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Review Article

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Complexities and Outcomes of Pulmonary Hypertension in Kidney Transplant Patients: A Comprehensive Review

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ABSTRACT

Pulmonary hypertension (PH) is often present in patients presenting for kidney transplant listing. While PH can complicate kidney transplantation (KTx), it can be managed with multidisciplinary management that includes both the transplant center and pulmonary hypertension center, or with experts both pre- and post-transplant. This review summarizes the approach and management of PH in KTx candidates and recipients, along with expected outcomes and controversies surrounding arteriovenous fistula and graft management.

Keywords: Pulmonary hypertension, pulmonary arterial pressure, kidney transplant, dialysis access, vascular access, right heart catheterization, echocardiogram

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INTRODUCTION

Pulmonary hypertension (PH) is a progressive disease with significant morbidity and mortality. Recent guidelines, both from the 2019 World Symposium on Pulmonary Hypertension (WSPH) and the European Society of Cardiology/European Respiratory Society (ESC/ERS), have updated our understanding of this disease as we gain more experience over time within our community. In 2019, the Sixth WSPH proposed the following definition of pulmonary arterial hypertension (PAH): 1) mean pulmonary arterial pressure (mPAP) >20 mmHg; 2) pulmonary artery wedge pressure (PAWP) <15 mmHg; and 3) pulmonary vascular resistance (PVR) >3 Wood units. In 2022, the ESC/ERS guidelines further refined the definition, which adjusted the PVR to ≥2 Wood units.

Both classifications divide patients with PH into 5 groups (Table 1, Figure 1). Group 1 is pulmonary arterial hypertension (PAH), which is comprised of diverse diseases that result in similar pathological changes within the pulmonary vasculature. The remaining 4 groups of PH are secondary to other conditions, including group 2 (heart disease), group 3 (lung disease), group 4 [chronic thromboembolic disease (CTEPH)], and group 5 (multifactorial). Treatment for these groups is focused on correcting the underlying original condition.

Group 1 PAH is a progressive disease that, without therapy, has poor outcomes. Over the last 3 decades, there have been significant advances in the field. Thirteen approved therapies have been introduced for PAH, which have improved outcomes for these patients. There is, however, still no cure for this progressive disease, and this remains an unmet challenge.

Group 5 PH is increasingly recognized as a condition associated with a variety of systemic disorders, including chronic kidney disease (CKD), with important prognostic implications for survival and outcomes before and after kidney transplantation (KTx). In this review, we summarize current knowledge related to the impact of PH among KTx candidates and patients.

Table 1. World Health Organization Pulmonary Hypertension Classification (Sixth World Symposium on Pulmonary Hypertension, 2018)[108]

1. **Pulmonary arterial hypertension**
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.3 Drug- and toxin-induced PAH
   - 1.4 PAH associated with:
     - 1.4.1 Connective tissue disease
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart diseases
     - 1.4.5 Schistosomiasis
   - 1.5 PAH long-term responders to CCBs
   - 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
   - 1.7 Persistent PH of the newborn syndrome
2. **PH due to left heart disease**
   - 2.1 PH due to HF with preserved LVEF
   - 2.2 PH due to HF with reduced LVEF
   - 2.3 Valvular heart disease
   - 2.4 Congenital/acquired cardiovascular condition leading to post-capillary PH
3. **PH due to lung diseases and/or hypoxia**
   - 3.1 Obstructive lung disease
   - 3.2 Restrictive lung disease
   - 3.3 Other lung disease with mixed restrictive/obstructive pattern
   - 3.4 Hypoxia without lung disease
   - 3.5 Developmental lung disorders
4. **PH due to pulmonary artery obstructions**
   - 4.1 Chronic thromboembolic PH
   - 4.2 Other pulmonary artery obstructions
5. **PH with unclear and/or multifactorial mechanisms**
   - 5.1 Hematological disorders
   - 5.2 Systemic and metabolic disorders
   - 5.3 Others
   - 5.4 Complex congenital heart disease

CCBs, calcium channel blockers; HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

Epidemiology in Kidney Transplantation

Published studies suggest that the prevalence of elevated pulmonary pressures, most often detected on routine testing with echocardiography, is estimated in 13%-40% of patients before and 17%-48% after kidney transplantation. In an analysis of Medicare-insured KTx recipients, 8.2% had a diagnostic code for PH within 2 years preceding the transplant.[1] By 3 years post transplant, PH was diagnosed in 10.6% of the study cohort.[1] After adjustment, posttransplant PH was more likely in KTx recipients who were older (adjusted hazard ratio [aHR] 2.40 for age >60 vs. 18-30 years) or female (aHR 1.24), who had pretransplant PH (aHR 4.79), coronary artery disease (aHR 1.15), valvular heart disease (aHR 1.32), peripheral vascular disease (aHR 1.18), chronic pulmonary disease (aHR 1.31), obstructive sleep apnea (aHR 1.28), longer dialysis duration, pretransplant hemodialysis (aHR 1.37), or who underwent transplant in the more recent era (aHR 1.39 for 2012-2016 vs. 2006-2011).[1]

MAIN POINTS

- Pulmonary hypertension is common in chronic kidney disease patients both pre- and post-kidney transplantation
- Kidney transplant candidates with pulmonary hypertension can be transplanted, but careful evaluation, monitoring, and management of pulmonary hypertension by a pulmonary hypertension center or expert.
- For successful kidney transplant, multidisciplinary management by the transplant team in conjunction with a pulmonary hyperatension center or expert is essential.

Clinical Manifestations and Diagnostic Tools

Clinically, PAH initially presents as dyspnea on exertion with symptoms classified by the New York Heart Association/WHO functional class (FC). Patients with FC IV symptoms have a mean survival of less than 6 months.[2] Right heart catheterization (RHC) remains the gold standard for the diagnosis, classification, and severity of PH. As RV function worsens, the mean pulmonary arterial pressure (mPAP) may decrease, allowing the use of mPAP and cardiac index to help determine the severity of PH.[3] In addition to diagnostic information, RHC can guide treatment options by ascertaining the response to acute vasodilator testing in some patients with group 1 PH to determine the efficacy of calcium channel blockers (CCBs). Right heart catheterization, along with other studies, also helps in considering when to refer patients for lung transplantation.[4] Although RHC is the definitive study to evaluate PH, an echocardiogram is a reasonable initial screening test and, as a baseline, can be a valuable tool for serial monitoring. Echocardiogram is also important as it provides vital information on other valvular disease, congenital heart diseases, and left ventricular function. Noninvasive measures of exercise testing, such as the 6-minute walk test and cardiopulmonary exercise testing, have prognostic value and categorize the severity of PH.[5] Pulmonary function tests and screening for acute or chronic pulmonary embolism should be conducted. Additional tests such as overnight oximetry, sleep study, serological testing for connective tissue disease, screening for HIV and sickle cell aid in identifying underlying or superimposed conditions with PH for treatment.[3]

Along with the somewhat historic ACCF/AHA 2009 Expect Consensus Document on Pulmonary Hypertension, the 2022 ESC/ERS Guidelines for the Diagnosis and Treatment

