Non-invasive detection of pulmonary hypertension prior to renal transplantation is a predictor of increased risk for early graft dysfunction

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Abstract

Background. Early graft dysfunction is a significant complication after renal transplantation and is a marker of adverse outcomes. Although multiple predictors of graft dysfunction have been previously described, the reported prevalence of pulmonary hypertension (pulmonary HTN) in the dialysis population (40–50%), along with biologic and physiologic principles, led us to hypothesize that pulmonary HTN might be an additional risk factor for early graft dysfunction.

Methods. We performed a retrospective study that screened all adult renal transplants performed at our institution over a 3-year period and limited the evaluation to those subjects who had an estimated pulmonary artery systolic pressure on a preoperative echocardiogram report (n = 55). The primary outcome of this study was to investigate the impact of pulmonary HTN on early graft dysfunction using a combined endpoint of delayed graft function or slow graft function.

Results. Among patients receiving a living donor kidney, early graft dysfunction was not observed regardless of pulmonary HTN status. However, among patients receiving a deceased donor kidney, pulmonary HTN was found to be associated with a significant increased risk of early graft dysfunction (56 vs 11.7%, P = 0.01). Univariate and multivariable logistic regression supported this observation as an independent risk factor beyond potential confounding recipient, donor and graft-based risk factors for early graft dysfunction (P < 0.05).

Conclusion. Pulmonary HTN detected on non-invasive imaging prior to renal transplantation appears to be an independent predictor of early graft dysfunction among those patients who receive a deceased donor kidney.

Keywords: delayed graft function; pulmonary hypertension; renal transplantation; slow graft function

Introduction

The prevalence of pulmonary hypertension (pulmonary HTN) among patients with end-stage renal disease (ESRD) on hemodialysis has been reported to be as high as 40–50% and results in higher mortality rates in affected individuals [1–5]. Recently, it has been reported that evidence of pre-transplant pulmonary HTN as detected using cardiac echocardiography is associated with reduced patient survival after renal transplantation [6]. However, the impact of pulmonary HTN on early graft function after renal transplantation has not been described. Prior research studying the pathogenesis of pulmonary HTN in this patient population has demonstrated a multifactorial etiology including haemodynamic changes and alterations in vasoactive substances which contribute to increased pulmonary pressures and pulmonary arterial vasoconstriction [4,5]. It has been hypothesized that similar factors affect the vasculature of renal grafts immediately after transplantation and contribute to the development of early graft dysfunction [7–12]. Furthermore, it is well recognized that early graft dysfunction results in increased patient morbidity and is also a surrogate marker for decreased long-term graft and patient survival [13–24]. Given the potential impact of pulmonary HTN on cardiac function and renal allograft perfusion, as well as similar mechanisms implicated in the pathogenesis of pulmonary HTN and early graft dysfunction, we hypothesized that pulmonary HTN in candidates for renal transplantation may be a predictor of early graft dysfunction.

Materials and methods

Study design and patients

A retrospective cohort of adult renal transplants performed at our institution was reviewed for a 3-year period (January 2003–August 2006). A total of 145 transplants (143 patients were included after excluding 2 in-
The most common indication for the echocardiogram was for pulmonary hypertension. In the immediate post-operative setting, haemodynamics are very unstable and need to be controlled. As per the protocol at our institution, all patients after renal transplantation receive intravenous fluids to attain a central venous pressure of 12–15 cm H₂O and renal perfusion is confirmed using Doppler ultrasonography. In the immediate post-operative setting, haemodynamics are very unstable and need to be controlled.

Pulmonary HTN: Definition

All study subjects were classified using a binary system based on the estimated PASP which required the application of a clinical ‘cut-off’ value. If the patient had an estimated PASP ≥35 mm Hg, then pulmonary HTN was deemed to be present. This criterion reflects current institutional practice based on the literature review of results in patients with ESRD [1–5].

Comparison of the baseline characteristics of the renal transplant candidates with a preoperative echocardiogram including a measured PASP to renal transplant candidates with a preoperative echocardiogram that did not include a measurement of the PASP.

Early graft dysfunction: Definitions

Early graft dysfunction was evaluated using the following definitions:

1. Delayed graft function (DGF): the need for haemodialysis within 1 week after transplantation [22].
2. Slow graft function (SGF): non-dialysed patients with a serum Cr ≥3 mg/dL on post-transplant day 5 [19].

The primary outcome of this study was to investigate a possible association between pulmonary HTN and early graft dysfunction using a combined endpoint of DGF or SGF.

