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The use of perioperative Doppler ultrasound as a screening test for acute tubular necrosis

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Abstract. For many years Doppler ultrasound has helped to identify the cause of renal allograft dysfunction. However, Doppler examinations were often performed after the onset of acute renal failure. In the present study we used Doppler ultrasound during grafting to follow changes in renovascular resistance. As early as 30 min after the renal artery had been unclamped, the calculated resistance index (RI) at the hilar part of the renal artery was significantly higher in the group of patients who developed acute tubular necrosis (ATN) than in the group of patients with early normalization of renal function ($P = 0.05$). This result did not correlate with raised cold and warm ischemia times and serum creatinine level on discharge in patients who presented with ATN. RI higher than 0.730 min after unclamping allows for an identification of those grafts at greater risk for the development of ATN and should be an indication for the early introduction of intensive therapy.

Key words: Kidney transplantation, Doppler ultrasound – Doppler ultrasound, kidney transplantation – Acute tubular necrosis, Doppler ultrasound – Ultrasound, kidney transplantation

The initial function of the transplanted kidney significantly influences long-term outcome [2]. While crossmatching procedures and intensive immunosuppressive treatment have markedly reduced the occurrence of early rejection, acute tubular necrosis (ATN) remains a very common cause of acute renal failure after transplantation. Unfortunately, no simple method is available for predicting which organs will develop ATN. Duplex Doppler sonography is a noninvasive technique that gives information concerning renal blood flow [1, 6, 13, 14]. The inadequacy of preservation can be demonstrated by abnormal Doppler velocity waveforms secondary to abnormal renal circulatory resistance [4].

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The aim of this prospective study was to evaluate the use of perioperative Doppler ultrasound to predict the subsequent development of ATN.

Patients and methods

Between 15 June and 15 December 1989, 17 consecutive patients (9 males, 8 females; mean age 46.8 years) who had received a first kidney cadaver transplant were studied. After harvesting, the kidneys were perfused with Euro-Collins (EC) solution and, immediately before transplantation, were reperfused with EC solution and diltiazem (50 mg for 15 min). T- and B-cell crossmatches were negative in all cases. The patients received an intravenous bolus of diltiazem (0.28 mg/kg) immediately before the renal artery was unclamped, followed by infusion (0.12 mg/kg per hour) for 72 h. The renal artery was anastomosed end-to-side with the external iliac artery in all patients.

Each patient received the following immunosuppressive regimen: (1) antithymocyte globulin (ATG; Mérieux, France) given for the first 14 days and monitored by blood T-lymphocyte counts, (2) prednisone given at 1 mg/kg per day for the first 3 weeks, then reduced to 5 or 10 mg/day over 6 weeks, (3) azathioprine started at 2.5 mg/kg per day and adjusted subsequently according to WBC counts, and (4) cyclosporin A, started at 6 mg/kg per day on the 13th day after transplantation and then adjusted to give whole blood trough levels of 100–200 mg/ml, as measured by RIA with monoclonal antibodies.

Without knowledge of the perioperative Doppler data, the patients were divided into two groups according to their renal function in the first 3 weeks after grafting. Group 1, comprising nine patients, had immediate graft function, defined as a serum creatinine level below 250 μmol/l by day 5 with the absence of dialysis. Group 2, comprising eight patients, had delayed graft function with oligoanuria related to ATN on echotomography (normal sonogram with distinct corticomedullary boundary and discrete hypoechogenicity of the medullary pyramids), radionuclide scanning (correct perfusion and normal mean transit time), or histological criteria. No rejection defined by these criteria was observed in these patients. In this group the serum creatinine level took 14 ± 2 days to fall below 250 μmol/l, and three patients required hemodialysis for the 1st week after transplantation.

Blood flow velocities in the renal artery were studied using a 4-MHz continuous wave Doppler and spectrum analyzer (Spectradop II, DMS equipements, France). Velocities (expressed as frequency shifts in Hz) were measured at the hilar part of the renal

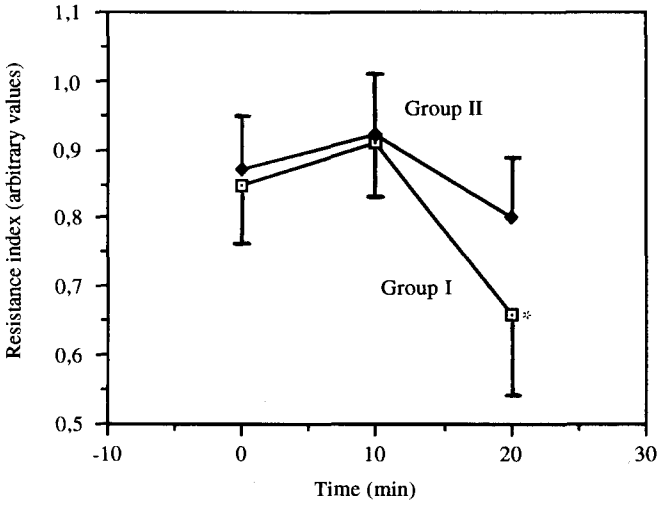

Fig. 1. Changes in renal vascular resistance measured at 0, 10, and 30 min after unclamping of the renal artery in patients with early normalization of renal function (group 1, mean + SD) and in patients with acute tubular necrosis (group 2, mean–SD). * $P = 0.05$

artery between the anastomosis site and the kidney. All examinations were performed by the same physician.