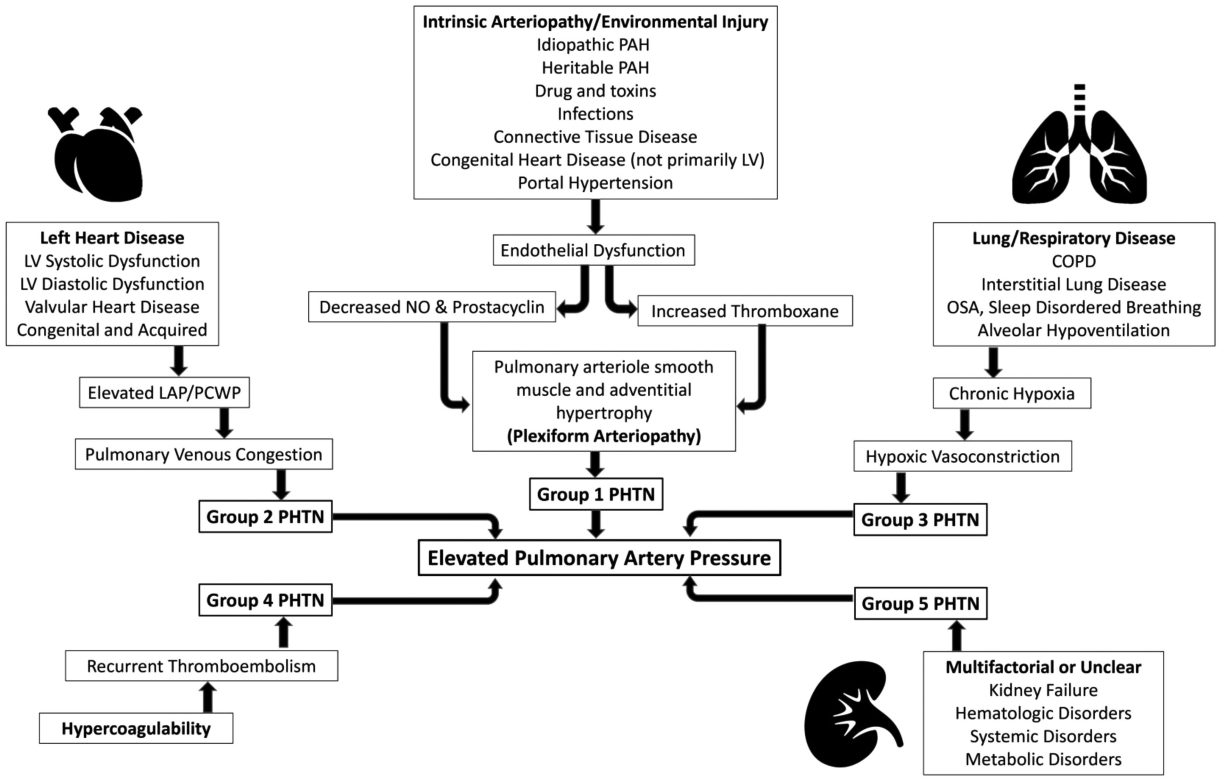

Figure 1. Conceptual framework for the physiology of pulmonary hypertension based on underlying disease states intrinsic to or affecting the pulmonary vasculature, as currently categorized by the World Health Organization. Reproduced from Lentine et al.[109,115] COPD, chronic obstructive pulmonary disease; LAP, left atrial pressure; LV, left ventricle; NO, nitric oxide; OSA, obstructive sleep apnea; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension.

of Pulmonary Hypertension and the Proceedings of the 2019 sixth World Symposium on Pulmonary Hypertension provide a comprehensive review of treatment modalities for PH.[3,6-8] A low-salt diet with judicious use of diuretics to establish euvolumia is particularly important. Supplemental oxygen is recommended to maintain oxygen saturation >90%. Medication such as calcium channel blockers, prostanoid derivates (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan, macitentan, and ambrisentan), and phosphodiesterase-5 inhibitors (PDE5-I) (sildenafil and tadalafil) are usually employed in combination therapy to improve hemodynamics (Table 2).

Pulmonary Hypertension in Kidney Transplantation

Chronic kidney disease patients, including transplant candidates and recipients, demonstrate many of the morbidities characterizing pulmonary hypertension (Table 1). Given that the incidence of many comorbidities increases with increased age, the prevalence of PH also rises among older end-stage kidney disease (ESKD) patients.[9] Chronic kidney disease has somewhat different implications, etiologies, and characteristics within each PH group. For example, the right heart failure in those candidates with group 1 PH (PAH) may result in recurrent bouts of acute kidney injury, with eventual progression to a formal CKD diagnosis.[10] In a small series of 31 ESKD patients with unexplained dyspnea, RHC identified precapillary PH [PAH in the absence of elevated pulmonary capillary wedge pressure (PCWP)] in 13% (4/31).[11] Additionally, there is some modest support in the connective tissue disorders literature that supports the coexistence of kidney dysfunction and PAH,[12-14] including 1 larger registry of 2459 patients with systemic sclerosis that demonstrated that 0.5% had histories of both scleroderma renal crisis and PH.[15]

By far, the most common type of PH among persons with kidney failure is group 2. This frequency is attributed to the 30%-50% prevalence of left heart failure in patients with CKD.[16-18] The transplant list is further enriched for this PH type, as there are new-onset heart failure diagnoses within 3 years for about 32% of candidates on the transplant waiting list.[19] Left ventricular (LV) systolic and diastolic function abnormalities result in elevated LV and left articular (LA) pressures. Chronically elevated LA pressures, in turn, led to pulmonary vascular congestion and, ultimately, the elevated PAP and PH needed to maintain the pressure gradient required for the pulmonary arterial circuit. In addition to coronary artery disease or ischemic cardiomyopathy, LV dysfunction is further exacerbated by myocardial damage and stiffening due to the uremia, diabetes mellitus, and chronic hypertension that are common in CKD patients.[20]

Table 2. Vasodilator Therapy Directed Toward Pulmonary Arterial Hypertension

Class of Agent (Mechanism of Action)	Name	Administration Route	Adverse Effects
Endothelin receptor antagonist (blocks binding of endothelin 1 to its receptors A/B)	Ambrisentan	PO	Headache, sinus congestion, lower extremity edema, anemia, and hepatotoxicity (10%) w/ bosentan
	Bosentan	PO	
	Macitentan	PO	
Phosphodiesterase type 5 inhibitor (prevents breakdown of cGMP, the downstream mediator of nitric oxide)	Sildenafil	PO, IV	Headache, flushing, sinus congestion, and visual color changes
	Tadalafil	PO	
Soluble guanylate cyclase stimulator (stabilizes soluble guanylate cyclase to nitric oxide binding to enhance production of cGMP)	Riociguat	PO	Hypotension, headache, and gastrointestinal
Prostacyclin analog (activates adenylate cyclase to produce cAMP)	Epoprostenol	IV, inhalation	Most severe, including flushing, headaches, jaw pain, lightheadedness, N/V, diarrhea, myalgia, and skin rashes
	Iloprost	IV, Inhalation	
	Treprostinil	PO, IV, SC, inhalation	

IV, intravenous; PO, by mouth; SC, subcutaneous.

To further complicate the CKD patient, even those CKD patients with normal LV systolic function have a high prevalence of abnormal LV diastolic function that worsens LV compliance. Echocardiographic measures of diastolic pathology, such as elevated LV mass, LV hypertrophy, and measures of diastolic dysfunction, are associated with adverse cardiovascular outcomes for both kidney transplant candidates and recipients, even with normal LV systolic function.[21-23] Finally, valvular disease is a potential cardiogenic contributor of group 2 PH and should be carefully assessed.[24,25] Thus, the impact of group 2 PH on transplant candidacy is modified by the presence and severity of multiple cardiac parameters, underlying coronary artery disease, LV and RV systolic function, LV diastolic function, LV hypertrophy, and symptom severity.

Group 3 PH is defined by hypoxic lung disease, which is often colinear with acute or chronic kidney dysfunction. In a large series of chronic obstructive pulmonary disease patients, 26% were affected by CKD or ESKD.[26] Obstructive sleep apnea (OSA) is prevalent in 60% of ESKD patients, which is 5 times the prevalence of OSA in the healthy general population.[17,27,28] End-stage kidney disease patients are often obese,[29] which is correlated not only with OSA and elevated PAP but also with increased levels of the pulmonary vasoconstrictor endothelin 1.[30]

End-stage kidney disease and CKD are known to be associated with hypercoagulability, which is associated with vascular thromboembolic events (VTEs). The risk of pulmonary VTEs is about 3-fold and 8-fold higher among CKD and ESRD patients, respectively.[17,31] This risk directly translates to a risk of CTEPH (group 4 PH).

Importantly, not all PH in the CKD/ESKD population can be explained by the conditions currently comprised by groups 1-4. “Unexplained PH in patients with renal failure” is a distinct subcategory of group 5, first recognized when a review of an echocardiographic series of 691 patients with PAP >45 mmHg identified 3 patients receiving hemodialysis via arteriovenous fistulas (AVF) who did not have significant cardiac or pulmonary disease.[32] While careful clinical evaluation including history, echocardiography, chest radiography, pulmonary function testing, computed tomography scans, and ventilation/perfusions scans has identified group 1-4 conditions in 40%-70% of hemodialysis cohorts with PH,[33-37] unexplained PH (group 5 PH) remains a common classification for PH in CKD/ESKD patients.

