Title

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Journal

Transplantation, 104(10)

ISSN

0041-1337

Authors

Bokoch, Michael P
Findlay, James Y

Publication Date

2020-10-01

DOI

10.1097/tp.0000000000003069

Peer reviewed

Transplantation

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--Manuscript Draft--

Manuscript Number:	
Full Title:	Pulmonary Hypertension and Mortality in Patients Awaiting Kidney Transplant: Cause for Concern and Potential Opportunity
Article Type:	Commentary - Invited
Corresponding Author:	Michael P. Bokoch, M.D., Ph.D. University of California San Francisco San Francisco, CA UNITED STATES
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of California San Francisco
Corresponding Author's Secondary Institution:	
First Author:	Michael P. Bokoch, M.D., Ph.D.
First Author Secondary Information:	
Order of Authors:	Michael P. Bokoch, M.D., Ph.D.
	James Y. Findlay, MB, ChB
Order of Authors Secondary Information:	

Pulmonary Hypertension and Mortality in Patients Awaiting Kidney Transplant: Cause for Concern and Potential Opportunity

Michael P. Bokoch, MD, PhD[1] and James Y. Findlay, MB, ChB[2]

[1]Department of Anesthesiology and Perioperative Care, University of California, San Francisco, San Francisco, CA.

[2]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN.

Correspondence:

Michael P. Bokoch, MD, PhD

Dept. of Anesthesia and Perioperative Care, University of California, San Francisco, 533 Parnassus Ave, San Francisco, CA 94143.

(Michael.Bokoch@ucsf.edu)

Authorship:

MPB conceived and wrote the manuscript, and made the figure.

JYF wrote and edited the manuscript, and edited the figure.

The authors declare no conflicts of interest.

The authors declare no funding was received for this study.

Pulmonary hypertension (PH) is a complex, heterogeneous disease of great importance to the field of kidney transplantation (KT). Patients with end-stage renal disease (ESRD) have comorbid cardiovascular and pulmonary disease, and often suffer from volume overload. Not surprisingly, they are frequently diagnosed with PH, with an overall reported incidence around 20-45% in dialysis patients.[1] The usual criterion for diagnosing PH is a mean pulmonary artery (PA) pressure ≥ 25 mmHg, corresponding to a right ventricular systolic pressure (RVSP) ≥ 35-40 mmHg measured by echocardiography. Simply diagnosing elevated PA pressures in patients awaiting KT is insufficient; it is also crucial to distinguish the etiology and hemodynamic phenotypes of PH (Figure).[2] Due to a high incidence of hypertensive heart disease and diastolic dysfunction, many ESRD patients have World Health Organization (WHO) Group 2 PH, also termed "post-capillary" or PH secondary to left heart disease.[3] A minority have WHO Group 1 PH, also known as "pre-capillary" or pulmonary arterial hypertension (PAH), due to remodeling and narrowing of pulmonary arterioles. Finally, PH due to ESRD itself, in absence of other clear etiologies, is categorized as WHO Group 5. Proposed mechanisms of Group 5 PH include high cardiac output from arteriovenous fistulae, neurohumoral changes of uremia, and hyperparathyroidism. In many cases it is challenging or impossible to tease out a single cause of PH in an individual ESRD patient. Mixed, overlapping etiologies may exist (Figure). The implications of various PH categories for pre- and post-transplant outcomes and prognosis, and the optimal treatment strategies for each, are incompletely known.

The article by Caughey et al. in this issue of Transplantation addresses several of these issues.[4] The authors utilize the University of North Carolina Cardiorenal Registry, a large (*n* = 788 patients) single-center, prospectively-collected cohort of ESRD patients evaluated for KT. All patients were screened for PH by transthoracic echocardiography (TTE), performed on an

interdialytic day, and read by a single cardiologist. Tricuspid regurgitant jet velocity ≥ 2.9 m/s, representing an RVSP of approximately 40 mmHg, was considered diagnostic of PH. Doppler measurements of left heart diastology were also performed to assess for elevated left atrial pressure (eLAP). The implication is that patients with PH and eLAP have a post-capillary (WHO Group 2 or 5) contribution to PH – largely expected for a heavily dialyzed population (73% of patients in the study). Surprisingly, over half of the patients in Caughey et al. with PH lacked Doppler evidence of eLAP – suggesting a pre-capillary etiology. In a survival analysis (median follow-up of 4.4 years), the subgroup of PH without eLAP was at highest risk for mortality within five years of evaluation for KT, with a hazard ratio (HR) of 2.96 compared to the reference group lacking both PH and eLAP. Patients with eLAP, regardless of PH status, had a modestly increased risk of death (HR ~1.6).

The reliance on a single echocardiogram in Caughey et al. to both diagnose and categorize PH has several potential problems. First, the gold standard for diagnosis of PH is right heart catheterization (RHC), which allows precise measurement of pulmonary hemodynamics. The agreement between TTE and RHC for diagnosing PH is imperfect, with a reported sensitivity of 83% and specificity of 72%.[5] The accuracy of eLAP determination by TTE may be particularly problematic considering that intravascular volume depends on timing relative to dialysis. PA pressures and pulmonary capillary wedge pressure are reduced after dialysis, and in one small study it was only possible to diagnose pre-capillary PH by RHC after dialysis with patients close to their dry weight.[6] In Caughey et al., all patients underwent TTE on the day before dialysis; in this setting, it is surprising that only 45% of patients with PH also had eLAP (compared to the 80-100% reported in comparable studies using RHC).[6,7] This discrepancy may

be due to the relatively strict TTE criteria (Grade 2 diastolic dysfunction) employed by Caughey et al. to diagnose eLAP.

Diagnostic dilemmas aside, how should providers caring for patients awaiting KT utilize this information? The poorer outcome in patients with predominantly pre-capillary PH begs the question of whether more aggressive identification and management of these can improve outcomes. While it is impractical to screen all candidates with RHC, patients with moderate or severely elevated RVSP (≥ 45 mmHg) on TTE, corresponding to about 10-15% of the UNC Cardiorenal cohort, are more likely to have PH physiology beyond simple volume overload.[3] Referring such patients for RHC will clarify the etiology as pre-capillary, post-capillary, or mixed. For those with predominantly pre-capillary PH, nephrologists should consider consultation with a PH specialist for advanced management (Figure). Specialists may initiate and titrate modern pulmonary vasodilator therapies such as endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclins.[3] Whether these will improve wait-list survival is unknown - management was not captured in the Caughey et al. study. Optimistically, it may be possible to improve post-transplant outcomes with targeted therapy. Several studies suggest worse allograft function and survival in PH patients after KT,[8,9] possibly due to reduced cardiac output and impaired graft perfusion.[10] The findings in Caughey et al. present both challenges and opportunities: to better characterize and appropriately manage PH in KT candidates, define the influence of PH on outcomes, and hopefully one day improve pre- and post-transplant survival in this population.

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Figure legend:

Figure. Diagnosis and categorization of pulmonary hypertension (PH) in patients with end-stage renal disease (ESRD) referred for kidney transplant. The blue pathway shows consequences, and possible opportunities, for patients with predominantly pre-capillary PH. Abbreviations: HR, hazard ratio; LAP, left atrial pressure; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; TTE, transthoracic echocardiogram; WHO, World Health Organization.

Figure