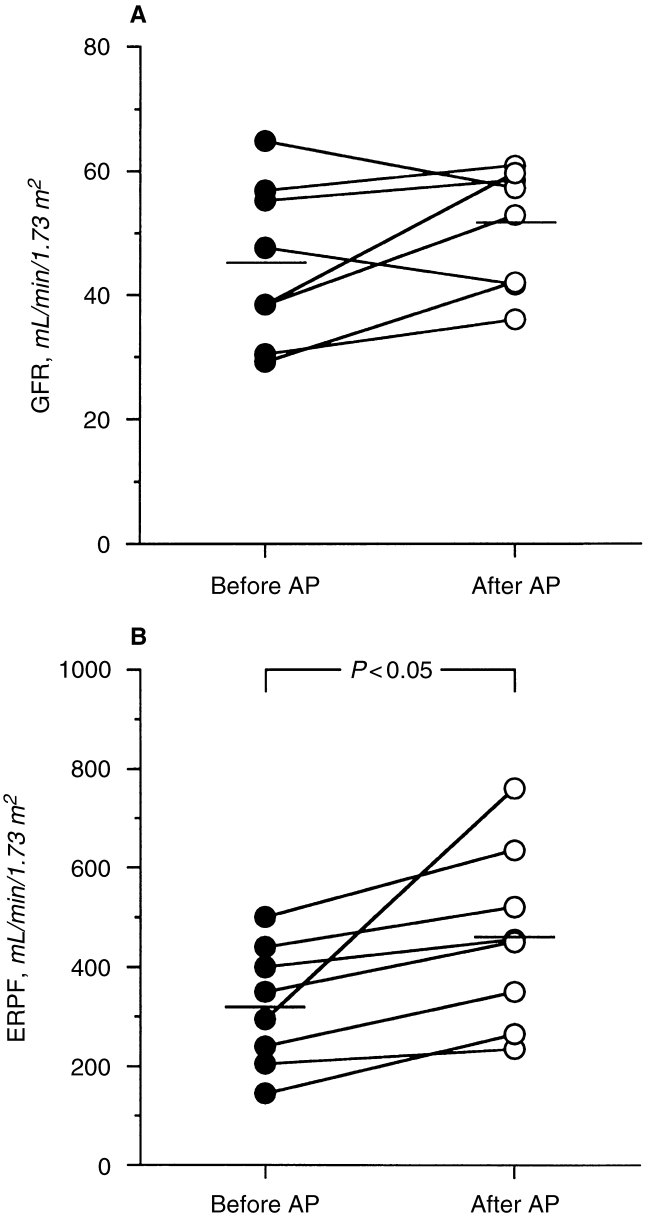

Fig. 3. Prestenting and poststenting glomerular filtration rate (GFR) (*A*) and effective renal plasma flow (ERPF) (*B*) measured in each individual patient.

also can be properly extended to humans. Of note, all patients were cured by the angioplasty combined with stent deployment with no residual stenosis after the procedure. The findings that the intervention decreased renal vascular resistances and restored kidney perfusion despite a slight concomitant decrease in arterial blood pressure provides additional indirect evidence of the hemodynamic relevance of the stenosis.

Before angioplasty, depressed ERPF was associated with less-depressed GFR and increased filtration fraction. Conceivably, GFR was relatively maintained by the remarkable increase in filtration fraction facing a substantial reduction of ERPF. A high filtration fraction might in turn depend on a relative increase in postglomerular resistance that would maintain glomerular filtration, as suggested by studies in experimental models [10, 19, 20]. Actually, while in humans, direct measurements of intracapillary pressure are not feasible, rat data are available showing that renal artery stenosis is followed by a postglomerular vasoconstriction, which maintains the intracapillary pressure despite the decreased renal perfusion pressure [10, 19, 20]. Of interest, restoring kidney perfusion relieves postglomerular vasoconstriction, which leads to a decrease of filtration fraction