Finally, some kidney transplant recipients may have comorbidities from more than 1 PH group. Uremicia in ESKD patients results in elevated endothelin and angiotensin II, both of which are potent vasoconstrictors that contribute to PH.[38] High cardiac output (CO) can be exacerbated by anemia. Additionally, there are conflicting reports on the effects of lower hemoglobin levels for PH patients.[33,35,37,39,40-44] The implications of the cardi opulmonohepaticorenal axis are well known to the transplant community. Maladaptive neurohormonal activation, oxidative stress, and abnormal immune cell signaling can cause derangements of this axis, resulting in end-organ damage and reciprocal disease progression.[45] While PH classification is complex, correct identification of PH etiology helps guide therapy and determine transplant candidacy. An algorithmic approach to the evaluation of kidney transplant candidates with echocardiographic evidence of elevated pulmonary artery systolic pressure (PASP) is shown in Figure 2.

Impact of Arteriovenous Fistula on Pulmonary Pressures

Kidney replacement modality before transplant can impact PH incidence and severity.[46] In 1 small study, hemodialysis patients with an AVF had 4 times the prevalence of PH (40% vs. 10%) when peritoneal dialysis or catheter-based dialysis,[33] likely as an iatrogenic (but intentional) result of the extra CO

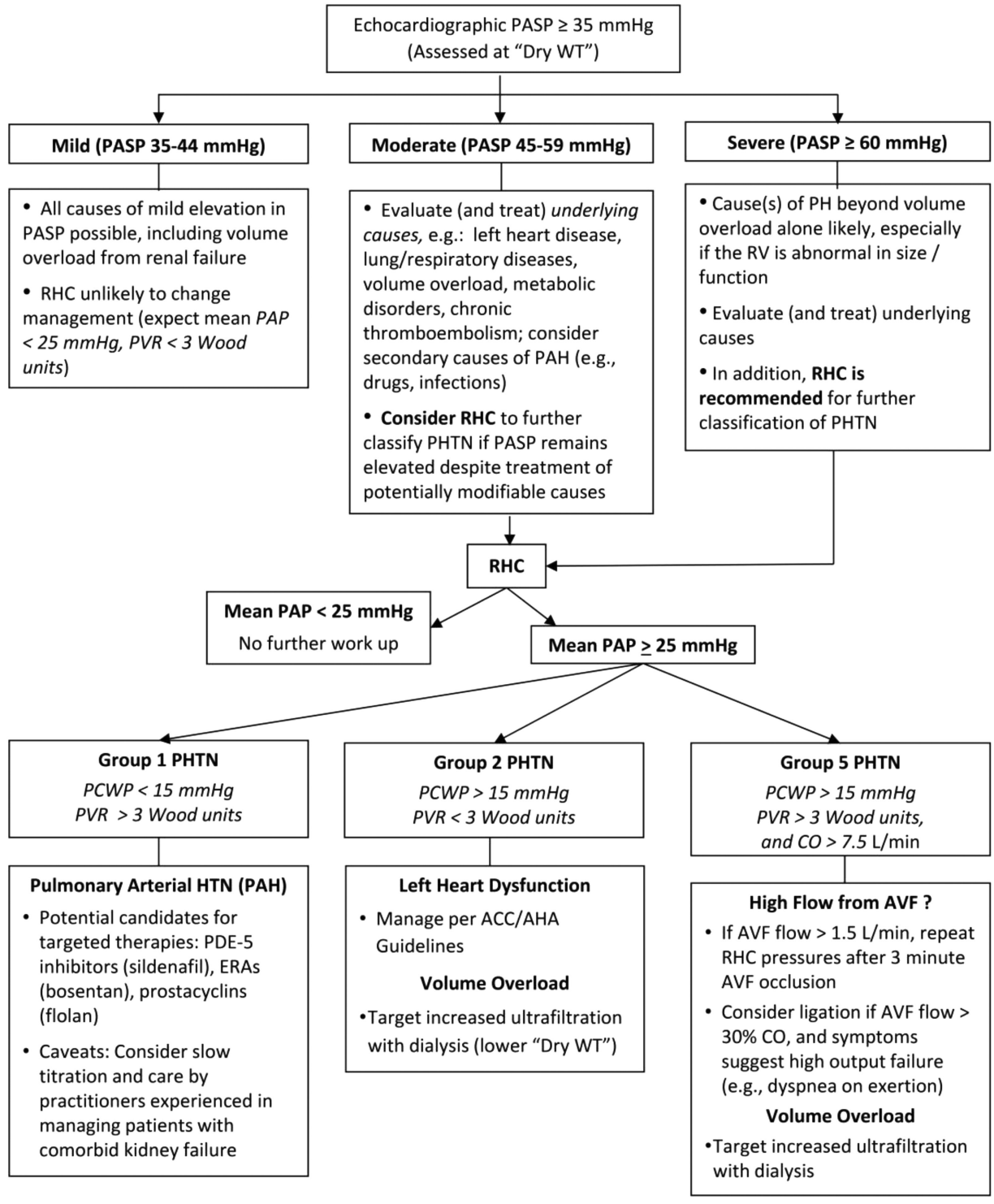

Figure 2. Suggested algorithm for the evaluation of kidney transplant recipients with echocardiographic evidence of pulmonary hypertension. Reproduced from Lentine et al.[109] ACC, American College of Cardiology; AHA, American Heart Association; AVF, arteriovenous fistula; CO, cardiac output; HTN, hypertension; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricle; WT, weight.

and shunted volume from the left to the right side. Mature AVF is also associated with increased RV diameter and reduced tricuspid annular plane systolic excursion, consistent with RV wall stiffening on echocardiography, which is not present in those dialyzing with catheters.[47]Further evidence of the long-term impact of the left-to-right shunt. Although AVF has been implicated as exacerbating or causing PH in some hemodialysis cohorts,[35,48-50] other studies have shown no significant

Table 3. Summary of Studies Describing the Frequency, Correlates, and Outcomes of Pulmonary Hypertension Among Kidney Transplant Candidates. Adapted in Part from Lentine et al (2017)[109]

Reference, Year	Design and Participants	Evaluation Modality/ Definition of PH	PH Prevalence	Factors Associated with PH	Associations of PH with Clinical Events
Stallworthy et al, 2013[23]	• Retrospective, longitudinal • Single center in New Zealand, 2000-2009 • 739 patients evaluated for KTx with TTE (subset of 862 evaluations)	• TTE • Threshold not defined; considered as "PH and/or RV dysfunction (PH/RVD)"	• Pre-KTx PH/RVD: 13% (94/739)	• Not assessed	• PH/RVD associated with 91% higher mortality (aHR 1.91, P = .001) over the median of 4.2 years post evaluation, after adjustment for age, dialysis duration, listing status, and LV function
Zlotnick et al, 2011[110]	• Retrospective, cross-sectional • Single center in USA, 2006-2011 • 12 KTx candidates with PASP >40 mmHg by TTE who subsequently underwent RHC • All participants on HD with AVF	• TTE used for initial screening • PH confirmed by RHC: mean PAP >25 mmHg	• Pre-KTx: PH suggested by TTE was confirmed in 92% (11/12)	• PH classification by hemodynamics: • WHO group 1 (PCWP <15 mmHg, PVR >3 Wood units), 18% (2/11) • WHO group 2 (PCWP >15, PVR <3), 27% (3/11) • WHO group 5 with high flow (PCWP <15, PVR >3, CO >7.5 L/min), 27% (3/11) • "Mixed" WHO groups 2 and 5 (PCWP >15, PVR >3, CO >7.5 L/min), 27% (3/11)	• No follow-up data
Yigla et al, 2003[33]	• Retrospective, cross-sectional, with longitudinal comparisons in subgroups • Single center in Israel, 1997-1999 • Original cohort included 58 HD patients with AVF, selected for absence of known cause of PH ("poor" clinical condition also an exclusion) • 5 received KTx during follow-up	• TTE, timed 1 hour after HD in HD patients • PASP >35 mmHg	• HD cohort (KTx candidacy not specified): 39.7% (23/58) • PD controls: 0/5 • Predialysis controls: 1/12	• Among the 5 HD patients with AVF transplanted during the study, after KTx • PH declined from 100% (5/5) to 20% (1/5) • Mean PAP declined from 41 + 11 to 32 + 8 mmHg, P < .05)	• Mortality was higher among HD cohort members with vs. without PH at 50 months: 30.4% vs. 8.5%, P < .02 • KTx candidacy among the cohort not defined
Bozbas H et al, 2013[111]	• Retrospective cohort, single-center study • 500 consecutive patients with ESRD undergoing KTx evaluation in Türkiye. • Mean age 32 years	• TTE • PASP >35 mmHg	• PH in 17% (85)	• Not reported	• Outcomes not reported
Foderaro AE et al, 2017[112]	• Retrospective cohort, single-center study of KTx recipients with pre-KTx TTE • Excluded if no RVSP reported, LVEF <50% or prior KTx • 82 KTx recipients	• TTE • RVSP[3] 40 mmHg	• PH in 27% (22)	• No baseline differences between groups • Increased deceased donor KTx in PH cohort	• 3-fold increased risk of death-censored allograft failure • 51% vs. 20% graft failure in PH vs. controls at 96 months (P = .01) • No difference when risk-factor adjusted

