# Pulmonary Hypertension in Patients With Chronic Kidney Disease: Noninvasive Strategies for Patient Phenotyping and Risk Assessment

Amresh Raina, MD Cardiovascular Institute Allegheny General Hospital Pittsburgh, PA Pulmonary hypertension (PH) is relatively common among patients with chronic kidney disease (CKD). PH is most prevalent in patients undergoing hemodialysis, ranging from 32%-58%, depending on the definition of PH used. The reported incidence of PH is less frequent for patients receiving peritoneal dialysis (12%-42%), and renal transplant recipients are typically the least likely to have PH than either of these dialysis cohorts.<sup>1-6</sup>

An important distinction must be made between PH, which is simply defined as mean pulmonary artery (PA) pressure >25 mm Hg or systolic PA pressure >35 mm Hg vs pulmonary arterial hypertension (PAH), which includes PA occlusive pressure <15 mm Hg, a chronic, progressive condition of pulmonary vascular remodeling, leading to right heart failure and ultimately death if left untreated.<sup>7</sup>

The etiology of PH in CKD patients is typically associated with left heart disease (WHO Group 2), as PAH (WHO Group 1) is rare in this patient population.<sup>4</sup> Moreover, in general, patients with CKD often have a variety of risk factors predisposing them toward pulmonary venous congestion, including systemic hypertension, left ventricular hypertrophy (LVH), ischemic heart disease, and left ventricular (LV) diastolic dysfunction.<sup>8,9</sup> Although pure pulmonary vascular disease (PVD)-based PH (high pulmonary vascular resistance [PVR], noncompliant conduit pulmonary arteries) is relatively rare in end-stage renal disease (ESRD), not infrequently a "mixed" phenotype of PVD with pulmonary venous hypertension is seen in this population.

PH in CKD patients is important to recognize for 3 major reasons. The first is that several studies have indicated that PH is an independent predictor of mortality in CKD patients, especially those receiving renal replacement therapy.<sup>5,10,11</sup>

Second, many CKD patients are evaluated for renal transplantation. In general, significant PH is felt to be a relative contraindication to renal transplantation in patients with CKD. In retrospective studies, PH has been associated with increased early renal allograft dysfunction in these patients,<sup>12</sup> and is also associated with reduced patient survival after renal transplantation.<sup>13</sup> Whether the PH is the direct, causal explanation for these differences in outcome is debatable and somewhat controversial. Nevertheless, in many centers, patients with significant PH are characterized as not being acceptable candidates for renal transplantation.

Perhaps most importantly from a clinical perspective, many patients with CKD present to their treating physicians with dyspnea. PH is often picked up on diagnostic echocardiograms in these patients, and not infrequently PH is invoked as a potential etiology of dyspnea and targeted with pulmonary vasodilating medications. However, the clinical phenotype of PH can be quite varied within this broad categorization, ranging from patients with "simple" diastolic heart failure and secondary PH, to those with severe reactive PVD, right ventricular (RV) dysfunction, and a clinical syndrome resembling PAH. The key physiologic differences in these subsets of patients warrant appropriate discussion and attention not only in terms of identifying patients who are

appropriate candidates for renal transplantation, but also in terms of identifying in which of these patients PH is the major cause of symptoms, vs others for whom PH is a marker of other underlying disease processes.

Though PH in CKD patients warrants a comprehensive evaluation often including invasive hemodynamic assessment, the first step in evaluation of these patients is typically a noninvasive assessment with physical examination and a transthoracic echocardiogram. Careful attention to the physical examination and the echo-Doppler assessment can provide clues to the underlying physiology of PH in these patients and can inform decisions regarding further assessment and treatment strategies, including appropriate maneuvers during invasive hemodynamic assessment.

From the 2-dimensional echocardiogram, LVH and left atrial enlargement suggest the presence of LV diastolic dysfunction and left atrial congestion. However, grade 2 or grade 3 LV diastolic dysfunction based on transmitral Doppler imaging will be present in many CKD patients with PH.<sup>8,9</sup> Therefore, echocardiographic assessment of PH in these patients should also focus carefully on evaluating RV size, structure, and function and evaluating for direct and indirect evidence of elevated PVR with detailed Doppler hemodynamic assessment.<sup>14</sup> This approach to the noninvasive assessment of PH in CKD patients is highlighted in the 3 case studies that reference the associated clinical histories.

Key Words—chronic kidney disease, end-stage renal disease, noninvasive assessment, pulmonary vascular disease, renal transplantation

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Figure 1

#### CASE 1

**Recap:** A 69-year-old man with obesity, hypertension, diabetes, and obstructive sleep apnea with ESRD on hemodialysis being evaluated for renal transplant.

