Beyond the Numbers: Pulmonary Hypertension in End-Stage Kidney Disease Patients on Hemodialysis

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EDITORIAL

Abstract

The authors discuss pulmonary hypertension pathogenesis and clinical features, the difference between pulmonary arterial and pulmonary venous hypertension. The similarities of pressure overload associated pulmonary venous hypertension (HFpEF) to precapillary pulmonary arterial hypertension. The dismal prognosis of patients with pressure overload pulmonary venous hypertension compared to patients with volume overload pulmonary venous hypertension or precapillary pulmonary arterial hypertension. They also converged on theimportance of diagnosis and treatment differences of HFpEF patients and PAH patients.

Keywords: *Pulmonary arterial hypertension, pulmonary venous hypertension, left heart disease, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, pressure overload, volume overload.*

Pulmonary arterial hypertension (PAH) is a rare disease with an estimated prevalence of 15-50 per million persons (1,2). PAH can affect individuals at any age, but the mean age at disease onset is mid-thirties. Women are disproportionately affected by PAH. Female to male ratios of 2:1 to 4:1 have been documented (1,3,4).

Pulmonary hypertension (PH) is an increasingly recognized cause of dyspnea in end-stage kidney disease (ESKD) patient on hemodialysis (5). It is a debilitating progressive disease of the pulmonary vasculature resulting in right side heart failure (RHF) and death.

The World Health Organization (WHO) classified PH to 5-categories according to the underlying pathogenetic mechanisms. This classification is complicated and difficult to adhere to. The Dana Point guidelines grouped PH into 2 groups.

a) Group one is pulmonary arterial hypertension (PAH), this is also known as pre-capillary pulmonary hypertension, it includes hereditary PAH, and PAH associated with connective tissue diseases, thromboembolic disease, congenital heart disease, portal hypertension, anorexigens, or human immune deficiency virus (HIV) (5).

b) Group 2 of PH is pulmonary venous hypertension (PVH) or postcapillary pulmonary hypertension, is a consequence of chronic Left-sided Heart Disease (LHD).

Patients with PVH may have reduced or preserved left ventricular function (LV) with associated valvular disease (6). Pulmonary venous hypertension is sometimes called post-capillary pulmonary hypertension to distinguish it from precapillary pulmonary arterial hypertension (PAH), (6). PVH can result from either.

a) Pressure overload causing left ventricular failure (POL-LVF) or

b) Volume overloads causing left ventricular failure (VOL-LVF).

VOL-LFV is associated with passive elevation of pulmonary venous pressure (postcapillary-PH). This type of PH is not associated with hypertrophy of the smooth muscles in the pulmonary vasculature and therefore, do not behave like PAH.

On the other hand, POL-LVF venous hypertensive patients are behaving like precapillary PAH because of reactive vasoconstriction and structural remodeling in the pulmonary vascular resistance (PVR) caused by pressure overloading of the left ventricle and atrium (6,7). Thus, patients with LHF with pressure overload can often disclose disproportionately elevated and severe pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) (8). These patients share similar clinical and hemodynamic characteristics to PAH patients (8).

The pathological changes in pulmonary vasculature in patients with precapillary PAH and pressure overload postcapillary pulmonary venous hypertension (HFpEF) have some common pathologic features regardless of their etiology, that is , medial hypertrophy of muscular and elastic arteries, plexiform dilation and intimal atheroma of elastic pulmonary arteries and right ventricular hypertrophy. All PAH is also characterized by constrictive and complex arterial lesions involving to a varying degree the pre-and intra-acinar pulmonary arteries (7,9).

It is very important to distinguish PAH from PVH as treatment is critical and different for these conditions and mistreatment can be fatal. Labeling PAH patients as having PVH and treating them with therapies intended for PVH will expose patients to unwanted side effects of therapy. In addition, the negative inotropic characteristics of some of these drugs and the associated bradycardia may alter normal compensatory responses of the heart and ultimately causes cardiogenic shock. This effect may be seen with the use of calcium channel blockers (3,10).