AVF, arteriovenous fistula; HD, hemodialysis; KTx, kidney transplantation; LVEF, left ventricular ejection fraction; LV, left ventricle; PCWP, pulmonary capillary wedge pressure; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RVD, right ventricular dysfunction; RVSP, right ventricular systolic pressure; TTE, transthoracic echocardiography; WHO, World Health Organization.

relationship between the presence of AVF and PH,[51] suggesting that AVF flows, dialysis adequacy, and patient factors interact to mitigate or exacerbate the impact. In a serial evaluation of 6 patients with AVF who underwent echocardiography before and after initiation of hemodialysis, mean PASP rose from 37 to 45 mmHg in 4 of 6 patients.[33] In a prospective study of 100 AVF patients, AVF occlusion led to reduced CO and improved oxygen delivery.[52] These changes were even seen in asymptomatic patients, although larger CO changes during AVF occlusion were associated with a trend toward increased symptomatic heart failure risk.

Ligation of high-flow AVF can result in improvements or resolution of symptomatic PH and improved pulmonary hemodynamics,[53,54] including ligation reserved for after kidney transplantation (Table 3).[55] In a single-center study of 12 kidney transplant recipients who underwent AVF flow reduction procedures or ligation, improvements in heart failure symptoms and cardiac status were universal. The single patient with poor cardiac function who underwent AVF ligation had dramatic cardiac improvements.[56] In the other 11 who underwent precision banding procedures with real-time flow monitoring, AVF access flow was reduced from 2280 mL/min (1148-3320 mL/min) before access banding to 598 mL/min (481-876), with clinical signs of heart failure resolving. In a larger series of 113 kidney transplant recipients in Austria referred for evaluation of high-flow AVF, 29 (27.5%) underwent shunt intervention in the form of ligation in all but 1 with residual kidney function; 15 had shortness of breath at referral, all of whom reportedly had symptom resolution after ligation.[57]

A randomized trial of elective AVF ligation was performed among 64 kidney transplant recipients in Australia, with 54 patients completing the study evenly divided between AVF ligation and control.[58] Compared to preintervention cardiac magnetic resonance (CMR), CMR after ligation showed a decrease of 22.1 g (95% CI, 15.0-29.1) in LV mass in the AVF ligation group. The control group demonstrated a small rise of 1.2 g (95% CI, −4.8-7.2) ($P < .001$). The AVF ligation group also demonstrated significant decreases in LV end-diastolic volumes, LV end-systolic volumes, CO, cardiac index, atrial volumes, and *N*-terminal pro-brain natriuretic peptide (NT-proBNP), although LV ejection fraction or pulmonary artery velocity did not change significantly. Similarly, a small retrospective Belgian study demonstrated elevation of diastolic blood pressure, drop of serum NT-proBNP levels, reduction of LV/LA dimensions, and stable estimated glomerular filtration rate (eGFR) slope.[59]

These data suggest that elective AVF ligation for stable kidney transplant recipients may lead to a reduction in LV myocardial mass. There are obvious pros and cons to ligation, as ligation results in the loss of the access site in a population that may need the AVF someday. The decision process for ligation is often guided by the likely difficulty of establishing new vascular access in the patient, the volume of flow in the AVF, and the degree of PH and/or congestive heart failure.[60] Close collaboration and clear communication between the vascular access surgeon, transplant nephrologist, and PH specialist is essential to maximizing patients' life expectancy, as well as their expectations of kidney function, PH and CHF, and future vascular access difficulties. Of note, a study of USRDS data demonstrated that posttransplant atrioventricular (AV) access ligation is relatively uncommon and generally seen in patients with steal syndrome or other direct access-related complications such as AVF aneurysms, although highly variable transplant center-specific rates were noted (Figure 3).[61] The same study did not find an association between AV access ligation and allograft failure or all-cause mortality.

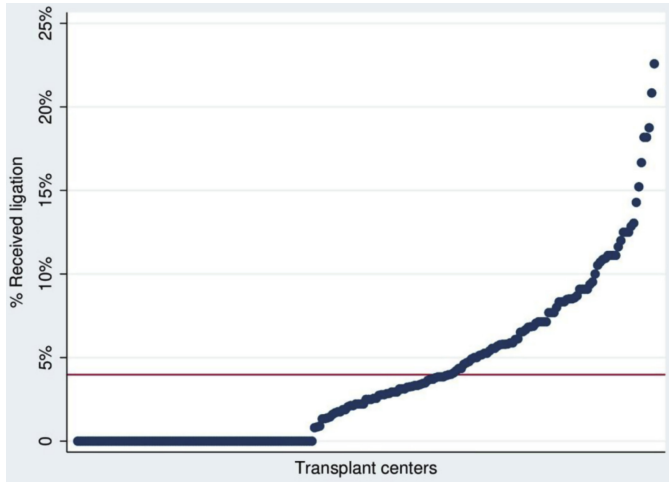

Figure 3. Center-level variation in posttransplant atrioventricular access ligation. On average, 4.2% of kidney transplantation patients underwent atrioventricular access ligation. From Hicks et al (2019),[61] used with permission.

Posttransplant Outcomes

Echocardiographic PASP estimates are only vaguely accurate, as they depend upon volume status at the time of the study and image quality, which are impacted both by habitus and user expertise. Despite these limitations, PASP can have prognostic significance for kidney transplant candidates and recipients. In a single-center study of the echocardiographic parameters of 739 New Zealand transplant candidates,[23] older age, diabetes, transplant listing status, severely impaired LV ejection fraction, echocardiographic regional wall motion abnormalities, and the presence of PH or RV dysfunction were independently associated with all-cause mortality over an average of 4.2 years of follow-up after the echocardiographic evaluation (Table 3). Furthermore, a graded mortality increase was seen with increasing number of such risk factors. Taken together, these data demonstrate the interaction of PH with other clinical and echocardiographic comorbidities that must be weighed and balanced during transplant evaluation.

Pulmonary artery systolic pressure measured before KTx has been found to be relevant to posttransplant outcomes. In a retrospective study of 215 transplant recipients in 2004-2007, over an average of 22.8 months of follow-up, pretransplant RVSP >50 mmHg was associated with nearly 4 times posttransplant mortality compared to RVSP <50 (aHR, 3.75; *P* = .025).[62] This association persisted with individuals adjusted for age, hypoalbuminemia, and DGF, but not EF. In a single-center study of 55 kidney transplant recipients with preoperative echocardiograms that included adequate evaluation of the PASP, PASP >35 mmHg was seen in 38% (21/55)[63] (Table 4). Using a combined endpoint of early, slow, or delayed graft dysfunction, living donor recipients were not at risk. However, graft dysfunction was more common in deceased donor transplant recipients (56% vs. 11.7% for deceased donor recipients without PH, *P* = .01). PH was associated with early graft dysfunction among deceased donor transplant recipients even after adjusting for recipient, donor, and transplant factors [aOR 15.0 (95% CI, 1.2-189), *P* = .03]. By using a PASP threshold of >45 mmHg, the specificity of PASP to predict the combined graft function outcome increased from 56% to 80%, with only a modest sensitivity change (75% vs. 88%). These data suggest an association between PH in the recipient and allograft perfusion, likely through a process of venous hypertension reducing effective allograft perfusion.