# Physical Examination

On examination, blood pressure is 178/60, pulse is 64 beats per minute, respiratory rate is 12 breaths per minute, and oxygen saturation is 90% on room air. There is a square-wave response in systolic blood pressure to Valsalva maneuver. In general, the patient is a mildly obese, well-appearing man in no apparent distress. Jugular venous pressure is 12 cm of water with normal venous contours. On cardiac examination, S1 and S2 are normal with normal P2 intensity. There is a 2/6 holosystolic murmur at the right upper sternal border. LV apical impulse is normal and nondisplaced. There is no RV heave. Lung auscultation showed diminished breath sounds at the right base up through the mid-right lung field. Abdomen is soft and nondistended. There is mild hepatojugular reflux noted. Extremities revealed 2-3+ bilateral pitting edema to the upper shins.

#### Echocardiogram

A transthoracic echocardiogram is performed and representative parasternal long and short axis views and apical 4 chamber views are shown. In addition, pulsed wave Doppler in the RV outflow tract and transmitral Doppler profiles are shown. LV systolic function is normal at 55%. Mitral regurgitation is noted as moderate (not shown). There is no mitral stenosis.

The parasternal long axis view (panel A) confirms normal LV size with significant LVH. The parasternal short axis views (panels B and C) reveal a notable absence of septal flattening in systole or diastole with a convexed septal profile. The apical 4 chamber view (panel D) illustrates significant left atrial enlargement, while RV size is mildly dilated with RV:LV ratio of roughly 1.0. Notably, the RV apical angle is relatively acute, does not form or share the apex of the heart, and there is minimal right ventricular hypertrophy (RVH). These 2-dimensional findings do not support the presence of PVD.

On hemodynamic assessment, pulse wave Doppler in the right ventricular outflow tract (RVOT) (panel E) reveals



Figure 1A

a normal parabolic profile without "notching." The RVOT acceleration time is low normal at 110 ms. These findings together strongly suggest a normal PVR. The velocity time integral (VTI) in the RVOT is in the normal range (14 cm), implying normal RV stroke volume. Transmitral pulse wave Doppler (panel F) shows a restrictive inflow pattern, consistent with high left atrial pressure. Lastly, tricuspid annular plane systolic excursion (TAPSE) performed via M-mode (panel G) confirms normal RV function with TAPSE of 23 mm.

In this case, the findings on history and physical examination combined with the echocardiographic findings strongly suggest a hemodynamic phenotype of heart failure with preserved ejection fraction and secondary PH, without concomitant PVD. The patient presents with several symptoms consistent with marked left heart congestion including orthopnea and paroxysmal nocturnal dyspnea (PND). In addition, there are objective signs on physical examination of elevated left atrial pressure, including square wave systolic blood pressure response to Valsalva and right pleural effusion.15

The echocardiogram in this case strongly points toward a left heart origin of PH. There is marked LVH, left atrial enlargement, and restrictive transmitral filling consistent with severe LV diastolic dysfunction and elevated left atrial pressure. Though the RV is mildly



Figure 2

dilated, RV function is preserved as evidenced by normal TAPSE and normal RVOT VTI. Lastly, there is no evidence of significantly elevated PVR as evidenced by the absence of septal flattening or notching of the pulse wave Doppler profile in the RVOT and relatively preserved RVOT acceleration time.<sup>16,17</sup>

Given the preserved RV function and a phenotype consistent with left sided diastolic heart failure, this patient would be considered an acceptable candidate for renal transplantation once volume status was optimized by volume removal with ultrafiltration and with blood pressure under better control; repeat evaluation with right heart catheterization may be needed. In the invasive hemodynamic assessment of such patients, it is not uncommon to find a top normal or only mildly elevated resting wedge pressure. In such cases, saline fluid challenge or exercise should be considered.

## CASE 2

**Recap:** A 74-year-old man with systemic hypertension, ESRD, previously on hemodialysis via arteriovenous (AV) fistula, now with progressive dyspnea and exercise intolerance post renal transplant.

## Physical Examination

On examination, blood pressure is 142/64. Pulse is 83 beats per minute and regular. Respiration is 18 breaths/minute and oxygen saturation is 92% on room air. There is a slow decay in systolic blood pressure with Valsalva. In general, the patient is an elderly appearing man in no apparent distress. Jugular venous pressure was 14 cm of water with prominent V wave. Arterial pulses are stiff and hyperdynamic with rapid upstroke. Point of maximum impulse (PMI) is nondisplaced and is hyperdynamic. S1 and S2 are normal with normal P2 intensity. A soft S4 is audible. There is a 3/4 systolic murmur at the left upper sternal border. Abdomen is soft; there is mild hepatojugular reflux. Extremities have no edema. There is a large right brachial AV fistula with palpable thrill.

