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# ECHOCARDIOGRAPHIC PULMONARY HYPERTENSION PREDICTS POST-TRANSPLANT RENAL ALLOGRAFT FAILURE

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## Abstract

**Background—**Pulmonary hypertension has been associated with early allograft dysfunction and increased mortality following renal transplantation however this relationship has not been extensively studied.

**Methods—**We performed a retrospective cohort study of adult patients who underwent their first renal transplantation from 2003–2009 and had pre-transplantation echocardiograms. Pulmonary hypertension was defined as a right ventricular systolic pressure ≥ 40 mmHg in the absence of left-sided valvular disease and/or left ventricular ejection fraction ≤ 50%. The relationship between pulmonary hypertension and death-censored allograft failure (hemodialysis dependence or re-transplantation) and serum creatinine was assessed using Cox hazard regression and generalized mixed models. Eighty-two of 205 (40%) patients met inclusion criteria.

**Results—**The presence of pulmonary hypertension was associated with a 3.00 fold increase in the risk of death-censored allograft failure (95% confidence interval 1.20 – 7.32, p=0.02). Failure

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A.E.F., A.B.L., P.E.M., R.Y.G., A.P., J.R.K., and C.E.V. participated in study concept and research design. A.E.F., G.L.B., A.B.L., P.E.M., R.Y.G., A.P., J.R.K., and C.E.V. participated in the writing of the manuscript. A.E.F., G.L.B., A.B.L., P.E.M., R.Y.G., A.P., J.R.K., and C.E.V. data collection. A.E.F., G.L.B., and C.E.V. participated in data analyses. All authors revised and approved the final manuscript.

rates were 19% at 24 months and 51% at 96 months for those with pulmonary hypertension versus 7% at 24 months and 20% at 86 months for those without pulmonary hypertension (p=0.01). Among those without graft failure, there was an increase in creatinine levels after transplant (p=0.01). Effect estimates were unchanged by adjustment for multiple covariates and when pulmonary hypertension was defined as a right ventricular systolic pressure ≥ 36 mmHg.

**Conclusions—**Pulmonary hypertension prior to renal transplantation carries a 3.00-fold increased risk of death-censored allograft failure. The relationship between the pulmonary circulation and renal allograft failure warrants further study.

## Introduction

Pulmonary hypertension (PH) is a disease state characterized by progressive dyspnea and exercise intolerance which can lead to right ventricular failure and death. A number of systemic diseases have been linked to pulmonary vascular disease, including end-stage renal disease (ESRD). PH in the setting of ESRD is currently classified as World Health Organization (WHO) Group 5 PH[1], which by definition indicates there is a poorly understood or multifactorial explanation for this association. PH has been estimated to affect between 17–56% of ESRD patients and is associated with increased morbidity and mortality in this population[2–12].

Preoperative PH has been associated with poor outcomes in general surgery[13–15] and other solid organ transplantation[16–20]. A single retrospective study of 215 patients demonstrated increased mortality following renal transplantation in patients with PH observed on echocardiogram prior to surgery[21], but the etiology of these deaths is not well characterized. Whether PH associated with ESRD has an effect on renal allograft function following transplantation, when many of the speculated causative factors (e.g., volume overload and fluid shifts, arterio-venous shunts, renin-angiotensin activation in ESRD[8–10,12,22]), have been removed or temporized is not known. Further, demonstration of an association between preoperative PH and post-transplant allograft function may have larger implications for organ allocation and recipient risk stratification.

Factors that directly regulate pulmonary arteriolar vasoconstriction and remodeling in pulmonary arterial hypertension (PAH), including nitric oxide, endothelin-1 (ET-1), and thromboxane A2, also have a role in renal disease[6,7,23] and may contribute to pulmonary-renal vascular crosstalk and ESRD-PH phenotypes. Ongoing alterations in these important signaling pathways and/or accompanying vascular changes with lasting hemodynamic effects accrued in the pre-transplant period may impact post-transplant allograft function. Our objective was to determine whether ESRD patients with evidence of PH (defined by an estimated right ventricular systolic pressure [RVSP] ≥ 40 mmHg on transthoracic echocardiogram) have an increased risk of death-censored allograft failure. We hypothesized that preexisting PH would increase the risk of dialysis after transplantation and the need for retransplantation. We also examined the relationship between preoperative PH and post-transplant serum creatinine values in those who did not experience allograft failure.

