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ORIGINAL ARTICLE

Spontaneous regression of initially elevated peak systolic velocity in renal transplant artery

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Summary

There is limited knowledge about the incidence, clinical implication and spontaneous course of transplant renal artery stenosis detected early after renal transplantation. We performed Doppler ultrasound examination of the transplant artery(s) 2 months after transplantation in 98 consecutive patients and peak systolic velocity (PSV) was measured. All patients with an elevated PSV ≥1.8 m/s were reexamined 20 months later and clinical data were followed for 3 years. At the initial examination 2 months after transplantation 15 recipients had a PSV ≥1.8 m/s, mean value for PSV 2.5 (1.8–3.6) m/s, whereas 83 recipients had a normal PSV of 1.3 (0.7–1.7) m/s ($P < 0.01$). At baseline there were no statistical significant differences in clinical parameters between the high PSV versus normal PSV recipients. Twenty (15–28) months after transplantation 14 patients with initial elevated PSV were re-examined. There was an overall mean reduction in PSV of 0.5 (−0.7 to 1.2) m/s from 2.4 (1.8–3.4) m/s to 1.9 (1.2–3.1) m/s ($P = 0.02$). Detection of a high PSV early after transplantation did not affect graft function or blood pressure 3 years after engraftment. We conclude that a high PSV, at 2 months after engraftment, seems to be more of an 'incidental finding' that should be re-challenged and carefully interpreted.

Introduction

The most common vascular complication following renal transplantation is development of transplant renal artery stenosis (TRAS) [1]. The condition normally presents within 3 years following engraftment and may cause hypertension and/or deterioration of graft function, both nonspecific findings after transplantation. The overall reported incidence of TRAS detected by Doppler ultrasound (US) varies from 1.5 to 23% [2,3]. In stable renal transplant recipients TRAS frequently presents with worsening or refractory hypertension and/or allograft dysfunction in the absence of rejection, immunosuppressive toxicity, ureteric obstruction, or infection. In the early post-transplant phase hypertension is common and often a consequence of high dosage calsinurin inhibitor [CNI; ciclosporin (CiA)/tacrolimus (Tac)] therapy [4,5]. As CNIs are tapered blood pressure and s-creatinine (as a measurement of graft function) tend to improve and stabilize. Early US-guided surveillance graft biopsies are becoming more common [6,7]. During such an US examination one might find an elevated peak systolic velocity (PSV) [8] raising a suspicion of TRAS. To our knowledge no controlled trial has been conducted to investigate the presence and spontaneous course of TRAS detected early after transplantation. The clinical implication of this finding in otherwise stable patients is unknown. To improve our understanding of such a finding we decided to assess the incidence of all degrees of TRAS in stable renal transplant recipients 2 months after transplantation. In addition, we aimed to investigate the spontaneous course of early detected TRAS by performing a re-evaluation of all recipients with elevated PSV 20 months post transplant and follow all patients with clinical data (blood pressure,

number of antihypertensive drugs and s-creatinine) until 3 years after transplantation.

Method

We performed a single center prospective investigation of all renal transplant recipients who received a transplant between January and September 2006 with functioning graft at 2 months. Recipients <18 years of age and recipients of pediatric kidneys were not studied. The study was regarded as a quality assurance analysis and thus informed consent was not required. It was approved by the local research committee. A Doppler US examination of the transplant artery(s) was performed 8 weeks after engraftment in all patients. Based on the results of the Doppler US examination the patients were classified into two groups; patients without suspicion of TRAS (PSV <1.8 m/s) and patients with suspicion of TRAS (PSV ≥1.8 m/s). Patients with an elevated peak systolic velocity (PSV ≥1.8 m/s) at the initial examination were re-examined 20 months later with Doppler US and clinical assessment.

At the time of the initial US the following data were recorded: Blood pressure, number of antihypertensive drugs, BMI at transplantation, s-creatinine, living/deceased donor, CMV status and infection/reactivation, early acute rejections, and cold ischemia time (CIT). Blood pressure, number of antihypertensive drugs, and s-creatinine were also recorded in all patients still alive and with functioning graft 3 years after transplantation.

