Hemodynamic Evaluation of Pulmonary Hypertension in Chronic Kidney Disease

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Chronic kidney disease (CKD) is a common condition and its prevalence is increasing. Likewise, the number of patients reaching end-stage renal disease (ESRD) continues to rise. In the United States in 2010, there were 413,275 patients on dialysis and 179,361 patients with a functioning renal transplant, bringing the rate of prevalent ESRD cases to 1752 per million population. Pulmonary hypertension (PH) is a commonly encountered comorbidity of patients with CKD and those who have progressed to ESRD. Although the true prevalence of PH in these populations is unknown, several small, single-center analyses using varied cutoffs for echocardiographically estimated pulmonary pressures have reported estimates as high as 56%.

The factors that likely contribute to the development of PH in ESRD are numerous and have been well described in a recent review by Kawar et al. These include persistent passive congestion from volume overload, decreased left ventricular compliance and/or systolic dysfunction, endothelial dysfunction, anemia, metabolic and hormonal derangements leading to pulmonary vasoconstriction, and the long-term effects of arteriovenous (AV) fistulas. While the latter’s contribution to the development of PH remains controversial, it is clear that in the right scenario, an AV shunt can cause high output heart failure. Creation of a systemic AV shunt leads to an increased cardiac output (CO) by several mechanisms. First, it decreases total peripheral resistance, leading to increased venous return to the right heart. This increase in preload leads to enhanced stroke volume via the Starling mechanism. Also, the reduced peripheral resistance activates sympathetic cardiovascular reflexes, increasing both heart rate and contractility. These combined mechanisms contribute to CO augmentation and increase the work done by both ventricles. The severity appears related to size of the shunt. Lastly, AV shunts may also increase total blood volume, which further increases preload. Patients with already stiff ventricles may have difficulty accommodating the increased preload, and the increased workload may lead to more maladaptive hypertrophy over time. More recently, Paneni and colleagues compared echo parameters of right ventricular (RV) systolic and diastolic function in controls, patients undergoing peritoneal dialysis (PD), and those undergoing hemodialysis via radial or brachial AV fistulas. When adjusted for confounding factors, patients with an AV fistula had an increased risk of RV dysfunction when compared to the PD group (OR 6.3; P<0.001).

Despite advances in noninvasive imaging, full hemodynamic characterization of PH requires invasively determined hemodynamics. Pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) requires normal left sided filling pressures (pulmonary capillary wedge pressure [PCWP] ≤15 mm Hg) in addition to the elevated mean pulmonary arterial pressure (MPAP). Group 1 PAH is rare, with an overall prevalence estimated at 6.6 cases per million. In keeping, Group 1 PAH is also rare in patients with ESRD. WHO Group 2 PH, ie, PH secondary to left heart disease, is diagnosed when the PCWP is >15 mm Hg. It is the most common cause of PH worldwide, and is also the most common cause of PH in the ESRD population. WHO Group 2 PH can be further subcategorized. “Passive” PH is usually defined as PCWP >15 mm Hg but a normal transpulmonary gradient (TPG) <12-15 mm Hg and/or pulmonary vascular resistance (PVR) <3 Wood units. Those with an elevated TPG >12-15 mm Hg and/or PVR >3 Wood units have been referred to as “mixed,” “reactive,” or “out of proportion” PH in the literature as there is no consensus terminology.

The aim of this review is to provide an overview of the hemodynamic assessment of patients with PH and CKD, with a particular focus on renal transplantation. We will consider 3 cases to illustrate these points, with the catheterization data serving as the invasive hemodynamic follow-up information for the same subjects discussed in the companion article by Dr Raina. As such, the hemodynamic information should dovetail with the corresponding echo-Doppler data discussed in the noninvasive article.

CASE 1
Initial review of the patient’s hemodynamic report (Table 1) suggests a diagnosis of heart failure with preserved ejection fraction (HFpEF) with mixed PH. Even without the hemodynamic...
assessment, it should be noted that the patient’s clinical characteristics suggest pulmonary venous hypertension (PVH) rather than WHO Group 1 PAH. Features of the metabolic syndrome, as seen in this patient, are more commonly associated with PVH (ie, HFpEF) as is older age and associated renal insufficiency.