## Methods and Materials

### Study Design

We conducted a retrospective cohort study of renal transplant recipients included in the Rhode Island Hospital's Transplant Center Database (TCDB) from January 1, 2003 – December 31, 2009. The study was approved by the Rhode Island Hospital Institutional Review Board (IRB #401303).

### Echocardiograms

Patients were included if they had available transthoracic echocardiograms and if these echocardiograms were performed prior to their first renal transplantation. Estimated RVSP was obtained using the modified Bernoulli equation and was recorded as a continuous variable; PH was defined as a RVSP ≥ 40 mmHg[3,10,24–26]. Sensitivity analyses were conducted in which PH was defined as a RVSP ≥ 36 mmHg and RVSP was treated as a continuous predictor of allograft failure[24]. Patients were excluded if they had a left ventricular ejection fraction (LVEF) ≤ 50% or had ≥ moderate aortic or mitral valve disease or ≥ moderate diastolic dysfunction.

### Variables of Interest

Data was extracted from the TCDB and by medical record review. Patient characteristics including age, sex, race/ethnicity, body mass index (BMI), and factors previously reported to impact renal transplantation outcome including cytomegalovirus (CMV) status and transplantation type (live versus deceased donor) were collected from the TCDB[27–30]. Additional risk factors for PH, including systemic hypertension, smoking history, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and connective tissue disease (CTD) were collected from the medical record. Allograft failure date (defined as progression to hemodialysis or retransplantation), serial values of post-transplant serum creatinine and date of death were also recorded. Baseline covariates were assessed as close as possible to the time of echocardiogram.

### Statistical Analysis

Continuous variables were expressed as median (interquartile range) and categorical variables were expressed as percentages. Independent sample t-tests were used to compare continuous variables and chi-square or Fisher's exact tests were used to compare categorical variables, as appropriate. Cox hazard regression was used to model the relationship between predictors (PH as a dichotomous outcome and RVSP as a continuous measure) with death-censored allograft failure. Kaplan-Meier estimation was used to estimate the median time until failure. Generalized mixed models with sandwich estimation were used to examine the relationship between PH and creatinine values at 90 days, one year, and three years post transplantation. Interactions and confounding with covariates of interest (age, sex, race, BMI, systemic hypertension, transplant type, left atrial size, COPD, and CMV status) were assessed for all models ($p < 0.2$). Models were assessed for goodness of fit using Akaike information criterion (AIC) and examined for multicollinearity. Data were collected using Excel 2007 (Microsoft, Redmond, WA) and analyses were performed using STATA 10.0

(StataCorp, College Station, TX) and SAS (SAS institute Inc., Cary, NC). Statistical significance was established at the 0.05 level and all interval estimates were calculated for 95% confidence.

## Results

A total of 415 patients received renal transplants between January 1, 2003 and December 31, 2009. During the seven year period, 172 patients (41%) had echocardiograms completed prior to transplantation. Of those with echocardiograms 73 (42%) patients were excluded due to no recorded RVSP, 17 (10%) patients had LVEF ≤ 50%, and 30 (17%) had previously had a transplant (Figure 1). Of the 82 patients included in analysis 22 (27%) patients had echocardiographic evidence of PH.

The median (interquartile range) age was 49 (17 – 80), 48 (42%) were women and 45 (55%) were white. The majority of patients were never smokers (55 [67%]) and had a history of systemic hypertension (66 [80%]). Among those with documentation of the mode of dialysis, 44 (72%) had fistulas for chronic dialysis prior to transplantation. Characteristics of those with and without PH are shown in Table 1. Demographics were similar between the two groups, except a greater proportion of those with PH had a deceased donor transplant (18/22 [82%] vs. 32/60 [53%], p=0.02). The median (interquartile range) RVSP for patients with PH was 45 mmHg (40 – 54 mmHg) and 32 mmHg (20 – 39 mmHg) for those without PH.