In a study of 215 kidney transplant recipients, RVSP ≥50 mmHg estimated by echocardiography was independently associated with an increased risk of posttransplant death (hazard ratio [HR] 3.75, *P* = .016), with time on dialysis as a strong predictor of elevated RVSP.[62] Mehra et al[64] performed a retrospective single-center analysis of 206 kidney transplant recipients and found that PH prior to kidney transplantation (defined as PASP >35 mmHg or tricuspid regurgitant jet >3 m/s by echocardiography) was present in 19%. Further, PH was independently associated with decreased graft function in the first 12 months post engraftment. Additionally, pilot data from another large center demonstrated an association between pretransplant PASP >35 mmHg and reduced 5-year graft survival.[65]

More recently, among 192 KTx recipients at 1 center with documented pretransplant PASP by echocardiography, elevated PASP >37 mmHg was present in 26% (n = 51).[66] Decreased LVEF <50% was more common among those with elevated vs. normal PASP (13.7% vs. 3.6%, *P* = .01). While 4-year mortality did not differ significantly by pretransplant PASP, in multivariate logistic regression adjusted for reduced LVEF, each 1 mmHg increase in PASP was associated with an 8.940 mL/min decrease in eGFR (95% CI, −15.8 to −2.1, *P* = .01). One single-center study described 363 KTx recipients (2005-2009) with PASP measurement by RHC at anesthesia induction as part of standard intraoperative monitoring at the center.[67] PASP >35 mmHg was identified in 36.6% (133/363). Median pretransplant dialysis duration was longer in those with PASP >35 mmHg vs. <35 mmHg (29 vs. 22 months, *P* = .004). Pretransplant PH was associated with a higher mortality risk over up to 8 years (aHR 1.98, 95% CI, 1.04-3.74, *P* = .4), after adjustment for comorbidities including CAD and heart failure. Pretransplant PH had a borderline, unadjusted association with graft failure risk (*P* = .05).

While there is a correlation between PH and increased rates of posttransplant morbidity, that in and of itself does not mean that it is not worth pursuing a kidney transplant for these patients, as the comparison condition is remaining on dialysis—with all its inherent morbidity and mortality. In fact, there is literature that supports the idea that successful kidney transplantation may improve PH and associated conditions, including elevated systemic blood pressure, LV hypertrophy, and LV systolic and diastolic dysfunction. Kidney transplantation has been associated with significant improvement in mean ambulatory blood pressures and a significant reduction in the LV hypertrophy prevalence at 12 months following transplantation in a small series of 24 patients[68]—an observation that is consistent with another study that demonstrated LVH regression following kidney engraftment.[69] In another small study of 22 men following successful kidney transplantation, Stokkel et al demonstrated a significant improvement in gated-SPECT-measured LVEF (from 52 ± 11% to 63 ± 10%; *P* < .001).[70] Among 52 recipients assessed pre- and post-transplant, Iqbal et al detected significant improvements in systolic (from 157 ± 17 to 126 ± 10 mmHg) and diastolic blood pressures (from 97 ± 10 to 85 ± 6 mmHg), as well as in LA diameter (from 39 ± 7 to 34 ± 4 mm), LV mass index (from 275 ± 91 to 159 ± 26 g/m^2), and LV end-diastolic volume index (87 ± 29 to 49 ± 24 mL/m^2) on echocardiogram.[71] Significant improvements in LV diastolic function have been demonstrated following KTx, as assessed by tissue Doppler.[72] Two small retrospective studies even suggest that there may be no association between pretransplant PH and 5-year posttransplant outcome, or at least that candidates with PH can be transplanted with good success with preoperative interventions and some reasonable candidate selection.[73,74]

Coupled with improvements in left heart failure,[68,70,75,76] functional KTx results in improved volume control, which also improves PH caused by group 2 physiology (chronic volume overload). Yigla et al, reported that 4 of 5 patients with PH (PASP >35 mmHg) on hemodialysis had normalized pulmonary pressures following KTx.[33] In another small study of KTx patients with a significant portion (80%) having pretransplant LV dysfunction and about half having PH (48.6%), significant improvements in LV diameters, wall thickness, and PASP were seen within 12 months post engraftment, with PH prevalence reduced to 14.3%.[77] By 1 year post engraftment, echocardiographic findings normalized in 67% of the patients with diastolic dysfunction and 56% with systolic dysfunction. A later study compared PASP measured pre-engraftment 1 hour after dialysis in 124 patients with PASP following KTx.[78] In that study, pre-engraftment PH was present in 28.2%, with 14% having moderate or severe elevations in PASP (>45-<55 and ≥55 mm Hg, respectively). There was

Table 4. Summary of Recent Studies Describing the Frequency, Correlates, and Outcomes of Pulmonary Hypertension Among Kidney Transplant Recipients. Reproduced from Lentine et al[109]

Reference, Year	Design and Participants	Evaluation Modality/ Definition of PH	PH Prevalence	Factors Associated with PH	Associations of PH with Clinical Events
Wang et al, 2019[66]	• Retrospective • Single center in USA, 2008-2015 • 192 KTx recipients with pre-KTx TTE and documented PASP	• TTE • PASP >37 mmHg	• Pre-KTx: 26% (51/192)	• Decreased LVEF <50% was more common among those with elevated vs. normal PASP (13.7% vs. 3.6%, *P* = .01)	• 4-year mortality did not differ significantly by pretransplant PASP • In multivariate logistic regression, each 1 mmHg increase in PASP was associated with 8.940 mL/min decrease in eGFR (95% CI −15.8- to −2.1, *P* = .01)
Goyal et al, 2018[113]	• Retrospective, single-center study in India • 170 KTx recipients	• TTE • PASP ≥35 mmHg	• Pre-KTx: PH 46.4% (79/170) • Mean age 36 yo • Mean PASP 42.3 (± 9.6) mmHg • PASP range: 35-70 mmHg	• No differences between PH and non-PH cohorts	• Delayed graft functioning (need for HD in first postoperative week) 8.86% vs. 1.1%, *P* = .026 in PH vs. non-PH • Perioperative hypotension (20% decrease from baseline) 26.58% vs. 9.89% (*P* = .004)
Jarmi et al, 2018[67]	• Retrospective • Single center in USA, 2005-2009 • 363 KTx recipients with PASP measurement by RHC at anesthesia induction (where Swan Ganz used by routine protocol)	• Swan Ganz RHC, at time of KTx anesthesia induction • PASP >35 mmHg	• Immediately Pre-KTx: 36.6% (133/363)	• Median pre-KTx dialysis duration was longer in those with PASP >35 mmHg vs. <35 mmHg (29 vs. 22 months, P = .004)	• Pre-KTx PH associated with higher mortality risk over up to 8 years (aHR 1.98, 95% CI, 1.04-3.74, *P* = .4), after adjustment for comorbidities including CAD and heart failure • Pre-KTx PH has borderline *unadjusted* association with graft failure risk (*P* = .05); adjusted results not reported
Lai et al, 2015[65]	• Retrospective, longitudinal • Single center in USA, 2006-2010 • 638 KTx recipients with pre-KTx TTE	• TTE • PASP >35 mmHg	• Pre-KTx: 32.8% (209/638)	• Not assessed	• Pre-KTx PH associated with lower 5 years graft survival: 54.6% vs. 76.0%, *P* < .05 • Association significant after adjustment (unspecified covariates, aHR 1.30, 95% CI, 1.11-1.51)
Alhamad et al, 2014[114]	• Retrospective, cross-sectional • Single center in Saudi Arabia, 2008-2010 • 44 KTx recipients • 55 HD and 17 PD patient controls	• TTE • PASP ≥40 mmHg	• KTx recipients: 18.2% (8/44) • HD controls: 21.8% (12/55) • PD controls: 23.5% (4/17)	• Among KTx recipients with vs. without PH, no differences in: demographics, PFT results, 6-minute walk test, or lab values (e.g., hemoglobin, PTH, calcium, phosphorous, creatinine, albumin levels)	• 1/8 KTx recipients with PH died during the study period (unspecified follow-up duration)
Reddy et al, 2013[78]	• Retrospective, longitudinal • Single center in India, 2001-2007 • 124 KTx recipients with TTE performed before and after KTx (subset of 425 recipients)	• TTE • PASP >35 mmHg • Mild: >35 to <45 • Moderate: >45 to <55 • Severe >60	• Pre-KTx: 28.2%, including 13.7% mild, 11.3% moderate, 3.2% severe • Post-KTx, same cohort: 16.1%	• Changes in PH post- vs. pre-KTx: • Pre-KTx Mild PH: 65% normal post-KTX • Pre-KTx Moderate PH: 57.5% normal post-KTx • Pre-KTX severe PH: 25% normal post-KTx	• No additional follow-up data

(*Continued*)

Table 4. Summary of Recent Studies Describing the Frequency, Correlates, and Outcomes of Pulmonary Hypertension Among Kidney Transplant Recipients. Reproduced from Lentine et al[109] (*Continued*)