In this case, the PCWP value is reported to be mildly elevated, but notice the discrepancy between the PCWP and the more markedly elevated left ventricular end diastolic pressure (LVEDP), obtained during simultaneous left heart catheterization. Discrepancy between the PCWP and the LVEDP has been reported previously; however, more recently it has been suggested that a large portion of this difference may be explained by operators reporting the software-generated or digitized “mean” PCWP values across the respiratory cycle rather than that measured manually at end expiration. This is particularly important in situations where swings in pleural pressure are more exaggerated, as is the case in the obese and in patients with significant lung disease (Figure 1). Although not present in this case, incomplete balloon occlusion of the pulmonary artery can lead to significant overestimation of the PCWP—ie, pulmonary artery pressures blend into the PCWP waveform (Figure 2)—leading to hemodynamic misclassification of PH. When there is a question as to the accuracy of the PCWP, proceduralists should confirm the PCWP position by checking the oxygen saturation to verify that the sample is consistent with oxygenated, pulmonary venous blood (PCWP saturation).

The patient in this case has many symptoms of left sided heart failure.

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<th>Table 1. Initial Hemodynamics</th>
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<td>Heart rate (bpm)</td>
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<td>DPAP-PCWP gradient (mm Hg)</td>
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<td>Cardiac output (L/min)</td>
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<td>Cardiac index (L/min/m2)</td>
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<td>PVR (Wood units)</td>
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<td>SVR (Wood units)</td>
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*Note discrepancy between PCWP and LVEDP. This difference suggests an error in the hemodynamic recordings (see text). Transpulmonary gradient, diastolic gradient, and pulmonary vascular resistance values using the LVEDP are shown in parentheses.

Figure 1. Marked respiratory variation is seen on both tracings: pulmonary capillary wedge pressure (PCWP, upper panel) and pulmonary artery pressure (PAP, lower panel). Digitized mean PCWP across the respiratory cycle underestimates the true wedge pressure at end expiration. Using the underestimated PCWP in this case leads to an overestimation of PVR. The correct diagnosis is WHO Group 2 pulmonary hypertension.
(orthopnea, paroxysmal nocturnal dyspnea [PND], pleural effusions), suggesting the mildly elevated PCWP may be inaccurate. Moreover, the echo-Doppler information presented in the companion article by Dr Raina strongly suggests markedly elevated left heart filling pressures and a PVR that is normal. By combining the information from echo-Doppler imaging with the hemodynamics, the clinician has a heightened sense of what the hemodynamics “should” be, thus making it more likely that pitfalls in the hemodynamic assessment (as seen here) are easily identified and avoided. Using the LVEDP instead of PCWP in the PVR calculation yields a value <3 Wood units, supporting the notion that a large portion of the PH is due to left heart failure, passive congestion, and normal to high CO. Although it has been demonstrated that an elevated TPG (and “mixed” PH) portends a worse prognosis in heart failure,\textsuperscript{22} it is important to remember that factors other than pulmonary vascular remodeling affect this parameter. Elevations in left atrial pressure directly affect the TPG. As pressures in the left atrium increase, this pressure is passively transmitted back to the pulmonary vasculature, resulting in elevation of the diastolic pulmonary artery pressure (DPAP). However, this increased venous pressure also leads to more pulmonary vascular stiffness (or lower vascular compliance) than one would predict based on the PVR alone.\textsuperscript{23} The lower compliance leads to enhanced pulmonary arterial wave reflections, which raise the systolic pulmonary artery pressure (SPAP) and MPAP, and in turn the TPG. PVR is also raised by these effects, given TPG is in the numerator of its calculation. Both parameters may also be affected by CO as elegantly described by Naeije and colleagues.\textsuperscript{24} Importantly, the enhanced pulsatile loading that serves to amplify the SPAP and MPAP does not affect the DPAP. Hence, emerging evidence suggests that the DPAP to PCWP gradient may be a better indicator of pulmonary vascular remodeling\textsuperscript{24,25} and how “proportionate” any degree of MPAP elevation is relative to left atrial pressure.\textsuperscript{26–29}