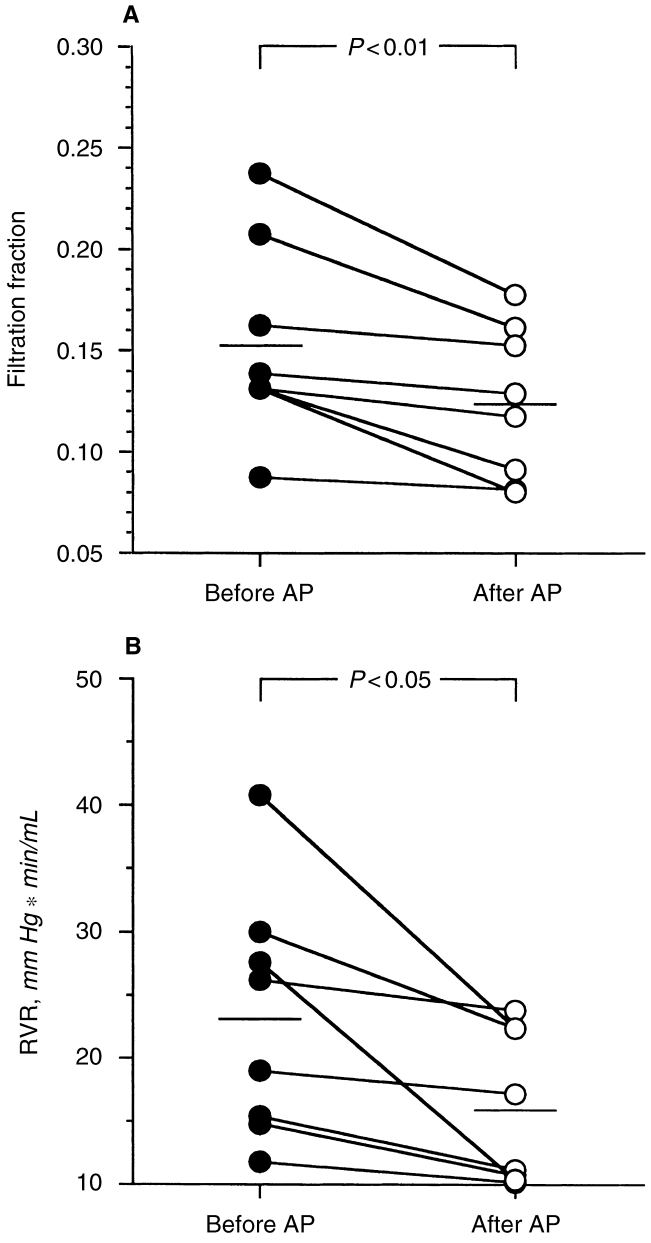

Fig. 4. Prestenting and poststenting filtration fraction (FF) (*A*) and renal vascular resistance (RVR) (*B*) measured in each individual patient.