Reference, Year	Design and Participants	Evaluation Modality/ Definition of PH	PH Prevalence	Factors Associated with PH	Associations of PH with Clinical Events
Mehra et al, 2013[94]	• Retrospective, longitudinal • Single center in USA, 2007-2011 • 206 KTx recipients with pre-KTx TTE records	• TTE • RVSP >35 mmHg or tricuspid regurgitation jet >3 m/s	• Pre-KTx: 19% (39/206)		• Pre-KTx PH associated with: • Significant worsening of SCr from 1 to 12 months post-KTx (mean 1.9-3.2 vs. 1.9-1.97 mg/dL, *P* = .04)
Casas-Aparicio et al, 2010[77]	• Retrospective, longitudinal • Single center in Mexico, 2000-2007 • 35 KTx recipients with TTE before and 1 years after transplant • Pre-KTx kidney replacement: 7% HD, 77% PD, 3% none	• TTE, scheduled after dialysis • PASP ≥ 40 mmHg	• Pre-KTx: 48.6% (17/35) • Post-KTx, same cohort: 14.3% (5/35)	• KTx was associated with a reduced in PH (*P* = .01), and in average PASP (36 ± 15 vs. 52 ± 19 mmHg, *P* = .03)	• No additional follow-up data
Zlotnick et al, 2010[63]	• Retrospective, cross-sectional and longitudinal • Single center in USA, 2003-2006 • 55 KTx recipients with estimated PASP before transplant (subset of 143 candidates, including 94 with TTE report)	• TTE • PASP ≥35 mmHg	• Pre-KTx: 38% (21/55) with available PASP	• Among those with vs. without PH: • HD vs. PD/no dialysis more common (86% vs. 50%, *P* = .01) • No significant (*P* < .05) differences in demographics, HTN, CAD, COPD, or LVEF • Trends towards more common LVEF <40% (14% vs. 3%, *P* = .15), presence of AVF (76% vs. 50%, *P* = .09), and less common predialysis state (14% vs. 38%, *P* = .07)	• Early graft dysfunction (DGF or slow function) more common in deceased donor KTx recipients with vs. without PH: 56% vs. 11.7%, *P* = .01 (no study events among live donor KTx recipients) • Association significant after adjustment for recipient, donor and transplant factors (aOR 15.0, *P* = .03)
Bozbas et al, 2009[44]	• Retrospective, cross-sectional • Single center in Türkiye (study period not reported • 500 KTx recipients • Pre-KTx evaluation TTE, performed routinely, was studied • Pre-KTx kidney replacement: 86.4% HD, 13.6% PD	• TTE • PASP ≥ 30 mmHg	• Pre-KTx: PH in 17% (82/500)	• Among those with vs. without PH: • HD vs. PD more common (18.8% vs. 5.9%, *P* = .008) • Longer preassessment dialysis duration (50.8 vs. 38.5 months, *P* = .008) • No differences in: demographics, COPD, smoking, diabetes, HTN, or lab values (e.g., hemoglobin, lipid, creatinine, glucose levels)	• No follow-up data

(*Continued*)

Table 4. Summary of Recent Studies Describing the Frequency, Correlates, and Outcomes of Pulmonary Hypertension Among Kidney Transplant Recipients. Reproduced from Lentine et al[109] (*Continued*)

Reference, Year	Design and Participants	Evaluation Modality/ Definition of PH	PH Prevalence	Factors Associated with PH	Associations of PH with Clinical Events
Issa et al, 2008[62]	• Retrospective, cross-sectional and longitudinal • Single center in USA, 2004-2007 • 215 KTx recipients with measured pre-KTx RVSP (among 472 KTx recipients, 324 underwent TTE based on high-risk for IHD; in 109, RVSP was not reported or could not be measured)	• TTE • PASP ≥35 mmHg	• Pre-KTx: PH 32% (69/215) with measured PASP • RVSP 35-50 mmHg: 22% (47/215) • RVSP >50 mmHg: 10% (22/215)	• Graded association of more common PH with longer preassessment dialysis duration: 25%, 25%, 38%, and 58% not on dialysis, on dialysis <1 years, 1-2 years, and >2 years, respectively • No associations of PH with: demographics, BMI, diabetes, LVEF, or smoking	• Over mean 22.8 months follow-up, pre-KTx RVSP >50 mmHg associated with nearly 4 times post-KTx mortality compared to RVSP <50 (adjusted HR 3.75, $P = .025$) • Association persisted with individual adjusted for age, hypoalbuminemia and DGF, but not EF • No association with graft survival

AVF, arteriovenous fistula; CAD, coronary artery disease; CO, cardiac output; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HD, hemodialysis; HTN, hypertension; IHD, intermittent hemodialysis; KTx, kidney transplant; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PD, peritoneal dialysis; PFT, pulmonary function testing; PH, pulmonary hypertension; PTH, parathyroid hormone; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricle; RVD, right ventricular dysfunction; RVSP, right ventricular systolic pressure; TTE, transthoracic echocardiogram; WHO, World Health Organization.

a significant reduction in PASP in most patients with PH at baseline following engraftment, with 65% of those with mild PH improving to normal PASP, while most of the patients with moderate or severe PH showing improved pulmonary pressures.

In an analysis of Medicare beneficiaries, post-KTx PH diagnosis was associated with >2.5-fold increased risk of mortality (aHR 2.84) and all-cause graft failure (aHR 2.64) within 3 years of KTx.[1] Outcome associations of newly diagnosed posttransplant PH were similar. Interestingly, KTx was associated with an increased likelihood of PH diagnosis within 6 months of transplant, although observation bias is certainly possible.[1] In this study, short-term risks included a 70% increase for patients aged <45 years (aHR 1.70) and a 3-fold risk for those aged >60 years (aHR 3.11) (Figure 4A). However, KTx was associated with a 47% reduction in the likelihood of PH after 6 months for those younger than age 45 years (aHR 0.53) and a 25% reduction in those aged 45-60 years (aHR 0.75), when

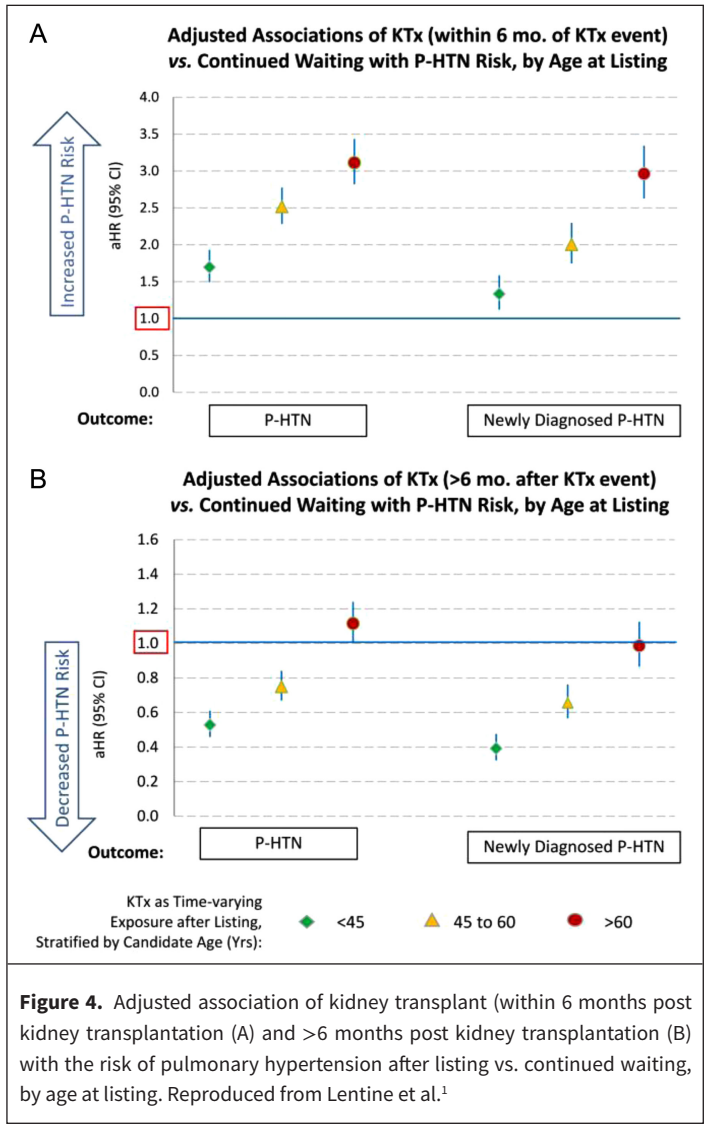

Figure 4. Adjusted association of kidney transplant (within 6 months post kidney transplantation (A) and >6 months post kidney transplantation (B) with the risk of pulmonary hypertension after listing vs. continued waiting, by age at listing. Reproduced from Lentine et al.[1]

compared to those on the waitlist. There was no a significant impact for older KTx candidates (Figure 4B).[1] Also using USRDS data, another group found similar inferior outcomes but found a 46% reduction in mortality for those listed patients who received a transplant compared to those who remained on the waitlist (HR 0.54).[79]