#### Echocardiogram

A transthoracic echocardiogram is performed. Parasternal long and short axis and apical 4 chamber views are illustrated below. In addition, pulse wave Doppler in the RVOT and transmitral Doppler profiles are shown. LV systolic function is normal with left ventricular ejection fraction (LVEF) of 70%. There



Figure 2A

is no mitral regurgitation or mitral stenosis.

The parasternal long axis view (panel A) reveals normal LV size with mild LVH with mitral annular calcification, a common finding in CKD. The parasternal short axis views (panels B and C) reveal mild diastolic and systolic septal flattening. The apical 4 chamber view (panel D) reveals a mildly dilated RV with RV:LV ratio of roughly 1.0, and the RV shares the apex with the LV. There is mild RVH.

On hemodynamic assessment, pulsed wave Doppler in the RVOT reveals a late systolic notch and an RVOT acceleration time that is mildly reduced at 90 ms. These findings suggest top normal or mildly elevated PVR. The VTI in the RVOT is high (22 cm), suggesting high RV stroke volume. Transmitral pulse wave Doppler (panel F) shows a "pseudonormal" inflow pattern, consistent with increased left atrial pressure. Lastly, TAPSE performed via M-mode (panel G) suggests normal to hyperdynamic RV function with TAPSE of 28 mm.

This patient presents with the insidious onset of progressive dyspnea several years after renal transplantation. On physical examination, he has several features that suggest underlying left heart stiffness and left atrial congestion such as an S4 gallop and slow decay in systolic blood pressure in response to Valsalva maneuver. However, there are also several findings suggesting high cardiac



Figure 3

output state, including hyperdynamic arterial pulses and PMI. The echocardiogram in this instance suggests a mixed picture of left sided congestion, high cardiac output, and mildly elevated PVR.

The RV is mildly dilated and in this case shares the apex of the heart with mild RVH. RVH function is near hyperdynamic with TAPSE of 28 mm. This is confirmed by pulse wave Doppler assessment of the RVOT with high RVOT VTI, suggesting high RV stroke volume.

Thus, the noninvasive assessment strongly suggests a high cardiac output syndrome due to the large brachial AV fistula with moderate left heart congestion, coupled with mild PVD and stiff, sclerotic central pulmonary arteries. In this case, hemodynamic assessment is clearly warranted, preferably with provocative maneuvers such as temporary fistula occlusion to assess the contribution of the fistula to cardiac output, left heart congestion, and PH (see article by Dr Tedford in this issue).

## CASE 3

**Recap:** A 47-year-old man with type 1 diabetes mellitus, prior renal and pan-creatic transplant, renal allograft failure,

being evaluated for repeat renal transplant.

## Physical Examination

On examination, blood pressure is 128/68, pulse is 57 beats per minute and regular. Respiratory rate is 16 breaths per minute. Oxygen saturation on room air is 91%. There is slow decay in systolic blood pressure in response to Valsalva maneuver. In general this is a wellappearing man in no apparent distress. Jugular venous pressure is 12 cm of water with normal venous contours. Arterial pulses are narrow, low amplitude. On cardiac examination, S1 is normal. S2 is normal with accentuated P2 component. There is a prominent S4 gallop audible. No murmurs or rubs are appreciated. LV apical impulse is nondisplaced. There is a shallow RV heave. Lungs are clear to auscultation bilaterally without rales, rhonchi, or wheezing. Abdomen is soft and nontender. There is an old midline surgical scar that is well healed. There is no hepatojugular reflux. Extremities are well perfused bilaterally. There is trace bilateral lower extremity edema. There is a left upper extremity AV graft with palpable thrill and audible bruit.



Figure 3a

#### Echocardiogram

A transthoracic echocardiogram is obtained and representative parasternal long and short axis and apical 4 chamber images are shown below. LV size and systolic function are normal, with LVEF of 65%. Mitral regurgitation is mild (not shown). There is no mitral stenosis.

The parasternal long axis view (panel A) again reveals normal LV size, mild LVH, and moderate left atrial enlargement. The parasternal short axis views (panels B and C) and apical 4 chamber view (panel D) reveal significant septal flattening in systole> diastole. The apical 4 chamber view also reveals a moderately dilated RV with RV:LV ratio of 1.2, and the RV shares the apex with the LV. There is moderate RVH.

On hemodynamic assessment, pulsed wave Doppler in the RVOT reveals a midsystolic notch pattern consistent with a PVR >5 Wood units. RVOT acceleration time is very short at 60 ms. The VTI in the RVOT is normal (16 cm), suggesting normal RV stroke volume. Transmitral pulse wave Doppler (panel F) shows an impaired relaxation pattern, also referred to as grade 1 diastolic dysfunction. Lastly, TAPSE performed via M-mode (panel G) suggests moderate RV dysfunction with TAPSE of 16 mm.