In this patient, the correct measure of left heart filling pressure was 26 mm Hg (in this case, from LVEDP), and thus, correctly calculated PVR was only 2.3 Wood units. Further inspection of the hemodynamics reveals a relatively low ratio of right to left heart filling pressure (right atrial pressure [RAP]/LVEDP, 0.54) and PVR/systemic vascular resistance (SVR) ratio (0.17), further supporting a relatively “pure” case of PVH, or PH related to left heart congestion.

In HFpEF patients as shown in this case, renal transplantation should allow
for better volume regulation and systemic blood pressure control, which are the mainstays of current therapy. One small, retrospective study has even suggested improvements in both systolic and diastolic function after renal transplantation along with improvements in parameters of left ventricular remodeling and reduction in echo-estimated pulmonary pressures.30

This patient’s volume status was optimized and ultimately underwent renal transplantation. Post-transplant the patient did quite well with robust improvements in exercise tolerance and had no diuretic requirement.

CASE 2
The patient’s hemodynamics (Table 1) are consistent with high output heart failure leading to left heart congestion and passive PH, as suggested by the imaging findings discussed in the companion article by Dr Raina. The right heart catheterization (RHC) data further reveal that the PVR is normal, as are the RAP/pulmonary artery wedge pressure (PAWP) and PVR/SVR ratio. The most obvious culprit is his persistent functioning left upper extremity AV fistula, which was not taken down after transplantation. An intracardiac oximetry run was negative for an intracardiac shunt, although the oxygen saturation in the superior vena cava (SVC) was higher than his pulmonary artery saturation. The “step-down” in saturation from the SVC to pulmonary artery is supportive of a shunt in the upper extremity, as typically the SVC saturation is lower due to cerebral oxygen extraction. Repeating hemodynamics during compression of the fistula is often helpful in determining the contribution to overall output.8,9 Although some have argued that a shunt output to CO ratio of more than 30% should raise concern, it is likely that no “set” amount of flow through an AV fistula clearly defines a range that is pathologic.8 Instead, the hemodynamic and clinical significance of any given shunt relates to the interaction between the size of the shunt and the degree to which the heart can accommodate the extra venous return. A patient with severe hypertensive heart disease and diastolic dysfunction may be highly intolerant to the excess flow provided via an AV fistula, whereas a patient without structural heart disease may accommodate a very large shunt without untoward clinical or hemodynamic effects. In this case, 1 minute of manual fistula occlusion led to a 2-liter reduction in the CO, and thus 2 liters of shunt flow at rest (not shown in Table 1). Taking all factors of this case into consideration, the patient was referred for surgical ligation of the AV fistula.

Following closure of the AV fistula, the patient’s symptoms resolved. Repeat RHC revealed essentially normal hemodynamics with a right atrium 4 mm Hg, MPAP 20 mm Hg, PCWP 11 mm Hg, and CO 5.9 L/min (index 2.8 L/min/m²). Even with the open fistula, his CO is in the “normal” range, consistent with restricted pulmonary blood flow via afterload-dependent RV dysfunction. A much larger proportion of this patient’s PH is arising from pulmonary vascular disease than was observed in the patients highlighted in cases 1 and 2. The patient was lost to follow-up and returned a year later for a repeat evaluation (Table 2). There has been an interval worsening of hemodynamics. CO has fallen along with an increase in pulmonary pressures. The PVR/SVR ratio is close to 0.5, an indication of more severe pulmonary vascular disease. RAP and PCWP are both elevated and almost equal, with a ratio near 1, a finding associated with higher PVR, RV dysfunction, and worse outcomes in heart failure.31 Occlusion of the AV fistula lowered CO (Table 2) as expected, but right and left heart congestion did not improve, nor did the pulmonary pressures. The PVR actually increased, which reflects a flow-related derecruitment of the pulmonary circulation. These hemodynamic findings were supported by repeat echocardiogram showing more marked RV dilation and lower tricuspid annular plane systolic excursion (TAPSE). Given the high-risk features of this case, he was not deemed a candidate for renal transplantation. Although the benefits of such therapy have not been evaluated systematically in large randomized trials, phosphodiesterase 5 inhibitor treatment might be beneficial in this more well defined HFrEF-PH phenotype and may