Those with PH prior to renal transplantation had a 3.00 fold (95% confidence interval [CI] 1.20 – 7.32, p=0.02) increased risk of experiencing death-censored allograft failure. Kaplan-Meier estimates showed renal transplant failure rates to be 19% at 24 months and 51% at 96 months for those with PH versus 7% at 24 months and 20% at 86 months for those without PH (p=0.01) (Figure 2). In individuals who did not meet the allograft failure end point, there was a trend towards higher creatinine values at three years in those with PH (3.3 mg/dL, 95% CI 1.9 – 4.7 mg/dL) as compared to those patients without PH (1.9 mg/dL, 95% CI 1.5 – 2.3 mg/dL), a difference (−1.4 mg/dL, 95% CI −3.5 – 0.79 mg/dL) which approached significance (p=0.06) at year 3 and was significant for the overall follow-up time (p = 0.01) (Figure 3).

We also assessed RVSP as a continuous predictor. For every 1-mmHg increase in RVSP there was a 2% increase in the risk of death-censored allograft failure however this did not reach statistical significance (p=0.50). Hazard rate was unchanged when PH was defined as RVSP ≥ 36 mm Hg (HR 2.2), however as expected there was a decrease in precision due to greater “noise” (95% CI 0.9 – 5.5, p=0.08) [24].

## Discussion

The results from this study support our hypothesis and suggest that echocardiographic PH prior to renal transplantation is associated with a three-fold increase in the risk of death-censored allograft failure and predicts declining renal function in those allografts that do not fail. To our knowledge, this is the first study to demonstrate a relationship between PH and the need for post-transplant hemodialysis or re-transplant and suggests that pre-existing PH

may be more than a “secondary” phenomenon due to transient fluid shifts, volume overload or mode of dialysis, but rather indicative of a true pulmonary vascular-renal vascular connection.

A previous study of 215 patients demonstrated increased mortality after renal transplantation in recipients with echocardiographic evidence of PH[21]. This study did not exclude patients with reduced LVEF and in fact effects were attenuated when LV dysfunction was adjusted for, such that PH no longer had a significant relationship with death; the relationship between PH and graft function was not explored. In our study, we excluded those with significant left-sided disease and other potentially important confounders did not impact the odds of graft failure in those with PH. The 2% increase in the odds of failure with each unit increase in RVSP (while not statistically significant perhaps due to sample size) and increasing creatinine over time even among those who avoided dialysis or retransplantation lends further support to our observations. Worsening creatinine after transplantation among those with PH is concerning as renal dysfunction is an independent risk factor for cardiovascular death and is the leading cause of mortality in renal transplantation patients[31,32].

Numerous studies have previously documented an association between echocardiographic PH (and a few have confirmed PAH by invasive hemodynamics) and chronic kidney disease[2–10,12,23,31–34]. It remains an elusive phenotype with multiple potential endotypes, however, and is therefore classified as WHO Group 5 PH. Certain obvious culprits, such as volume overload, may lead to pulmonary venous hypertension and transient pulmonary pressure elevation which are resolved by a return to euvolemia with HD or transplantation. Shared pulmonary-renal vascular and metabolic signaling pathways suggest that a “feed forward” cycle may also lead to long-lasting effects after transplant, and explain our observations. For example, the addition of the human ET-1 transgene leads to increased ET-1 activity in the brain, lung, and kidney and results in reduced glomerular filtration rate and fatal renal fibrosis in mice[35]. Given the shared importance of such pathways in PAH and ESRD, altered ET-1, thromboxane A2, nitric oxide, or parathyroid signaling[36–40] in patients who develop renal failure may lead to pulmonary vascular changes that eventually cause renal allograft dysfunction post-transplant[41–46].