This patient has several features suggesting the etiology of his PH has contributions from left sided heart disease, including slow decay in systolic blood pressure response to Valsalva and S4 gallop. However, other elements of his examination and his echocardiogram suggest a more "right sided" phenotype with narrow, low amplitude pulses, accentuated P2, and RV heave.

Although the echocardiogram demonstrates LVH and left atrial enlargement, it also shows marked RV enlargement, systolic septal flattening, and moderate RV dysfunction, all of which indicate right heart dysfunction on the basis of increased pulmonary arterial afterload. Most notably, there are several features suggesting significant PVD including a midsystolic notch profile in the RVOT, very short RVOT acceleration time, and predominant systolic septal flattening.<sup>14,16,17</sup> Notably, transmitral Doppler shows an impaired-relaxation pattern, implying a normal or at most mildly elevated left atrial pressure.

Based on the above assessment, we can conclude that this patient has developed significant PVD secondary to chronic left heart congestion and now has a predominantly "right sided" phenotype with RV enlargement and RV dysfunction rather than classic signs or symptoms of left heart congestion. This is a more complex situation, where the PH is not simply a marker of high left atrial pressure or high cardiac output, but instead is of major hemodynamic import with manifest and clinically significant right heart dysfunction. This patient would be at much higher risk for adverse events with renal transplantation than the patient in Case 1, and likely would not be a candidate without addressing the manifest PVD. Chronic thromboembolic disease must also be excluded by ventilation-perfusion scintigraphy. Certainly, invasive hemodynamic assessment is warranted prior to consideration of elective surgery.

## DISCUSSION

PH in CKD patients is associated with a varied pathophysiology, of which 3 discrete phenotypes are illustrated in the cases above. In clinical practice, there is often considerable overlap between features of each of the phenotypes described, and the purpose of this review is not to describe every scenario of patients with CKD and PH. In addition, there are rare cases of idiopathic PAH or connective tissue disease-associated PAH

with associated CKD, but the physiology of these patients is typically driven primarily by PVD more so than pathophysiologic features unique to CKD. Indeed, some features are common to many patients with PH associated with CKD, including impaired salt and water handling, systemic hypertension, LV diastolic dysfunction, and left heart congestion.

In addition, patients with CKD and in particular those with long-standing diabetes and hemodialysis patients often develop a diffuse arteriosclerotic process involving large arteries including conduit pulmonary arteries, leading to increased arterial stiffness and diminished arterial compliance, which has been associated with adverse cardiovascular mortality.<sup>18,19</sup>

Some CKD patients may also develop large stroke volumes and high cardiac output syndromes secondary to longstanding systemic shunts such as large dialysis AV fistulas. Although there is debate as to whether an AV fistula alone can lead to PH, it is clear from clinical observation and physiologic rationale (mean PA pressure = cardiac output \* PVR + left atrial pressure) that coupling an inappropriately high cardiac output with a noncompliant, hypertrophied left heart will lead to left heart congestion, with PH being an inevitable consequence.<sup>20-22</sup>

Lastly, patients with chronic left heart congestion can develop significant PVD, which may be severe enough to manifest as a clinical syndrome similar to PAH, particularly when right heart dysfunction results. Noninvasive assessment using history, physical examination, and an echo-Doppler examination forms the cornerstone of the initial evaluation of patients with CKD and suspected PH, not just because these are typically the first tests obtained, but also because much information can be gleaned from these initial tests that can guide subsequent invasive evaluations.

At the bedside, using blood pressure response to Valsalva maneuver can provide a simple estimation of elevated left atrial pressure and provide clues in the clinic to the hemodynamic basis of PH.<sup>15</sup> Similarly, a simple echo-Doppler scoring system can help to differentiate a pulmonary vascular from a pulmonary venous etiology of PH.<sup>14</sup> In CKD patients, the PH clinician must take this assessment a step further in that many if not most patients with CKD will have some stigmata of left heart disease on physical examination or echo-Doppler assessment.

The keys to noninvasive assessment of PH in these patients rest in the assessment of RV structure and function, to evaluate for high cardiac output syndromes, and to evaluate carefully for evidence of elevated PVR using a thorough assessment of the pulsed wave Doppler signal in the RVOT.<sup>14,23</sup> Using this type of comprehensive physical examination and echo-Doppler assessment should provide the PH clinician with an overall impression of the hemodynamic basis of PH in the majority of patients presenting with dyspnea even prior to cardiac catheterization.

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