Statistical analysis

Comparison of means between two groups for continuous variables was performed using an unpaired t-test. The Fisher’s exact test was utilized for comparison of the baseline characteristics of the renal transplant candidates with a preoperative echocardiogram including a measured PASP to renal transplant candidates without a preoperative echocardiogram.

Results

Subject characteristics

Of the 143 patients that underwent renal transplant over the 3-year period, 94 patients had a preoperative echocardiogram available for review of which 55 studies included an estimate of the PASP (38% of total). In order to evaluate whether the study subjects who had an echo with a recorded PASP were ‘higher risk’, we compared the study subset (n = 55) to the excluded patients who had an echo that did not include a measureable PASP at rest (n = 39) and the patients who did not have an echo performed prior to transplantation (n = 49). There was no difference in patient baseline characteristics between the study subjects and the patients without a preoperative echocardiogram.
with an echo that did not include a measurement of the PASP (Table 1). When compared to the excluded patients who did not receive a pre-transplant echo, the study group was older in age (53 ± 11 vs 47 ± 13 years, P < 0.05), but there were no other significant differences (Table 1).

The patient characteristics of the 55 study subjects that met inclusion criteria separated by the presence or absence of pulmonary HTN can be found in Table 2. The only significant baseline difference between the two groups was the need for haemodialysis prior to transplant which was more prevalent within the pulmonary HTN group (86 vs 50%, P = 0.01). Of the study patients, 71% had an echo performed within 1 year prior to transplantation and 86% had an echo performed within 2 years of transplantation. The average time between the echo and the day of transplant for all patients included in the analysis was 10.9 months. The aetiologies of renal failure among the study subjects are shown in Table 3.

### Table 2. Baseline characteristics of the study subjects with a preoperative echocardiogram including a measurement of the PASP

<table>
<thead>
<tr>
<th>PASP, mm Hg (mean ± SD)</th>
<th>PASP ≥35 mm Hg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range, mm Hg</td>
<td>35.1 ± 6.3</td>
<td>0.10</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>54.6 ± 13.2</td>
<td>0.49</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>97</td>
<td>1.00</td>
</tr>
<tr>
<td>Male (%)</td>
<td>59</td>
<td>0.78</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>15</td>
<td>0.30</td>
</tr>
<tr>
<td>Systemic hypertension (%)</td>
<td>88</td>
<td>1.00</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (%)</td>
<td>6</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>35</td>
<td>1.00</td>
</tr>
<tr>
<td>LVEF, % (mean ± SD)</td>
<td>63.5 ± 6.3</td>
<td>0.15</td>
</tr>
<tr>
<td>Peritoneal dialysis (%)</td>
<td>12</td>
<td>0.29</td>
</tr>
<tr>
<td>No dialysis (%)</td>
<td>38</td>
<td>0.07</td>
</tr>
<tr>
<td>Transplant graft (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living donor</td>
<td>17</td>
<td>0.09</td>
</tr>
<tr>
<td>Deceased donor</td>
<td>17</td>
<td>0.07</td>
</tr>
</tbody>
</table>

### Table 3. Aetiology of renal failure among study subjects with a preoperative echocardiogram including a measured PASP

<table>
<thead>
<tr>
<th>Aetiology of renal failure</th>
<th>PASP &lt;35 mm Hg</th>
<th>PASP ≥35 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus (%)</td>
<td>8 (24%)</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Systemic hypertension (%)</td>
<td>5 (15%)</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (%)</td>
<td>3 (9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Congenital or structural urologic abnormality (%)</td>
<td>3 (9%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Polycystic kidney disease (%)</td>
<td>5 (15%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>IgA nephropathy (%)</td>
<td>4 (12%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>6 (18%)</td>
<td>4 (19%)</td>
</tr>
</tbody>
</table>

### Fig. 1. Comparison of the incidence of early graft dysfunction (EGD) in study subjects without pulmonary HTN (PASP <35 mm Hg, −pHTN) to study subjects with pulmonary HTN (PASP ≥35 mm Hg, +pHTN). (A) All transplants. (B) Subgroup analysis including type of renal transplant graft (deceased donor or living donor).

#### Prevalence of pulmonary HTN
Among the 55 study subjects, 21 patients (38%) were classified as having pulmonary HTN based on an estimated PASP ≥35 mm Hg. Only one patient in this study carried a previously identified clinical diagnosis of pulmonary HTN per documentation in the EMR.