Table 2. Case 3 Repeat Hemodynamics

<table>
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<tr>
<th>Case 3</th>
<th>Baseline</th>
<th>AV fistula compression</th>
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<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Pulmonary pressures – systolic/diastolic (mean) (mm Hg)</td>
<td>119/45 (70)</td>
<td>118/43 (69)</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Transpulmonary gradient (mm Hg)</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>DPAP-PCWP gradient (mm Hg)</td>
<td>17</td>
<td>17</td>
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<tr>
<td>Cardiac output (L/min)</td>
<td>5.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>3.1</td>
<td>2.3</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>7.6</td>
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<tr>
<td>SVR (Wood units)</td>
<td>16.2</td>
<td>17.1</td>
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</tbody>
</table>

Review of the initial hemodynamic data (Table 1) is consistent with HFrEF with mixed PH. These findings are consistent with the patient’s echo-Doppler examination discussed in the companion article by Dr Raina, which showed evidence of both left heart congestion and RV morphologic and Doppler evidence that strongly suggested an increased PVR. His TPG is quite elevated in comparison to the mildly elevated PCWP, as is the DPAP-PCWP gradient. Even with the open fistula, his CO is in the “normal” range, consistent with restricted pulmonary blood flow via afterload-dependent RV dysfunction. A much larger proportion of this patient’s PH is arising from pulmonary vascular disease than was observed in the patients highlighted in cases 1 and 2. The patient was lost to follow-up and returned a year later for a repeat evaluation (Table 2).
be useful to test for reversibility of the PH. Therefore, measures of RV function are a strong predictor of prognosis in left heart failure. Therefore, measures of RV function are a strong predictor of prognosis in left heart failure.41, 42 Moreover, in relation to this case, pharmacologic lowering of the PVR here may lead to an increase in pulmonary blood flow, and in turn lead to worsening left heart congestion. Thus, caution must be exercised in treating pulmonary vascular disease in this setting, particularly recognizing that the AV fistula represents an additional flow reservoir that may be more fully “appreciated” clinically in this patient once the PVR is lowered.

**DISCUSSION**

There are little existing data to guide the clinician when considering the risk associated with renal transplantation in individuals with PH. Although one study has suggested increased post-transplant mortality in patients with a right ventricular systolic pressure (RVSP) >50 mm Hg, the retrospective nature, small number of patients (and deaths), and lack of adjustment for comorbid conditions make it difficult to draw meaningful conclusions from the data. It is curious that despite the fact that some 30%-50% of patients with ESRD have PH, patient and renal allograft survival at most transplant centers is outstanding. This observation suggests that PH itself is not the direct causal link to changes in outcome post renal transplant, or that factors that contribute to PH in ESRD are positively impacted by renal transplantation. It is also important to note that in PAH, pulmonary pressures alone are not robust predictors of survival; rather, prognosis is more closely related to RV dysfunction. RV function is also a strong predictor of prognosis in left heart failure. Therefore, measures of RV function and the integration of RV function with RV afterload (ie, PVR) are likely the best indicators of prognosis in patients being considered for renal transplantation.

**CONCLUSION**

In summary, PH is common in the CKD and ESRD disease populations. Proper hemodynamic assessment along with noninvasive imaging studies should be used in concert when evaluating a PH patient. These techniques can give important insight into the contributions of volume overload, systolic and diastolic dysfunction, and CO to PH as well as the degree of pulmonary vascular disease and RV dysfunction. Elevated pulmonary pressures alone should not necessarily exclude a patient from renal transplantation, especially when RV function is well preserved.

**References**