The Doppler US exams were performed by two experienced radiologists (KB + AG) using a Siemens Acuson Sequoia ultrasound scanner (CA, USA) using a 1–4 MHz curved-linear array transducer or a 1–4 MHz vector transducer. The peak systolic velocity was measured at four levels in the transplant renal artery; at the site of anastomosis, 2–3 cm distally of the anastomosis, in the middle and in the lateral part of the artery. The highest PSV value measured in each patient was reported as maximum PSV. PSV was also measured in the pelvic artery; in the external iliac artery near the anastomotic site in patients with an end to-side anastomosis with the external iliac artery, and in the proximal segment of the internal iliac artery in patients with an end-to-end anastomosis. In addition intrarenal resistance index (RI) and acceleration time (AT) were registered.

Statistics

Mann–Whitney test and Fisher exact test were applied where appropriate using GraphPad Prism version 5.00 for Windows (GraphPad Software, CA, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Ultrasound Doppler was routinely performed in 98 consecutive renal transplant recipients [63 male patients/35 female patients, mean age 54 (19–79) years] 2.1 (1.3–3.9) months after transplantation. All patients received CNI (CiA/Tac), steroids and mycophenolate mofetil (MMF) at the time of transplantation. Sixty-five received CiA and 33 received Tac. As a result of adverse events/earlier cancer/side-effects 15 recipients were switched from CiA/Tac to everolimus before the first US examination. Median prednisolone dose at the first US examination was 10 mg (range 5–30) and all patients were at that time within the center CNI trough windows (CiA C0 100–200, Tac 5–12).

Fifty-three recipients had received a transplant from a deceased donor (DD) and 45 had received a transplant from a living donor (LD). Sixty-seven donor transplant arteries were anastomosed to the external iliac artery and 31 arteries to the internal iliac artery. Fifty-eight percent of the LD recipients had their transplant renal artery anastomosed to the internal iliac artery whereas 91% of DD recipients had their transplant renal artery anastomosed to the external iliac artery.

A total number of 105 arteries were evaluated in the 98 kidney transplant recipients at the first US examination. The overall mean PSV in the transplant renal arteries was 1.4 (0.7–3.6) m/s. In 15 patients (15 arteries) PSV in the renal artery was ≥1.8 m/s [2.5 (1.8–3.6) m/s]. Ten of the 15 patients (66%) had received a transplant from a LD which was not different from 35 of 83 recipients (42%) in the nonelevated PSV group. One patient in the elevated PSV group experienced graft loss because of non compliance 7 months after transplantation. The 14 remaining recipients were re-examined with Doppler US at 20 (15–28) months after engraftment. Mean PSV for these 14 patients at the first Doppler US was 2.4 (1.8–3.4) m/s and at the second Doppler US 1.9 (1.2–3.1) m/s ($P < 0.01$). None of the arteries had occluded during the observation period. In 12 patients there was a spontaneous regression of PSV by a mean of 0.58 m/s. One patient experienced unchanged PSV (1.8 m/s) and one patient experienced an increase in PSV from 2.4 to 3.1 m/s (Fig. 1). There was no statistical significant difference in either AT [42 ms (17–85) vs. 38 ms (22–63)] or RI [0.69 (0.54–0.87) vs. 0.71 (0.49–0.85)] in the groups with elevated and normal PSV, respectively.

At the initial US investigation there was no difference between the groups regarding blood pressure, s-creatinine, number of antihypertensive drugs, cold ischemia time, number of patients with delayed graft function, rejection or incidence of CMV infection/reactivation (Table 1). Early detected elevated PSV did not affect graft function or blood pressure 3 years after engraftment (Table 2).