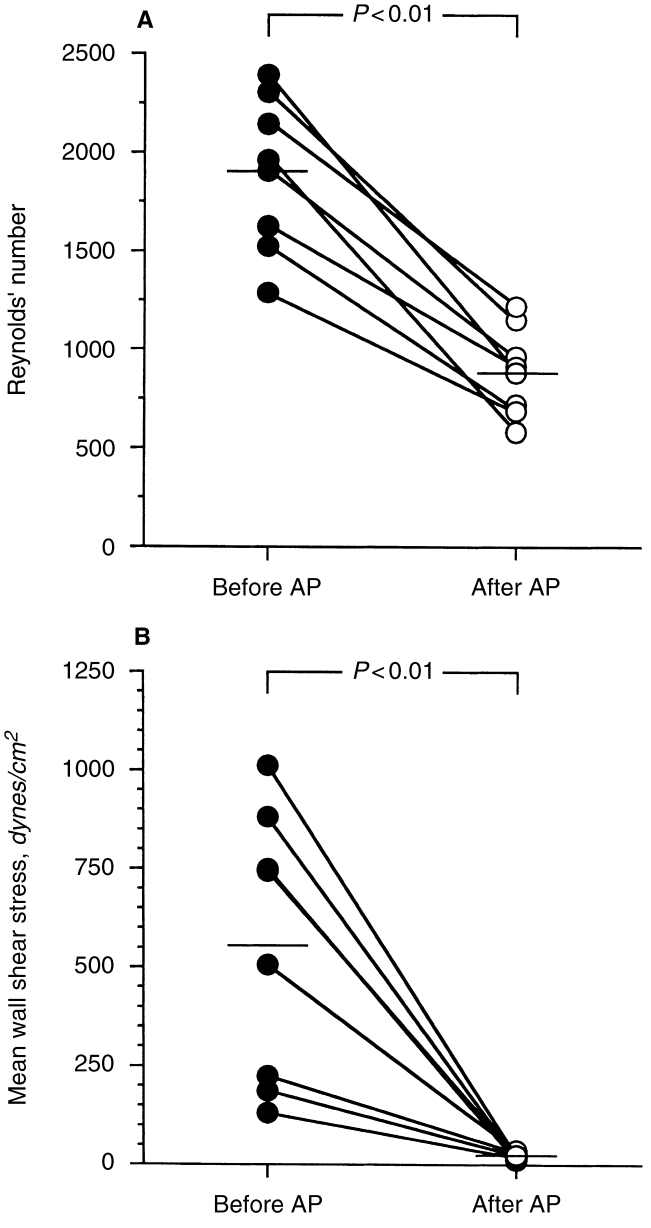

Fig. 5. Prestenting and poststenting Reynolds' number (*A*) and mean wall shear stress (*B*) measured in each individual patient.

to normal ranges [10, 19, 20]. Thus, the finding that restoring kidney perfusion was associated with a decreased filtration fraction in our patients indicated, albeit indirectly, that after angioplasty and stenting the GFR was less dependent on postglomerular vasoconstriction. This interpretation is consistent with the finding that the prestenting and poststenting filtration fraction and ERPF were negatively correlated.

In animals, resolution of one-kidney, one-clip renovascular hypertension has been associated with prompt diuresis and natriuresis [21, 22]. That this might possibly apply to our patient population is suggested by our patients' remarkable weight loss and by the trend to increased sodium and free water clearances observed one month after transluminal angioplasty and stenting. Collectively, these data indicate that the trend to a blood pressure reduction in our patients was at least in part dependent on the relief of sodium and water retention sustained by kidney hypoperfusion.

To evaluate the effect of kidney reperfusion on glomerular size-selective function, we compared the clearances of neutral dextrans of a broad-size distribution relative to those of free-permeable inulin measured be-

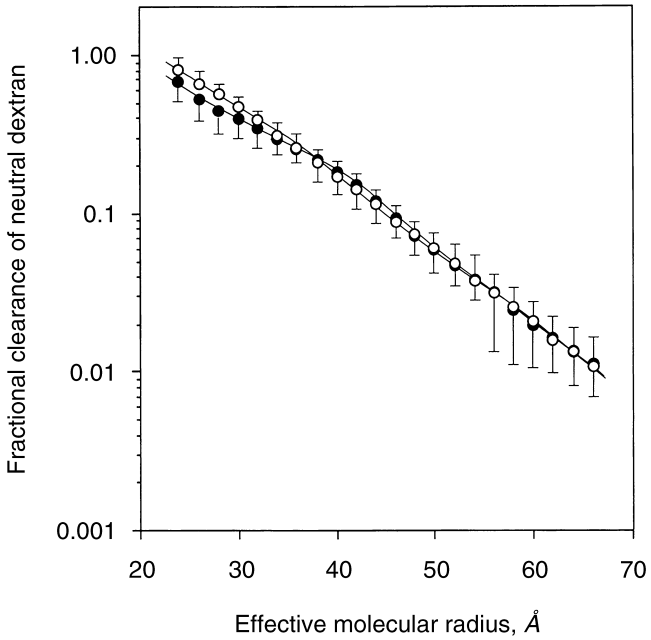

Fig. 6. Prestenting (●) and poststenting (○) fractional clearances of neutral dextrans of different radii.