Our study has limitations, including all that apply to a retrospective study. The study population was derived from a single transplant center. The results may not be generalizable to an unselected population of renal transplant recipients, but rather applied to those who have echocardiograms as part of their evaluation. Further, we had to exclude a number of patients due to inadequate echocardiograms, which may have created additional sampling bias. Baseline characteristics of those excluded were similar to those included however (data not shown). We attempted to collect tricuspid annular plane systolic excursion values however this was not routinely included during standard echocardiograms at the time the studies were completed. As our institution is a referral transplant center we were unable to obtain the cause of initial renal failure or concurrent medication use for most patients. Pulmonary vascular disease would have ideally been characterized by hemodynamics using right heart catheterization, especially to distinguish pulmonary arterial from pulmonary venous hypertension and high output states in this population. While hemodynamic data is

not available for this cohort, we did carefully consider covariates of interest (e.g., left atrial size and systemic hypertension) and excluded those with overt left-sided abnormalities in an effort to address the potential for confounding. We were able to detect a signal (and in fact a large effect estimate which persisted when we re-categorized PH as RVSP ≥ 36 mm Hg) in spite of this but we cannot exclude residual confounding and our results need to be validated in a population with hemodynamically defined PAH. There was a low event rate for our outcomes of interest and the sample size was small, limiting our power; models were assessed for goodness of fit and multicollinearity and effect estimates did not change with covariate adjustment.

We have for the first time documented a link between pre-transplant echocardiographic PH and death-censored allograft failure. Our findings should be validated prospectively (in both PH and PAH) and further mechanistic work should delineate the pulmonary-renal vascular connection.

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## Research Highlights

- Pulmonary hypertension increases the risk of renal allograft failure
- Pulmonary hypertension may be a risk factor for renal allograft dysfunction
- The relationship between the pulmonary and renal vasculature should be further elucidated

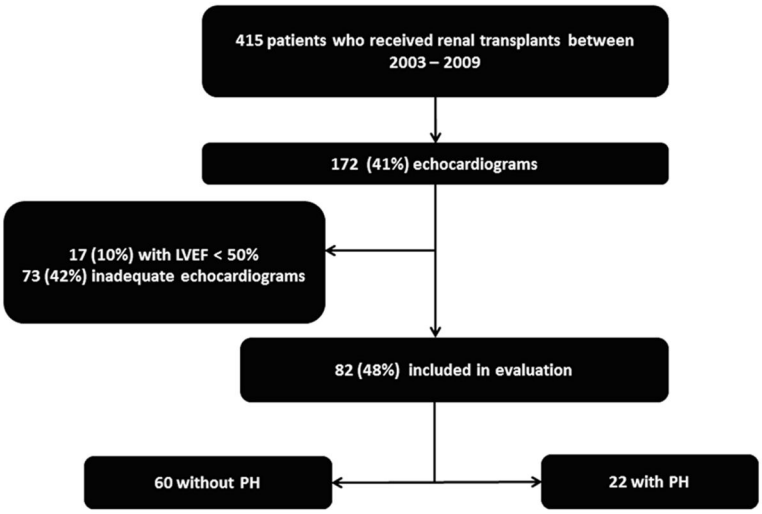


**Figure 1.**
Study flow

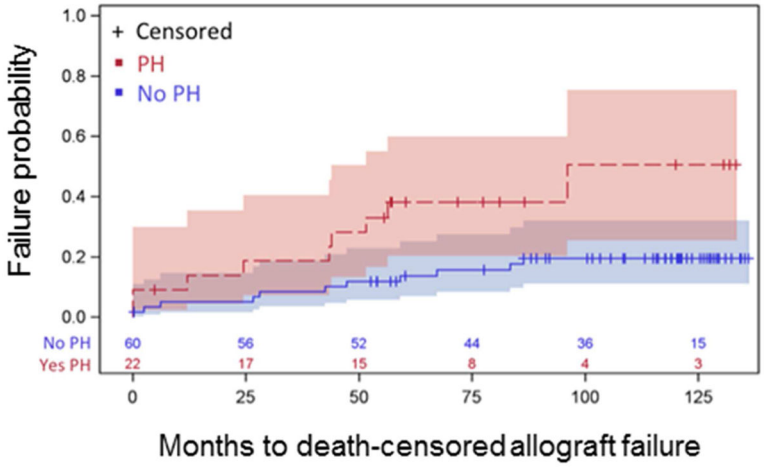


**Figure 2.**

Kaplan Meier curves demonstrating death-censored allograft failure, 19% at 24 months, 51% at 96 months for those with PH vs. 7% at 24 months, 20% at 86 months for those without PH (p=0.01). PH=pulmonary hypertension.