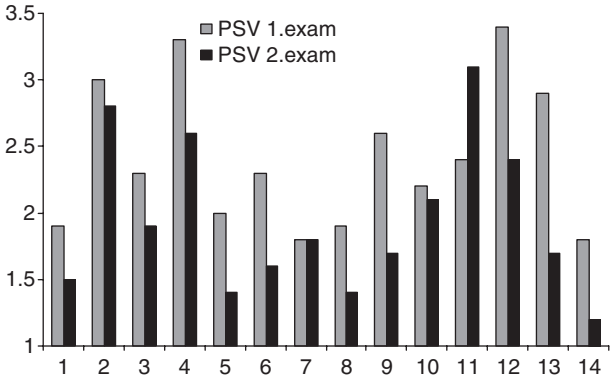

Figure 1 Peak systolic velocity in the transplant renal arteries in 14 recipients with peak systolic velocity (PSV) ≥1.8 m/s at 2 months (gray bars) and in the same arteries at 20 months (black bars) after transplantation. In one patient (patient 11) PSV was higher at the second Doppler ultrasound (US) and in one (patient 7) it was unchanged, whereas in all the other patients PSV was lower at the second Doppler US.

Table 1. Clinical data at 8 weeks US investigation.

	Normal PSV (n = 83)	High PSV (n = 15)
Systolic blood pressure (mmHg)	141 ± 16	138 ± 19
Diastolic blood pressure (mmHg)	82 ± 12	78 ± 9
s-Creatinine (μmol/l)	125 ± 35	115 ± 25
Number of antihypertensive drugs	1.7 (0–5)	1.8 (0–4)
Cold ischemia time (min)	601 (50–1619)	482 (63–1177)
Delayed graft function (yes/no)	10/72	2/13
Rejection (yes/no)	29/53	2/13
CMV infection/reactivation (yes/no)	26/57	3/12

There were no statistical significant differences between the two groups for any of the parameters listed in the table.

Table 2. Clinical data at 3 years post engraftment.

	Normal PSV (n = 76)	High PSV (n = 14)
Systolic blood pressure (mmHg)	137 (100–190)	139 (119–160)
Diastolic blood pressure (mmHg)	79 (60–115)	78 (58–90)
s-Creatinine (μmol/l)	129 (62–244)	132 (76–293)
Number of antihypertensive drugs	2 (0–5)	2.2 (0–4)

There were no statistical significant differences between the two groups for any of the parameters listed in the table.

Discussion

In the current study, we found that TRAS affects 15% of renal transplant recipients examined 2 months after engraftment. Our finding does not establish a causal relationship of TRAS with clinical consequences such as hypertension and/or renal dysfunction early after transplantation. As spontaneous regression is frequently observed a finding of a high PSV, at 2 months after engraftment, seems to be more of an 'incidental finding' that should be re-challenged and carefully interpreted.

The TRAS is one of the major vascular complications in renal transplantation, which usually presents with uncontrolled hypertension and/or unexplained renal dysfunction. The prevalence of detected TRAS has increased during the last decade as a result of strict post-transplant surveillance and increased use of routine US examination and other sophisticated imaging techniques [9]. Since both hypertension and kidney allograft dysfunction are multifactorial clinical suspicion of TRAS in the early postoperative phase is difficult. Hypertension may be attributable to CNI toxicity, acute rejection, diseased native kidneys or TRAS. Similarly, causes for kidney allograft dysfunction range from drug toxicity, volume status, recurrence of primary disease, urinary tract infections, urinary outlet problems or rejection. In addition, a long cold ischemia time/reperfusion injury in some patients leads to delayed graft function without any other known or detectable cause [10–12].

Over time, we observed a reduction and normalization in PSV in the majority of patients with elevated PSV at the initial Doppler US. One possible explanation could be that the artery in the early postoperative phase is temporarily narrowed because of postoperative edema and inflammation, and with time it can be assumed that some remodeling occurs at the site of the anastomosis whereby the vessel restores its luminal diameter leading to a reduction in flow velocity. These effects are frequently observed in the early postoperative phase. If this was the explanation one would, however, expect an increased CIT in patients with TRAS. This was not verified. A reduction in blood volume flow could possibly affect the flow velocity, however, little is known about the development of blood volume flow in renal transplants within the first 2 years.