fore and after angioplasty and stenting. Indeed, both in experimental [23–25] and human [26–29] proteinuric nephropathies, maneuvers—such as colloid volume expansion or fluid immersion—that increase glomerular perfusion induce an increase in proteinuria accompanied by an emergence of larger pores ("the shunt pathway") and decreased glomerular barrier size selectivity [29, 30]. In normal individuals, however, the opening of larger pores is not accompanied by an increase in neutral dextran ultrafiltration and proteinuria, since the effects of a reduced glomerular barrier size selectivity sustained by the augmented shunt pathway are nullified by the tendency for high plasma flows to decrease fractional clearances [31]. Of interest, the comparable neutral dextran sieving profiles observed in our patients before and after angioplasty and stenting most likely reflected the opposite effects of decreased intrinsic glomerular barrier selectivity and increased glomerular perfusion rate previously observed in healthy individuals [31]. The finding that net macromolecules ultrafiltration and urinary protein excretion were not substantially affected by angioplasty suggest that the maneuver does not increase protein traffic and tubular protein overload and, therefore, should not have a long-term detrimental effect on kidney graft function [32].

An additional interesting finding of the present study was that at the site of the stenosis, the blood flow was importantly disturbed and almost turbulent, as suggested by the high Reynolds' number calculated for each patient (1260 to 2405; Fig. 5). At the same time, the calculated mean wall-shear stress dramatically exceeded (by more than one order of magnitude) physiological values that range between 10 and 30 dynes/cm^2 [33]. Blood flow turbulence and elevated shear stress are recognized as determinants of endothelial dysfunction and progressive vascular injury, and have been implicated in thrombotic vascular occlusion in atherosclerotic disease [33, 34]. Thus, because of the remarkable increase in secondary flows and turbulence, and the elevation of wall shear stress found at the renal artery stenosis site, it could be inferred that, if untreated, these patients would be at risk for renal artery thrombosis that would eventually lead to graft loss. Of note, angioplasty and stent deployment allowed the achievement of an important reduction of Reynolds' number (570 to 1240) and lowered mean wall shear stress values to within the normal range in all individual patients (values ranging from 13 to 34 dynes/cm^2).

Finally, we observed that renal artery stenosis was accompanied by a remarkable increase in peak blood flow velocities and decreased resistive indices recorded by Doppler ultrasound scanning from the renal artery and parenchyma, respectively. Both parameters fully normalized in parallel with the relief of the stenosis. Of note, the findings that changes in peak systolic velocities were negatively correlated with ERPF, but were positively correlated to a highly significant extent with the actual flow velocity at the stenosis site, strongly suggested that this echographic parameter is a reliable indicator of stenosis severity. Even more interesting, parenchymal-resistive indices, which currently are taken to reflect overall intrarenal resistances, were uniformly decreased in all of our cases of post-transplant renal artery stenosis. Most likely this would depend on an intrarenal vasodilation finalized to maintain kidney perfusion despite a poststenotic drop in arterial pressure. This assumption is in harmony with findings of a negative correlation between the changes in intrarenal-resistive indices and the extent of artery stenosis or peak systolic velocities. Taken together, these data suggest that Doppler ultrasound scanning is a useful, reliable, and noninvasive tool to monitor the renal functional response to artery revascularization.

In conclusion, renal graft artery stenosis is effectively and safely corrected by transluminal renal artery angioplasty and stent deployment. Correcting the renal artery stenosis improved blood pressure control, fully restored kidney perfusion, relieved the reflex postglomerular vasoconstriction, and normalized blood flow and vascular shear stress without inducing appreciable and potentially detrimental acute increases in intracapillary pressure and/or glomerular barrier permeability. Doppler ultrasound scanning is a reliable and reproducible technique to monitor the renal functional response to revascularization.

ACKNOWLEDGMENT

The authors thank Dr. Eliana Gotti, who carefully screened all suspected cases of post-transplant renal artery stenosis among the renal transplant patients referred to our outpatient clinic, and managed the patients throughout the entire study period.