Changes in renal vascular resistance were evaluated using the calculated resistance index (RI; Pourcelot's index) defined by S-D/S, where S is the maximum systolic frequency and D the maximum end-diastolic frequency [8]. Changes in the RI during the first 30 min after unclamping of the renal artery were studied. Recordings were taken immediately after unclamping (t = 0), 10 min (t = 10), and 30 min (t = 30) later.

Results were expressed as the mean ± standard deviation. The unpaired Student's *t*-test was used for comparison of the RI between the two groups. The significance of the relationship between RI and ischemic times was determined using Pearson's correlation test. The nul hypothesis was rejected when *P* was greater than 0.05.

Results

When we consider all the patients, RI at t = 0 was high (0.87 ± 0.08) in comparison with our observations at day 1 after grafting (0.71 ± 0.06). RI slightly increased at t = 10 (mean increase 0.09), then decreased at t = 30 (0.72 ± 0.11; $P < 0.001$ versus t = 0).

When we compare the two groups (group 1 without and group 2 with ATN), there was no difference in RI between these at t = 0 (0.85 ± 0.08 and 0.87 ± 0.08, respectively) or t = 10 (0.91 ± 0.08 and 0.92 ± 0.08, respectively). However, at t = 30 there was a significant difference, with RI falling more often in group 1 than in group 2: 0.66 ± 0.12 versus 0.80 ± 0.09, $P = 0.05$ (Figs. 1,2). Therefore, an RI higher than 0.7 is associated with a positive predictive value of 0.8 for the diagnosis of ATN.

In order to try to identify some possible factors correlated with ATN, we compared certain pretransplant and post-transplant data from the two groups. As shown in Table 1, there was no significant difference in age (of either recipient or donor), sex, incidence of underlying disease, or anti-HLA antibodies. However, both cold and warm ischemia times were longer in the group of patients who developed ATN ($P < 0.01$). Nevertheless, we did not find a positive correlation between either cold or warm ischemia times and RI at t = 30 ($r = 0.46$ and $r = 0.59$, respectively; $P > 0.05$). Looking at the post-transplant data, serum creatinine 1 month after transplantation was significantly higher in patients with initial ATN (120 ± 38 μmol/l versus 88.7 ± 20 μmol/l in group 1; $P < 0.01$).

Discussion

Diagnosing the cause of renal allograft dysfunction is an important clinical problem because management of the different causes of post-transplant oliguria or anuria varies. ATN complicates the diagnosis of rejection or drug toxicity and the use of immunosuppressive agents such as cyclosporin A. An early, accurate, and noninvasive test to diagnose ATN would be extremely helpful.

For many years, Doppler ultrasound has been used in the diagnosis of renal transplant complications [7, 10, 11]. Measurement of the RI in the allograft arteries is a simple technique. It is related to the level of diastolic flow [9]. When blood flow to the allograft is disturbed, this ratio should change. Many authors have described changes in vascular resistance in association with ATN or rejection [7, 11, 12]. Despite these observations, it remains very difficult to distinguish between ATN and rejection. Moreover, the diagnosis is suspected only after observation of delayed graft function in the postoperative period.

In the present study we used Doppler ultrasound during grafting and we identified a clear difference in RI between grafts with and without ATN as early as 30 min after unclamping of the renal artery. In the group of patients who developed ATN, the diastolic flow was reduced due to the persistance of high vascular resistance. As we did

Table 1. Pretransplant data of both groups of patients. * $P < 0.05$

Group	Sex	Age (years)	Hemodialysis treatment before transplantation (months)	HLA antibodies (patients)	Donor age (years)	Ischemia time	
						Cold	Warm
1	5 Males 4 Females	42.5 ± 14.3	30 ± 4.2	3	30.9 ± 11.5	20 h 50 ± 7 h 47	0 h 45 ± 0 h 30
2	4 Males 4 Females	51.2 ± 10.5	34 ± 3.3	3	37.8 ± 17.06	37 h 30 ± 2 h 55	1 h 10 ± 0 h 30
	NS	NS	NS	NS	NS	*	*