Doppler US is a well accepted screening tool for assessment of renal transplant arteries [13,14]. The method is highly observer dependent which in itself is a limitation of our study. It is, however, noninvasive, inexpensive and a highly reliable tool when used by an experienced investigator and does not imply the use of nephrotoxic contrast media. The 14 recipients in our study who had high PSV at baseline all remained stable in s-creatinine and had no increase in blood pressure during the 36 months observation period. There was also a 'normalization' of PSV in 50% and a reduction in PSV in 85% of the patients during this time interval. This reinforces the fact that the combination of elevated PSV and clinical features should decide the necessity of further interventions i.e.

DSA with/without angioplasty. In stable patients the detection of elevated PSV early after transplantation should initially only indicate that the patients require a closer follow up.

In the literature various Doppler parameters are used to detect and define TRAS including elevated PSV, elevated PSV ratio (PSV in the renal artery/PSV in the pelvic artery), intra-renal tardus parvus flow curve, increased acceleration time and low resistance index [13]. In the diagnosis of native renal artery stenosis measurement of an elevated PSV in the stenosis itself has proved to be more reliable than intrarenal measurements of acceleration time and resistance index. The intrarenal Doppler parameters (AT, acceleration and RI) can be normal despite the presence of a significant TRAS. However, a pathological prolonged AT is a strong predictor of a significant TRAS. In our study we did not find any statistically significant difference in either RI or AT between the groups with elevated and normal PSV.

We used a PSV of 1.8 m/s as a threshold for the Doppler US diagnosis of TRAS as we wanted to include all degrees of possible stenosis. The in-depth review by O'Neill and Baumgarten use 2 m/s [13]. With this definition 11 of our patients would have had TRAS at the initial examination. There is, however, no universally accepted PSV threshold as a criterion for the Doppler US diagnosis of TRAS. Some centers use a PSV threshold value of 1.8 m/s [15] whereas others use a 2.5 m/s [16]. 1.8 m/s is also the standard threshold used by most centers for the diagnosis of a significant stenosis in a native renal artery [17,18].

Earlier publications have described that both CMV infection and DGF are predisposing factors for development of TRAS [10,19] This was not confirmed in our study. Audard *et al.* also found a tendency toward increased number of acute rejections in patients with TRAS compared with a control group [10]. Our results do not support this either. One must, however, remember that a finding of TRAS in our patients was an 'incidental finding' and not TRAS detected in patients with high suspicion of TRAS. Our patients experienced a spontaneous improvement and normalization over time.

Hypertension was common in patients with and without elevated PSV. At 20 months 4 of the 14 recipients were treated with a low dose renin–angiotensin system blocker always in addition to other antihypertensive medication (primarily a Calcium channel blocker) [20]. All four had tolerated the use of a renin-angiotensin system blocker but two had experienced a slight but not significant increase in s-creatinine supporting the suspicion of a TRAS.

There are some limitations of our study. We only re-examined patients with an elevated PSV at the primary Doppler US exam, thus we cannot exclude the possible development of TRAS in the other group of patients with normal PSV at the primary exam.

However, the purpose of the study was to assess the spontaneous development of TRAS in the rather early postoperative period. Secondly, we did not perform intra-arterial angiography to confirm the diagnosis of TRAS. Intra-arterial angiography is considered the gold standard in the evaluation of TRAS. We found it difficult to defend the use of an invasive procedure including the use of nephrotoxic contrast in patients with a well-functioning graft and elevated PSV without symptoms of TRAS.

To conclude, elevated PSV giving suspicion of TRAS is a common US finding early after kidney engraftment. Spontaneous regression and normalization of PSV is frequently observed. We highlight the fact that a high PSV early after kidney transplantation seems to be more of an 'incidental finding' that should be re-challenged and carefully interpreted.

Authorship

KB: designed and performed research/study, collected and analyzed data, wrote paper. AG: designed and performed research/study, collected data, wrote paper. HH: designed study, collected data, wrote paper. KM: designed study, collected data, wrote paper.

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