Reprint requests to Piero Ruggenenti, M.D., "Mario Negri" Institute for Pharmacological Research, Via Gavazzeni 11, 24125 Bergamo, Italy. E-mail: ruggenenti@marionegri.it

APPENDIX

Renal vascular resistances (RVR) were calculated using this formula:

$$RVR = MAP \times (100 - Hct)/ERPF$$

where MAP is the mean arterial pressure, Hct the blood hematocrit, and ERPF the effective renal perfusion flow. Mean blood velocity was calculated as the ratio between the mean flow rate and vessel cross-sectional area, assuming the transverse section of the vessel in the stenotic area is circular. The mean wall shear stress was estimated with the formula:

$$\tau_w = \mu \cdot \gamma$$

where the wall shear rate (γ) was calculated on the basis of the blood flow rate and vessel diameter (assuming parabolic velocity profile), while blood viscosity (μ) was calculated using the formula of Gijsen et al as a function of plasma protein concentration and hematocrit [35]. The mean value of the Reynolds' number for each patient before and after the interventional procedure was computed as a function of blood viscosity, mean blood velocity, vessel diameter, and blood density. Sodium and potassium filtration fractions (FF) were calculated as:

$$FF = (C_{Na} \text{ or } C_K)/GFR$$

where C_{Na} or C_K is the sodium or potassium clearance, respectively, and GFR is the inulin clearance. Free water clearance (C_{H_2O}) was calculated as:

$$C_{H_2O} = U - C_{Osm}$$

where U is urine output, and C_{Osm} is the osmolar clearance.

Abbreviations used in this study are: C, clearance; D_o, reference diameter; D_s, diameter at the stenosis site; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; Hct, hematocrit; LDF, lowest diastolic frequency; MAP, mean arterial pressure; PAH, para-aminohippuric acid; PSF, peak systolic frequency; RI, resistive index; RPF, renal plasma flow; RVR, renal vascular resistance; $(U/P)_D$ and $(U/P)_{IN}$, urine-to-plasma concentration ratios of dextran and inulin.