#### Pulmonary HTN and early graft dysfunction
The presence of pulmonary HTN on the pre-transplant echocardiogram was observed to be a significant risk factor for early graft dysfunction (43 vs 6%, P = 0.002; Figure 1A). This effect was confined to patients who received a deceased donor kidney transplant as there were no instances of early graft dysfunction in the recipients of living donor transplants (Figure 1B). Among the patients who received a kidney from a deceased donor (n = 33), pulmonary HTN was associated with a significantly increased risk of early graft dysfunction (56 vs 11.7%, P = 0.01; Figure 1B). In deceased donor allograft recipients, pulmonary HTN is associated with a crude unadjusted odds ratio for early graft dysfunction of 9.64 (P = 0.01). Using the logistic model, when the odds ratio measuring the association between pulmonary HTN and early
Pulmonary hypertension predicts early graft dysfunction

Table 4. Risk adjusted analysis to evaluate pulmonary HTN as an independent predictor of early graft dysfunction

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary HTN, crude unadjusted</td>
<td>9.6</td>
<td>0.01</td>
<td>1.6-56.9</td>
</tr>
<tr>
<td>Pulmonary HTN, adjusted for recipient characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of recipient</td>
<td>9.4</td>
<td>0.01</td>
<td>1.5-56.0</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>11.2</td>
<td>0.01</td>
<td>1.7-72.0</td>
</tr>
<tr>
<td>LVEF</td>
<td>11.7</td>
<td>0.01</td>
<td>1.8-74.1</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>8.0</td>
<td>0.03</td>
<td>1.2-53.0</td>
</tr>
<tr>
<td>AVF</td>
<td>8.0</td>
<td>0.03</td>
<td>1.2-53.0</td>
</tr>
<tr>
<td>Pulmonary HTN, adjusted for all recipient characteristics</td>
<td>11.6</td>
<td>0.02</td>
<td>1.4-96.3</td>
</tr>
<tr>
<td>Pulmonary HTN, adjusted for donor and renal graft characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of donor</td>
<td>9.9</td>
<td>0.01</td>
<td>1.6-59.6</td>
</tr>
<tr>
<td>Cold ischaemia time</td>
<td>11.0</td>
<td>0.01</td>
<td>1.7-71.4</td>
</tr>
<tr>
<td>Donor graft criteria</td>
<td>10.8</td>
<td>0.01</td>
<td>1.7-69.0</td>
</tr>
<tr>
<td>Pulmonary HTN, adjusted for all donor and renal graft characteristics</td>
<td>12.5</td>
<td>0.01</td>
<td>1.7-89.3</td>
</tr>
<tr>
<td>Pulmonary HTN, adjusted for all recipient, donor and renal graft characteristics</td>
<td>15.0</td>
<td>0.03</td>
<td>1.2-188.9</td>
</tr>
</tbody>
</table>

*Odds ratio for pulmonary HTN as a predictor of early graft dysfunction.  
*Donor graft criteria: adjusted for ECD and DCD as defined by UNOS criteria.

Early graft dysfunction and length of hospitalization at time of transplantation

To further explore the impact of early graft dysfunction on immediate post-transplant outcomes, we evaluated the length of hospitalization at time of transplantation. Patients included in our analysis who developed early graft dysfunction had a significantly longer length of hospital stay as compared to patients with immediate graft function (10.7 vs 5.8 days, P < 0.0001; Figure 2).

Sensitivity and specificity of PASP cut-off values for predicting early graft dysfunction

ROC curve analyses were performed to determine the accuracy of different PASP ‘cut-off’ values to predict early graft dysfunction (Table 5). The cut-off value of ≥35 mm Hg that was used to define our pulmonary HTN group yields a sensitivity of 88% and specificity of 56% in predicting early graft dysfunction. This initial cut-off value was based on prior studies not specific to a renal graft dysfunction endpoint and therefore the sensitivity and specificity may be improved by increasing the cut-off value. A PASP ≥ 40 mm Hg yields a sensitivity of 83% and a specificity of 70%, while an increase to ≥45 mm Hg yields a sensitivity of 75% with a specificity of 80%.

Discussion

Our study suggests that abnormally elevated pulmonary pressures detected by echocardiography in preoperative renal transplant patients appear to be an independent predictor of early graft dysfunction after deceased donor transplantation. The renal transplant patients included in our study had a 38% prevalence of pulmonary HTN which is consistent with prior studies which have reported a 40–50% prevalence among ESRD patients [1–5]. We demonstrated that the identification of pulmonary HTN during a preoperative echocardiogram was associated with an increased incidence of early graft dysfunction from 12 to 56% after deceased donor transplantation. Logistic regression using covariate and multivariable models supports this finding as independent of previously described risk factors and potential confounders including haemodialysis and the presence of an AVF. Furthermore, as our institution has a protocol in place to maintain strict blood pressure parameters in the perioperative setting, it is unlikely that additional haemodynamic parameters were impacting these results. Finally, though our study did not evaluate the long-term impact of early graft dysfunction on graft and patient survival, we did demonstrate...
that early graft dysfunction was associated with increased perioperative morbidity as evidenced by the significant increase in length of hospitalization at time of renal transplantation.