The available data on the impact of PH on KTx have several limitations. Many of these studies are single-center retrospective studies with the typical smaller sample sizes and limited follow-up duration; observational designs using administrative data; incomplete reporting of other clinical characteristics that have a continuous rather than binary presentation (e.g., coronary artery disease severity); and frequent reliance on somewhat inaccurate echocardiography findings to define PH. However, a recent systematic review and meta-analysis generally supports many of these findings.[80] However, the overall literature support that the identification of PH by echocardiography as a marker for adverse outcomes following kidney transplantation. However, this outcome difference should not inherently exclude transplantation but rather be part of the assessment both as a potential modifiable and potential unmodifiable risk, as ESKD patients with PH do not do well on dialysis either. Multidisciplinary assessment with the integration of pulmonary hypertension expertise can result in better classification of the underlying cause of PH in transplant recipients and may guide management that can improve outcomes. Given the limitations of literature and the usual small sample sizes, a prospective study carefully assessing the impact of KTx and residual AVF function on cardiac hemodynamics and pulmonary hemodynamics is needed. In the interim, the relative risks of graft dysfunction and mortality after transplant among patients with PH when compared to unaffected recipients should be contextualized with the high mortality faced by patients with PH and ESKD who remain waitlisted or on dialysis, as successful KTx with savvy PH management likely offers superior outcomes through reduction in volume overload, reversal of hemodynamic abnormalities, anemia reversal, bone metabolism, and uremia clearance. Intriguingly, there is some recent animal model evidence suggesting beneficial

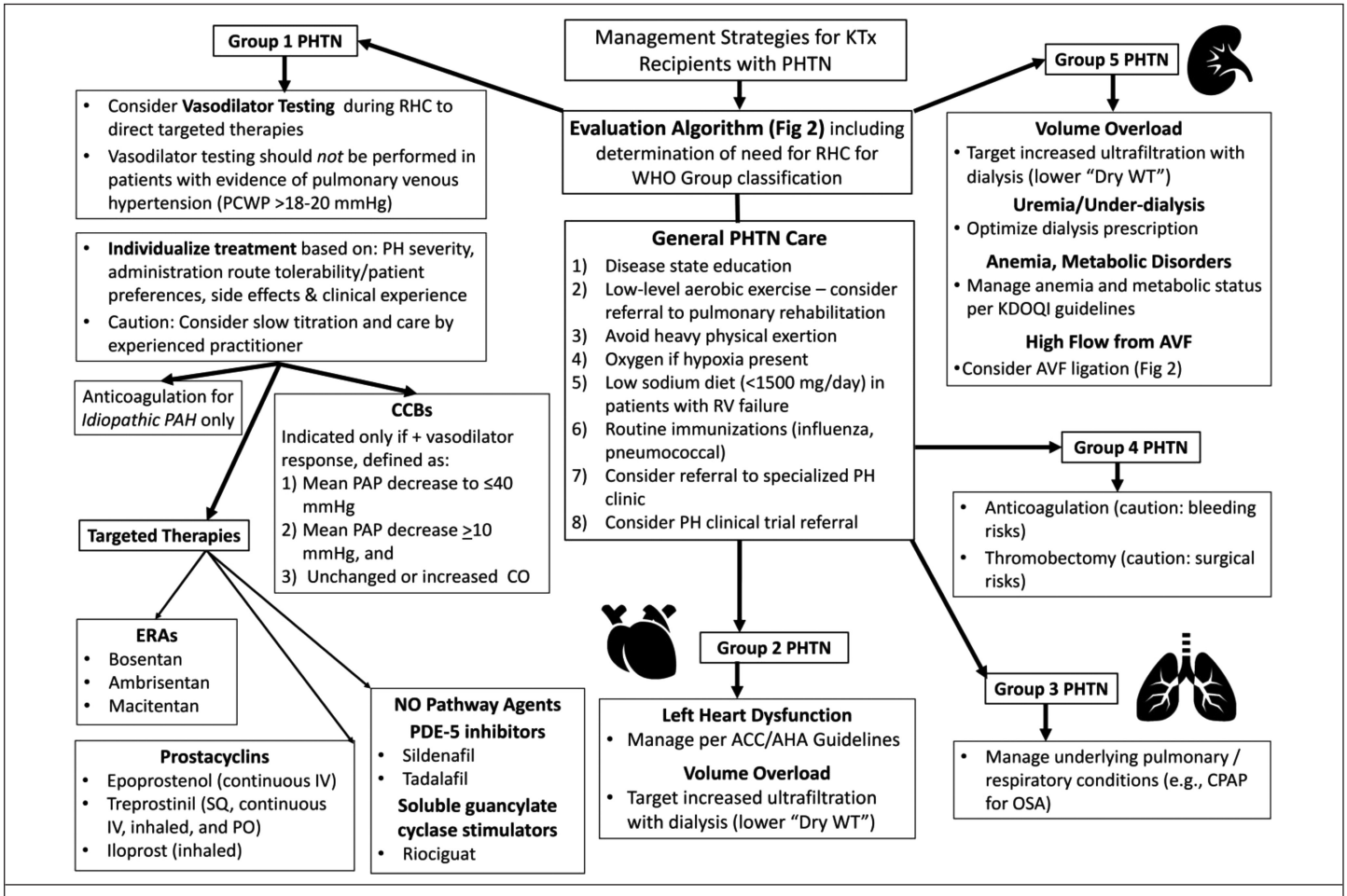

Figure 5. Current management strategies for kidney transplant recipients with pulmonary hypertension, including recommendations for general care for all affected patients and treatments specific to World Health Organization (WHO) diagnosis group. Reproduced from Lentine et al.[109] AVF, arteriovenous fistula; CO, cardiac output; CPAP, continuous positive airway pressure; ERAs, endothelin receptor antagonists; NO, nitric oxide; OSA, obstructive sleep apnea; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PDE-5, phosphodiesterase type 5; PH, pulmonary hypertension; RHC, right heart catheterization.

effects of calcineurin inhibitors on PH,[81] which warrants further investigation in the human clinical setting.

POSTTRANSPLANT MANAGEMENT

Management strategies for kidney transplant recipients with PH are summarized in Figure 5, including general recommendations and treatments specific to the WHO diagnosis group. It is worthy of comment that the efficacy of treatment for PH in patients with ESKD prior to or post-KTx are largely unproven; ESKD patients are complex and are often excluded from clinical trials, including PH trials.

The most important management consideration if that the optimal therapeutic approach depends on which group of PH (groups 1-5) the patient is diagnosed with. The importance of defining the underlying cause of PH before attempting targeted therapy cannot be overemphasized. Group 1 patients are unique in that there are focused therapies that may improve outcomes in this group. These same therapies could be detrimental to other PH groups.

Group 1 Pulmonary Hypertension (Pulmonary Arterial Hypertension)

For patients with group 1 PH (PAH), management needs to be individualized by taking into account disease severity, medication administration route tolerance, patient preferences, side effect profile, and local clinician experiences and expertise. Patients with PAH and kidney dysfunction should be followed either by a PH expert or at a PH center to both carefully diagnose as well as manage these therapies. Experience with these medication classes among the population with kidney disease is limited, and careful dosing, slow titration, and close follow-up are imperative.