REFERENCES

1. Luke RG, Curtis J: Biology and treatment of transplant hypertension, in *Hypertension Pathophysiology, Diagnosis and Management*, edited by Laragh JH, Brenner BM, New York, Raven Press, 1995, pp 2471–2483
2. Talbot-Wright R, Alcaraz A, Puyol M, *et al:* Complicaciones vasculares del trasplante renal: Estenosis de la arteria renal. *Actas Urol Esp* 14:352–355, 1990
3. Sankari BR, Geisinger M, Zelch M, *et al:* Post-transplant renal artery stenosis: Impact of therapy on long-term kidney function and blood pressure control. *J Urol* 155:1860–1864, 1996
4. Rengel M, Gomes-da-Silva G, Inchaustegui L, *et al:* Renal artery stenosis after kidney transplantation: Diagnostic and therapeutic approach. *Kidney Int* 54(Suppl 68):S99–S106, 1998
5. Fervenza FC, Lafayette RA, Alfrey EJ, Petersen J: Renal artery stenosis in kidney transplants. *Am J Kidney Dis* 31:142–148, 1998
6. Sierre SD, Raynaud AC, Carreres T, *et al:* Treatment of recurrent transplant renal artery stenosis with metallic stents. *J Vasc Interv Radiol* 9:639–644, 1998
7. Nicita G, Villari D, Marzocco M, *et al:* Endoluminal stent placement after percutaneous transluminal angioplasty in the treatment of post-transplant renal artery stenosis. *J Urol* 159:34–37, 1998
8. Chang RLS, Robertson CR, Deen WM, Brenner BM: Permselectivity of the glomerular capillary wall to macromolecules. I. Theoretical considerations. *Biophys J* 15:861–886, 1975
9. Brenner BM, Bohrer MP, Baylis CH, Deen WM: Determinants of glomerular permselectivity: Insights derived from observations in vivo. *Kidney Int* 12:229–237, 1977
10. Chang RLS, Deen WM, Robertson CR, *et al:* Permselectivity of the glomerular capillary wall: Studies of experimental glomerulonephritis in the rat using neutral dextran. *J Clin Invest* 57:1272–1280, 1976
11. Chang RLS, Ueki IF, Troy JL, *et al:* Permselectivity of the glomerular capillary wall to macromolecules. II. Experimental studies in rats using neutral dextran. *Biophys J* 15:887–895, 1975
12. Imanishi M, Akabane S, Takamiya M, *et al:* Critical degree of renal artery stenosis that causes hypertension in dogs. *Angiology* 43:833–842, 1992
13. Perico N, Ruggenenti P, Gaspari F, *et al:* Daily renal hypoperfusion induced by cyclosporine in patients with renal transplantation. *Transplantation* 54:56–60, 1992
14. Remuzzi A, Ruggenenti P, Mosconi L, *et al:* Effect of low-dose enalapril on glomerular size-selectivity in human diabetic nephropathy. *J Nephrol* 6:36–43, 1993
15. Remuzzi A, Perticucci E, Ruggenenti P, *et al:* Angiotensin-converting enzyme inhibition improves glomerular size-selectivity in IgA nephropathy. *Kidney Int* 39:1267–1273, 1991
16. Battilana C, Zhang H, Olshen R, *et al:* PAH extraction and the estimation of plasma flow in the diseased human kidney. *Am J Physiol* 261:F726–F733, 1991
17. Oliver JD, Anderson S, Troy JL, *et al:* Determination of glomerular size-selectivity in the normal rat with Ficoll. *J Am Soc Nephrol* 3:214–228, 1992
18. Scott TA, Melvin EH: Determination of dextran with anthrone. *Anal Chem* 25:1656–1661, 1953
19. Navar LG, Rosivall L: Contribution of the renin-angiotensin system to the control of intrarenal hemodynamics. *Kidney Int* 25:857–868, 1984
20. Lohmeier TE, Cowley AW: Hypertensive and renal effects of chronic low level intrarenal angiotensin infusion in the dog. *Circ Res* 44:154–169, 1979
21. Liard JF, Peters G: Mechanism of the fall in blood pressure after "unclamping" in rats with Goldblatt-type hypertension. *Experientia* 26:743–745, 1980
22. Liard JF, Cowley AW, McCaa RE, *et al:* Renin, aldosterone, body fluid, volumes, and the baroreceptor reflex in the development and reversal of Goldblatt hypertension in conscious dogs. *Circ Res* 34:549–560, 1974
23. Arendhorst WJ, Gottschalk CW: Glomerular ultrafiltration dynamics: Euvolumic and plasma-expanded rats. *Am J Physiol* 239:F171–F186, 1980
24. Blantz RC, Rector FC, Seldin DW: Effect of hyperoncotic albumin expansion upon glomerular ultrafiltration in the rat. *Kidney Int* 6:209–221, 1974
25. Tucker BJ, Blantz RC: Effects of glomerular filtration dynamics on the glomerular permeability coefficient. *Am J Physiol* 240:F245–F254, 1981
26. Chinard FP, Lanson HD, Eder HA, *et al:* A study of the mechanisms of proteinuria in patients with the nephrotic syndrome. *J Clin Invest* 33:621–628, 1954
27. Gregoire F, Malmedier C, Lambert PP: The mechanism of proteinuria and a study of the effects of hormonal therapy in the nephrotic syndrome. *Am J Med* 25:516–531, 1958
28. Hardwicke Squire JR: The relationship between plasma albumin concentration and protein excretion in patients with proteinuria. *Clin Sci* 14:509–530, 1955
29. Aurell M: Renal response in man to plasma volume expansion and angiotensin. *Scand J Clin Lab Invest* 24:3–59, 1969
30. Deen WM, Bridges CR, Brenner BM, Myers BD: Heteroporous

model of glomerular size selectivity: Application to normal and nephrotic humans. *Am J Physiol* 249:F374–F389, 1985
31. Shemesh O, Deen WM, Brenner BM, *et al:* Effect of colloid volume expansion on glomerular barrier size-selectivity in humans. *Kidney Int* 29:916–923, 1986
32. Remuzzi G, Bertani T: Mechanisms of disease: Pathophysiology of progressive nephropathies. *N Engl J Med* 339:1448–1456, 1998
33. Giddens DP, Zarins CK, Glagov S: The role of fluid mechanics in the localization and detection of atherosclerosis. *J Biomech Eng* 115:588–594, 1993
34. Davies PF, Remuzzi A, Gordon EJ, *et al:* Turbulent fluid shear stress induces vascular endothelial cell turnover in vitro. *Proc Natl Acad Sci USA* 86:2114–2117, 1986
35. Gijsen FJH, Brands PJ, Van De Vosse FN, Janssen JD: Assessment of wall shear rate measurements with ultrasound. *J Vasc Invest* 4:187–196, 1998