Identifying patients with PVH as PAH will also delay the proper diagnosis and treatment of PAH. Current treatment of PAH can improve exercise tolerance, quality of life, and life expectance (11). However, the use of these therapies in late stages of PAH when pathological changes are advanced and irreversible, may not be effective (3,12-14). Clinical trials on patients with PAH who have delayed treatment appear not to catch up in terms of response when later provided Correct treatment (13,15,16), suggesting that treatment delayed is treatment denied. Patients with PAH diagnosed and treated late have dismal outcome (12,17-19). In the current literature late diagnosis of PAH constitute 55% to 75% in their disease course (functional class III/IV), (1,3,4). This delay in the diagnosis and treatment is probably the cause of dismal outcome of these patients.

On the other hand, treating PVH patients with therapy intended for PAH can exacerbate LHD and compromise patient outcome (20,21). Mislabeling patients with PVH as PAH inflicts unnecessary personal and social burdens. The cost of therapy can also convey a heavy financial burden with unproven benefit. Correct diagnosis of PAH and PVH patients, via thorough physical, clinical, and hemodynamic assessment is essential.

PH due to LHD occurs more frequent than PAH andis properly the most encountered PH in clinical practice. The estimated prevalence of PH due to LHD is 19-35% (5,22). Intriguingly, further upsurge of PVH prevalence due to LHD are expected to increase due to aging population with increased left diastolic dysfunction (HFpEF), (23,24). These patients have preserved ejection fraction of 40-50% and constitute more than 50% of all heart failure population (25-27). Likewise, patients with HFpEF have also poor prognosis as patients with heart failure with reduced ejection fraction (HFrEF) but additionally, these patients lack a well-recognized therapy.

Pulmonary arterial hypertension in patients with diastolic dysfunction (PH-HFpEF) have distinct characteristics compare to patients with precapillary PAH, that might help in their diagnosis and recognitions.

1. These patients are often older (mean age 64-years),
2. Have a higher prevalence of cardiovascular comorbidities (hypertension, obesity, DM, coronary artery disease, atrial fibrillation, worse exercise capacity, and renal function), (7).
3. The echocardiographic findings (left atrial enlargement, concentric remodeling (relative wall thickness >0.45), left ventricular hypertrophy, elevated left ventricular filling pressures (grade II to IV diastolic dysfunction)
4. Symptomatic response to diuretic drugs

5. Exaggerated increase in systolic blood pressure with exercise

6. Cardiopulmonary hemodynamics are characterized by

a. (right atrial pressure (RAP)- normal or increase,

b. Right ventricular systolic pressure (RVSPmmHg >30)

c. Right ventricular diastolic pressure (RVDPmmHg-normal or increase)

d. Pulmonary artery systolic pressure (PASPmmHg - >30)

e. Pulmonary artery diastolic pressure (PADPmmHg - >15)

f. Mean pulmonary arterial pressure (PAP mmHg - $\geq$25)

g. PCWP mmHg - >15,

h. Cardiac output (L/min) – normal or increased,

i. Cardiac index (CI L/min/m2) – normal or increased,

j. Transpulmonary gradient {TPG mmHg (mean PAP-PCWP)} – increased,

k. Pulmonary vascular resistance (PVR Wood units, =TPG/CO} is increased.

Patients with PH-HFpEF have worse prognosis compared to patients with PAH. The average one-year survival in full cohort of 339 PH-HFpEF patients was (81% vs 85%) in the incident cohort patients with PAH (3,28).

Right heart and sometimes left heart catheterization are essential in accurate diagnosis of PAH and PVH patients. The PCWP and PVR, which are used for differentiation of PAH and PVH proposed by the 4th World Symposium on Pulmonary Hypertension (29) are the basis of diagnostic strategy. PCWP at end-expiration >15mmHg, PVR >3, and TPG>10 would differentiate PVH from PAH. If there is any doubt in PCWP measurements, then direct measurement of left ventricular end-diastolic pressure (LVEDP) is mandatory through left heart catheterization. In patients with PVH, by creating a shunt at the level of the atria or the left pulmonary artery and the descending aorta might relieve the pressure of the left side of the heart and improve the preload of the left ventricle. Theoretically, creating a shunt at the atrial or pulmonary artery levels would also decompress the right ventricle and ameliorate cardiac pump failure. Thus, improving systemic blood flow and cardiac output.

Conclusion: differentiating PVH from PAH are essential for appropriate diagnosis and treatment. There is no magic bullet to accurately differentiate the two. Taken together the clinical features, non-invasive procedures like echocardiographic criteria, chest X-ray, ECG, and hemodynamic findings from cardiac catheterization are all important measures in arriving at the definitive diagnosis.

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