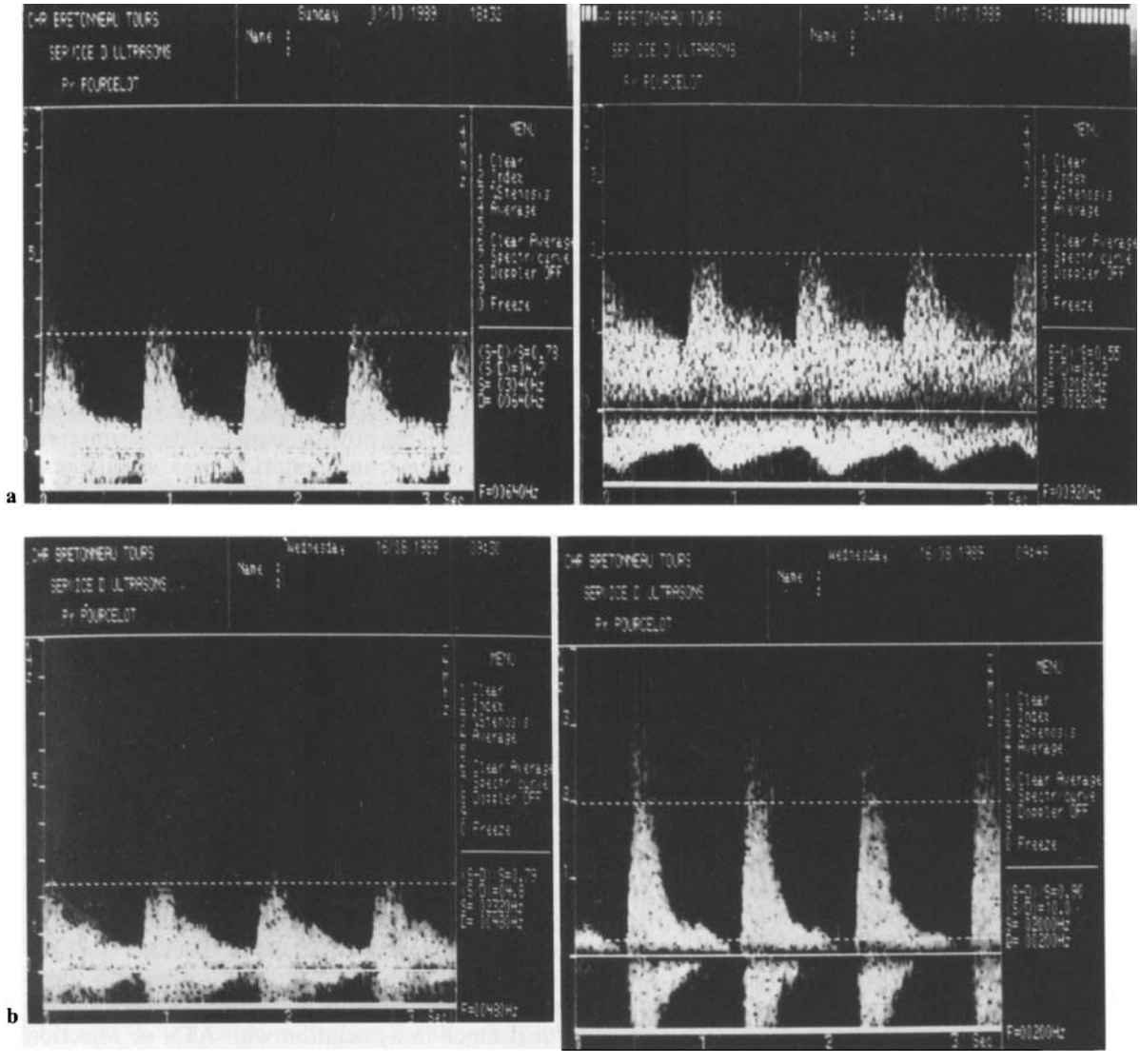

Fig. 2 a, b. Doppler waveform recordings from renal artery after unclamping. **a** Without ATN at 2 min *(left)*, at 30 min *(right)*; **b** with ATN at 2 min *(left)*, at 30 min *(right)*

not observe any vascular rejection in this group of patients, we cannot draw any conclusion on the use of the Doppler method to distinguish between ATN and rejection. Nevertheless, the observation of RI higher than 0.7 at 30 min seemed to be of predictive value for the development of ATN.

In cadaver kidney transplants with delayed function in relation to ATN, 20 min after the renal artery was unclamped, Benoit observed a significant flow decrease in this artery related to cortical vasospasm [3]. These results are in accordance with the increase in vascular resistance observed in our study. These vascular changes are associated with a higher risk of ATN as demonstrated by Anderson and Etheredge [2].

Long cold and warm ischemia times, even with an improved preservation procedure, could be deleterious to the graft [6]. Halloran et al. [5] reported that cold and/or anastomosis ischemia times are significantly longer in the group of patients with ATN. However, in the present study, there is no correlation between these ischemia times and RI at t = 30. Other risk factors for ATN could not be determined because of the relatively small number of patients. The changes in RI early after kidney transplantation could be related to the quality of the graft, donor factors, cold and warm ischemia times, adequacy of preservation, and recipient management. The changes in metabolic stock exchange induced by preservation and reperfusion of kidneys might entail an alteration of local vascular conditions that could be responsible for the increase in vascular resistance [4, 6].

Our data suggest that measurement of the RI in the renal artery performed during the 1st hour following unclamping could be very helpful in identifying those grafts likely to develop ATN. The development of ATN could have a deleterious effect on allograft function, as evidenced by the elevated serum creatinine level at 1 month in patients with ATN. Thus, abnormal RI values above 0.7 at t = 30 after renal unclamping could be an indication for early intensive treatment with agents such as superoxide dismutase to try to prevent ATN.

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