The mechanisms behind the increased prevalence of pulmonary HTN in the ESRD population have been previously examined [1–5]. Patients with ESRD have been found to have elevated levels of the potent vasoconstrictor endothelin-1 [4]. It has also been demonstrated that ESRD patients with pulmonary HTN have decreased circulating levels of the vasodilator nitric oxide and its metabolites [4]. The increased levels of endothelin-1 and decreased levels of nitric oxide and its metabolites are believed to be a result of endothelial dysfunction resulting in pulmonary vasoconstriction [4]. Simultaneously, the presence of an AVF leads to a high cardiac output state that the noncompliant pulmonary vasculature is unable to compensate for and thus further increases pulmonary pressures [1]. Moreover, patients with ESRD often have significant hypertension and left ventricular diastolic dysfunction that increase pulmonary venous pressures as a contributor to pulmonary HTN. Lastly, the initiation of haemodialysis has been shown to increase pulmonary pressures by mechanisms that have yet to be identified [2].

The relationship between pulmonary HTN and early graft dysfunction may reflect both haemodynamic changes and alterations in vasoactive substances. Prior research utilizing thermodiffusion probes inserted into the renal cortex of kidney transplant recipients demonstrated that patients who developed DGF had evidence of lower renal microperfusion compared to patients with immediate graft function [7]. The impact of pulmonary HTN on kidney perfusion has not been well described, but there is usually an inverse relationship between the PASP and cardiac output. Invasive studies are needed to clarify to what extent high output from the AVF and low output due to pulmonary HTN contribute to impaired renal perfusion and graft dysfunction. The fact that most patients are initially made hypertensive during the first 24–48 h after transplant to assist with graft perfusion puts further stress on the pulmonary vasculature and perhaps, paradoxically, leads to lower overall cardiac output.

Prior studies evaluating the pathogenesis of DGF have demonstrated that the decrease in renal microperfusion is thought to be, in part, the result of increased renovascular resistance from vasoconstriction [8–11]. The vasoactive substance endothelin has been implicated in the development of ischaemia-reperfusion injury after renal transplantation as it has been previously demonstrated that patients with DGF have high circulating serum levels of endothelin-1 [9]. Furthermore, experimental findings that endothelin-receptor antagonists ameliorated ischaemia-reperfusion injury and early renal dysfunction in rats support the hypothesis that endothelin mediates vasoconstriction which perpetuates post-transplant renal damage [10,11]. Studies have also demonstrated that nitric oxide helps to maintain vascular relaxation and renal medullary oxygenation, and thus may play an important role in protecting the renal graft against post-transplant vasoconstriction [8,12]. It is possible that pulmonary HTN in renal transplant candidates may be a marker of patients with altered levels of vasoactive substances which may potentiate post-transplant vasoconstriction and ischaemia-reperfusion injury resulting in early graft dysfunction. In addition, endothelial dysfunction secondary to immunologic factors may also be a contributing factor as prior research has demonstrated a potential role of anti-endothelial cell antibodies in the pathogenesis of both pulmonary HTN associated with connective tissue diseases and renal transplant failure [30,31].

Several potential limitations of this study need to be addressed. First, our data demonstrate an association between pulmonary HTN and early graft dysfunction; however, as this is a retrospective study, it is not designed to definitively demonstrate causality. In addition, because of the small sample size of our study, it may have been underpowered to detect certain differences. Because of this, the crude and adjusted odds ratios may have been inflated slightly in the risk adjusted analysis. Furthermore, there were no events of early graft dysfunction in the living-related donor group although some patients in that group had an elevated PASP. A larger study might be powered to detect a relationship, but prior research has demonstrated the incidence of early graft dysfunction in living-related donor recipients to be very low [32,33].