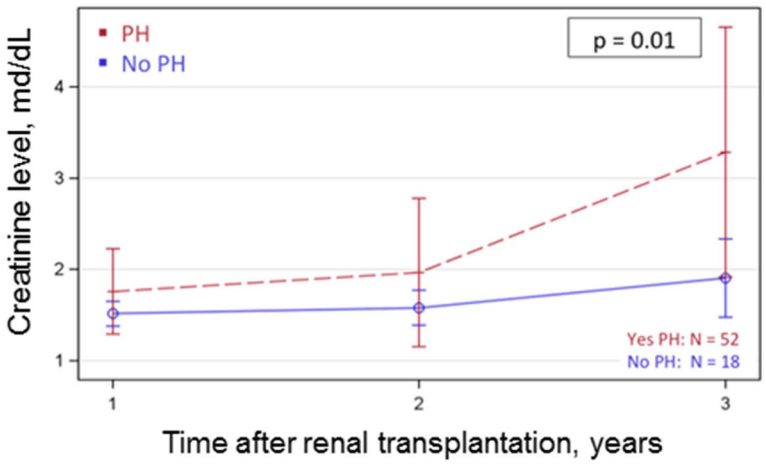


**Figure 3.**

Mixed modeling displayed as least squares means showing creatinine levels at 90 days, 1 year, and 3 years after transplantation. P-value refers to overall F-test for total follow-up time. PH=pulmonary hypertension.

## Table 1

Patient characteristics at time of transplantation

| Variables | No PH | PH | P value |
|---|---|---|---|
| Number | 60 (73) | 22 (27) | |
| RVSP, mmHg | 32 (20–39) | 48 (40–74) | |
| Male sex, n (%) | 37 (62) | 11 (50) | 0.34 |
| Age (yrs) | 48 (40–61) | 50 (47–55) | 0.51 |
| BMI | 26 (22–30) | 26 (23–28) | 0.72 |
| Race/ethnicity, n (%) | | | 0.06 |
| White | 37 (62) | 8 (36) | |
| Black | 16 (27) | 8 (36) | |
| Hispanic | 5 (8) | 6 (27) | |
| Asian | 2 (3) | 0 (0) | |
| Systemic HTN, n (%) | 48 (80) | 18 (82) | 0.85 |
| Diabetes mellitus, n (%) | 15 (25) | 8 (36) | 0.31 |
| Hyperlipidemia, n (%) | 17 (28) | 4 (18) | 0.41 |
| COPD, n (%) | 4 (7) | 3 (14) | 0.38 |
| CTD, n (%) | 4 (7) | 1 (5) | 0.99 |
| Left atrial enlargement*, n (%) | 22 (37) | 14 (64) | 0.05 |
| Time echo to transplant, yr | 1.3 (1.3) | 1.8 (1.6) | 0.12 |
| CMV status, n (%) | | | 0.99 |
| donor (−)/recipient (−) | 4 (67) | 1 (5) | |
| donor (− or +)/recipient (+) | 38 (63) | 16 (73) | |
| donor (+)/recipient (−) | 6 (10) | 3 (14) | |
| Transplant type, n (%) | | | 0.02 |
| live donor | 28 (47) | 4 (18) | |
| deceased donor | 32 (53) | 18 (82) | |
| Allograft failure, n (%) | 11 (18) | 9 (41) | 0.02 |
| Time to allograft failure, yr | 2.9 (0.8) | 3.3 (0.8) | 0.75 |
| Death, n (%) | 2 (3) | 1 (5) | 0.80 |

Data are shown as median (interquartile range) or absolute number (%).

* ≥ mild left atrial enlargement on an ordinal scale. BMI=body mass index, HTN=hypertension, COPD=chronic obstructive pulmonary disease, CTD=connective tissue disease, RVSP=right ventricular systolic pressure, CMV=cytomegalovirus