Group 2 Through Group 5

Many patients with kidney disease have group 2 PH, and pulmonary vasodilation against a noncompliant LV may result in worsened volume overload and pulmonary edema,[82] and these patients should not be treated with PAH-focused therapy. Pulmonary vasodilator treatment may also exacerbate the ventilation–perfusion mismatch in patients with group 3 PH.[83,84]

Oxygen is the cornerstone of therapy for group 3 PH and should be administered to any patient with hypoxic PH. Obstructive sleep apnea should be evaluated and treated—likely with CPAP. The impact of weight loss therapies, including bariatric surgery or newer weight loss medications, on PH and other forms of cardiovascular disease in obese OSA patients in the context of ESKD is not well studied and is speculative at this point.[85-87]

Anticoagulation is usually indicated for CTEPH (group 4 PH), but carries elevated bleeding risks for CKD patients.[88] Pulmonary endarterectomy and balloon pulmonary angioplasty (BPA) are additional options for patients with CTEPH. During a pulmonary endarterectomy, large, proximal thromboembolic material may be removed, which may improve or resolve PH. Kidney failure, however, may increase surgical risks and may be a contraindication in some CTEPH centers.[89]

For group 5 multifactorial PH, it is unclear what therapies for conditions such as hyperparathyroidism and anemia accomplish. While some experimental models support the protective effect of erythrocyte-stimulating agents against PH,[90] others suggest more of an exacerbating effect.[91,92] In a small human study, intravenous erythropoietin increased PVR for both those with and those without PH.[92] The approach to functional vascular AVF is evolving (Table 5). Current literature suggests support for AVF flow restriction or ligation for a patient with PH with high CO hemodynamic profile and high AVF flow (>1.5-2.0 L/min and AVF flow >30% CO), as this hemodynamic profile is associated with an increased risk of high output heart failure.[48,52,93,94] Clinically, many consider symptomatology reflective of high output failure as an indication for AVF flow reduction or banding, although outcomes data on such interventions are somewhat limited.[53,54] The role of AVF flow reduction through image guided banding and other newer techniques in hemodialysis patients with a documented high output state and response to an AVF occlusion study is a topic of active study.

Even with PH literature limitations, we suggest that volume status management is of utmost importance for the CKD population. LV systolic dysfunction and group 2 PH result from chronic pressure and volume overload.[95,96] Chronic volume overload creates a vicious cycle with OSA, resistant systemic hypertension, increased central pressure, and increased PAP, all of which contribute to PH. Additionally, the rostral overnight fluid shift with decumbency is associated with an increased risk of OSA for patients with CKD,[97] consistent with the known increased prevalence of OSA in CKD patients.[98-100] This OSA results in nocturnal hypoxia, which further stimulates excess sympathetic nervous system activity, hyperaldosteronism, systemic hypertension, and PH.[101-103] Care must be taken to differentiate between high blood pressure requiring antihypertensive medications and more aggressive volume management.[104] Successful KTx usually results in better volume control, especially with living donor kidneys or other rapidly functioning allografts. Functioning kidney transplants are more responsive to diuretics and mineralocorticoid receptor antagonists, further facilitating volume and consequent blood pressure reduction, with diuretics sometimes necessary to control resistant hypertension.[105-107]

SUMMARY AND CONCLUSIONS

The following strategies are recommended in KTx recipients in whom PH is a concern:

- If the patient had significant PH prior to kidney transplant (PASP >50 mmHg), it would be reasonable to get a follow-up echo at 3 months post transplant to reassess pulmonary pressures.

Table 5. Summary on Literature on Impact of AVF Flow Reduction/Ligation on PH and Related Outcomes

Reference, Year	Design and Participants	Evaluation Modality/ Definition of PH	Indication for/Timing of AVF Flow Reduction/Ligation	Impact of AVF Flow Ligation/ Ligation on PH Measures	Other Outcomes/Clinical Events
Masson et al, 2023[59]	• Prospective, single-center, single armed observational study of transplant patients undergoing AVF ligation 1 year post transplant • N = 43	• Transthoracic echocardiogram • mPAP ≥25 mmHg	• Kidney transplant patients with GFR >45 mL/min/1.73 m^2 at 1 year post transplant or signs or symptoms of heart failure	• Some improvement of mPAP	• DPB elevation • Decreased serum NT-proBNP • Reduction of LV/LA dimensions • Stable eGFR slope
Hicks et al, 2019[61]	• Retrospective observational study of USRDS Data • All adult patients on HD prior to KTx with pretransplant AVF or AVG who underwent post-KTx ligation of the access • Of 16,845, 779 (4.6%) underwent such ligation	• PH not directly measured	• Study sought to explore these practice patterns, but specific indications only inferentially available in the dataset	• PH not specifically addressed	• Significant transplant center practice variation • Patients who underwent ligation more likely to have steal syndrome or AV access infection • No reduction in all-cause mortality following ligation or 3-year allograft failure
Rao et al, 2019[58]	• Prospective randomized clinical trial of 64 patients status-post KT >12 months prior with stable graft function • Intervention: AVF surgical ligation • Primary outcome: Change in LV mass at 6 months on cardiac MRI • Study size: 33 ligations, 31 controls • 54 completed trial (27 in each group)	• PH was not assessed or reported	• Successful KTx >12 months prior with stable kidney function for >6 months prior to enrollment • No clinical symptoms were reported	• No measures of change in PH except for pulmonary artery velocity using cardiac MRI (secondary outcome measure) • Mean LV mass decrease of 22.1 g in ligation group vs. 1.2 g increase in control. • $P < .001$	• Decrease in LV EDV: from 161.5 to 133.5 mL • Decrease in LV end-systolic volume: from 56.3 to 45.0 mL • Decrease in CO: from 6.38 to 4.8 L/min • Decrease in LA volume: from 93.5 to 75.2 mL • Decrease in NT-proBNP: from 411 to 166 ng/L • No change in EF, pulmonary artery velocity • No significant complications of ligations
Schier et al, 2016[57]	• Retrospective, single-center study • N = 113 subjects post KT with AVF and stable kidney function • 29 of 113 clinically referred for ligation or banding (intervention group) • 16 with high-output heart failure • 5 with AVF aneurysm • 6 due to high-access flows • 2 for esthetic purposes • Mean flow 2197 mL/min in intervention group vs. 851 mL/min nonintervention group.	• Modality: transthoracic echocardiogram and clinical assessment for right heart failure	• Indication: clinical evidence of right heart failure or development of pulmonary hypertension on echocardiography	• PH measures post intervention not assessed	• All ligated patients reported subjective improvement in dyspnea • In 7 patients with NT-proBNP measured pre/post-ligation, NT-proBNP decreased from 3709.4 to 1290.9 ng/L (median; P = NS)

(*Continued*)

Table 5. Summary on Literature on Impact of AVF Flow Reduction/Ligation on PH and Related Outcomes (*Continued*)

Reference, Year	Design and Participants	Evaluation Modality/ Definition of PH	Indication for/Timing of AVF Flow Reduction/Ligation	Impact of AVF Flow Ligation/ Ligation on PH Measures	Other Outcomes/Clinical Events
Gkotsis et al, 2013[56]	• Retrospective, single-center study • Referred population of 12 successful KTx with heart failure or other symptoms felt secondary to fistula presence	• PH not defined	• Indication: heart failure post KT with high-flow AVF • Duration following KT not reported • Duration of AVF prior to ligation: 24-86 months • Flow reduced via suture banding to goal of 4 mm diameter, with targeted post-banding flow 500-800 mL/min	• Impact of banding on PH was not assessed	• Pulse rate declined from 90 to 72/min during pre-banding occlusion • AVF flow decreased from 2280 mL/min to 598 mL/min after banding • Heart failure symptoms/signs resolved in all patients • All AVF remained patent during follow-up period of 12 months (mean)

AVF, arteriovenous fistula; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; CO, cardiac output; EDV, end-diastolic volume; GFR, glomerular filtration rate; HD, hemodialysis; KTx, kidney transplantation; LA, left atrium; LV, left ventricle; MRI, magnetic resonance imaging; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension.

- There is no standard for surveillance, but if the patient has a history of elevated pulmonary pressures prior to kidney transplant (PASP >50 mmHg), then a repeat echocardiogram every 1-2 years seems reasonable. If the patient reports a change in symptoms, such as increased dyspnea on exertion, then this should be sooner.
- If the estimated PASP remains >50 mmHg and/or there is new evidence of right heart strain (abnormal RV size/function), consider right heart catheterization for a full hemodynamic profile (consider referral to a pulmonary hypertension specialist).
- If an AVF is present, consider ultrasound of the AVF to assess for high flow rates (>1.5 L/min).
- If the RHC demonstrates high CO (>7.5 L/min) that decreases with AVF occlusion, the patient has an AVF with high flow, and the patient has symptoms of CHF such as significant dyspnea on exertion, then consider ligation or banding of the AVF.
- There is some cardiac imaging data to suggest a benefit to AVF occlusion even in some asymptomatic posttransplant patients (improvements in LV mass, LV size, LA volume, and NT-proBNP), but the main benefit has been demonstrated to improve clinical symptoms. Therefore, there is no formal recommendation for AVF ligation or flow-restricting intervention in asymptomatic individuals.
- Guidelines consistently recommend evaluation, monitoring, and management of PH by a PH center or expert. For successful KTx, multidisciplinary management by the KTx team in conjunction with a PH center or expert is essential.

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