Second, our study was limited to echocardiographic data. It was not our intent to perform an invasive study, and being retrospective, we were limited to available data. A potential concern is that in the absence of standardization, fluid status at time of echocardiography may have impacted the measured PASP. Although factors such as volume overload and elevated left-sided filling pressures can increase pulmonary pressures, even in the presence of these influences, a measured PASP above a ‘threshold level’ of 35 mm Hg is considered abnormal and suggests that additional mechanisms are contributing to the reduced compliance of the pulmonary vasculature. In addition, although an invasive study would increase the precision of measured PASP, it is worth noting that the Doppler techniques used on echo can possibly underestimate pressure gradients due to angle dependence, but very rarely over-estimate. Thus, the recorded PASP that were high were likely real findings; however, some patients with pulmonary HTN may have gone undetected. Another concern is possible error in risk stratification as the mean length of time between the echocardiogram and renal transplantation for all patients was 10.9 months. The most common indication for echocardiography in our study patients was ‘preoperative testing prior to renal transplantation’. In the absence of cardiac ischaemia or another indication testing generally does not need to be repeated if there is a prolonged time between the initial study and transplantation. Many of our study patients received deceased donor transplants which contributed to the increased time between echo and transplantation as surgery is not scheduled but rather performed on short notice when an organ becomes available. It has previously been reported that non-invasive identification of pulmonary HTN by echocardiography within 3 years of non-cardiac surgery is a marker of increased perioperative morbidity and mortality [34]. In our study, the majority of the patients, 86%, had a preoperative echocardiogram performed within 2 years of transplantation. Thus, we suspect that the identification of
patients with an abnormal PASP ≥35 mm Hg at any point in the preoperative setting appears to confer additional risk for the development of early graft dysfunction.

Third, there was a concern that our study subjects represented a cohort of patients at higher risk of developing early graft dysfunction, and therefore these results may not be applicable to a more broad population of renal transplant candidates. We addressed this issue by collecting demographic data on all 143 consecutive transplant patients over the 3-year period. Among the patients who had a pretransplant echocardiogram (n = 94), there was no difference in baseline clinical characteristics between patients who had an estimated resting PASP and those that did not. In comparing the study group (echo + reported PASP) to the patients who did not have an echo (n = 49), age of the recipient was the only variable that was significantly different (53 ± 11 vs 47 ± 13 years). We later controlled for age among deceased donor recipients in the logistic regression, and the association between pulmonary HTN and early graft dysfunction was maintained.

This study suggests that pulmonary HTN in renal transplant candidates receiving a deceased donor kidney is associated with an increased risk of early graft dysfunction. A larger prospective study would be needed to confirm these findings as this is a novel observation. Given the sensitivity/specificity analysis, one might consider further evaluation with a right heart catheterization in patients with an estimated PASP ≥40 mm Hg. This would help determine the number of patients who have WHO classification type II pulmonary HTN (secondary to diastolic dysfunction) as compared to other causes. Further research studying the impact of modern medical therapies for the treatment of pulmonary HTN on the development of early graft dysfunction in the context of a randomized controlled trial could be performed to guide clinical practice.

Conflict of interest statement. Research conducted by E.C. is sponsored by Actelion. He serves on the speaker’s bureau for Actelion and Gilead and on the consultant bureau for United Therapeutics and Actelion.

References
A 50% reduction in cyclosporine exposure in stable renal transplant recipients: renal function benefits

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Abstract

Background. Although cyclosporine maintenance therapy reduces the risk of acute rejection and increases short-term graft survival in renal transplant recipients, its associated nephrotoxicity increases the risk of chronic graft dysfunction. The dose that allows an optimal risk-to-benefit ratio has not been established.

Methods. This multicentre study enrolled stable renal allograft recipients receiving cyclosporine and mycophenolate mofetil without corticosteroids in their second year post-transplant. Patients were randomized to a cyclosporine dose targeted to a standard area under the concentration–time curve (AUC)0–12 h (usual exposure, n = 104) or 50% of the study standard AUC0–12 h (low exposure, n = 108) using a three-point pharmacokinetic sampling. The primary endpoint was the percentage of patients with treatment failure at 24 months (graft loss/acute rejection/nephrotoxicity/>15% serum creatinine level increase).

Results. Treatment failure was reported in 37 out of 101 (37%) patients in the usual-exposure and 19 out of 106 (18%) patients in the low-exposure groups (P = 0.003). Mean estimated glomerular filtration rate decreased from baseline to 2 years with usual exposure and increased with low exposure (P < 0.001). Mean systolic and diastolic blood pressures were lower with low exposure (P = 0.03 and P = 0.008, respectively).

Conclusion. In renal transplant recipients receiving maintenance therapy without corticosteroids, a minimization strategy using three-point pharmacokinetic sampling to reduce and maintain cyclosporine exposure to 50% of the usual levels is safe and reduces the risk of graft dysfunction.

Keywords: cyclosporine; drug dose-response relationship; kidney transplantation; mycophenolic acid; pharmacokinetics