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Review article

Management of combined pre- and post-capillary pulmonary hypertension in advanced heart failure with reduced ejection fraction

Sandeep Sahay [a, *], Ghaleb Khirfan [b], Adriano R. Tonelli [c]

[a] Weill Cornell Medical College, Institute of Academic Medicine, Houston Methodist Lung Center, Houston Methodist Hospital, Houston, TX, USA
[b] Department of Internal Medicine, Cleveland Clinic, Cleveland, OH, USA
[c] Department of Pulmonary, Allergy and Critical Care Medicine, Respiratory Institute, Cleveland Clinic, Ohio, USA

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ABSTRACT

Management of pulmonary hypertension (PH) has remained an unmet need in advanced left heart failure with reduced ejection fraction. In fact, patients are frequently denied heart transplant due to untreated pulmonary hypertension. The availability of mechanically circulatory devices and PH therapies has provided a ray of hope. PH specific therapies are currently not FDA approved for patients with left heart failure with reduced ejection fraction. However, clinicians have used these medications in anecdotal manner. With this review, we want to highlight the expanding use of PH specific therapy and mechanical circulatory devices in the management of PH in the setting of advanced heart failure with reduced ejection fraction.

Contents

1. Introduction

Results of REMATCH trial have revolutionized the management of advanced heart failure with reduced ejection fraction [1]. Mechanical circulatory devices like left ventricular assist devices (LVAD) have prolonged survival in these patients [1–3]. Right ventricular (RV) failure and persistent pulmonary hypertension (PH), frequently complicate LVAD placement. In fact, RV failure and PH remain the most common cause of mortality in these individuals [4]. Over the last decade, multiple PH therapies have been approved for the treatment of pulmonary arterial hypertension (PAH). There is a growing number of studies testing the use of PAH-specific therapies for combined pre- and post-capillary PH after

* Corresponding author. Weill Cornell Medical College, Houston Methodist Lung Center, Houston Methodist Hospital, 6550 Fannin St, 1001 Smith Tower, Houston, TX 77030, USA.
E-mail address: ssahay@houstonmethodist.org (S. Sahay).

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LVAD placement [5–7]. In this review, we attempt to highlight the pathophysiology of "persistent" PH in patients with advanced heart failure after LVAD placement and the potential role of PAH-specific therapies in the management of this condition.

2. Pathophysiology of pulmonary hypertension in left heart failure with reduced ejection fraction

Management of PH remains a challenge in patients with left heart failure with reduced ejection fraction [8]. In fact, PH is an important factor associated with poor outcomes in patients undergoing heart transplant [9–11]. Pulmonary hypertension secondary to left heart disease is characterized by the presence of post-capillary PH which is defined by a mean pulmonary artery pressure of ≥25 mmHg with pulmonary artery wedge pressure >15 mmHg [12]. When left ventricular dysfunction ensues, PH develops as a result of increased left ventricle (LV) filling pressures. This passive PH is largely reversible and normalizes upon reduction of the LV filling pressures [13]. However, lasting changes in the pulmonary vasculature can occur with long-standing exposure to increased intravascular pressures in the pulmonary venous circulation, namely, "fixed or persistent" PH[13]. This vascular changes result in an elevation of pulmonary vascular resistance (PVR) and the transpulmonary gradient (TPG), which is referred to as combined pre- and post-capillary PH (Cpc-PH) [14]. A similar pathophysiology is seen in patients with pronounced mitral stenosis, where a decrease in mitral valve area leads to elevated left atrial filling pressures that with time causes remodeling of the pulmonary vascular bed leading to increase in PVR and PH [15].

Pulmonary artery endothelial dysfunction plays a pivotal role in the development of PH. A fine balance exists between the vaso-constricting and vaso-dilatory endothelial derived mediators like endothelin-1 and nitric oxide. PH develops when the balance shifts towards the vaso-constrictive mediators [16,17]. Fig. 1 describes the pathophysiology behind the development of PH in patients with advanced left heart failure. Over time, the histological changes noted in the pulmonary artery start to resemble those seen in idiopathic PAH [18,19]. In fact, patients with congestive vasculopathy commonly have medial hypertrophy and less frequently intimal fibrosis and pulmonary venule obstruction [20,21]. Similar changes in the pulmonary vascular bed have also been described in patients with advanced mitral stenosis, where increased medial and adventitial thickness occurs [22], in part mediated by increased levels of endothelin-1 [23].

As PH develops, the afterload of the right ventricle (RV) increases which leads to compensatory changes such as RV hypertrophy. This hypertrophy impairs the subendocardial perfusion of the RV, and with time, the RV dilates and eventually progress to RV failure and cor-pulmonale [24]. As a result of ventricular interdependence the RV dilation pushes the interventricular septum leftward, further decreasing the cardiac output and causing global dysfunction [24].

3. Role of mechanical circulatory devices in combined pre- and post-capillary PH

Patients with combined pre- and post-capillary PH and elevated PVR are considered high risk and are often denied heart transplantation. A linear relationship has been reported between PVR and heart transplant mortality [10]. In fact, almost 40% of potential heart transplant candidates have persistent PH along with elevated PVR at the time of evaluation [25,26]. Taylor et al. [27] reported significantly better survival in patients undergoing heart transplantation with PVR between 1 and 3 Wood units (WU) in comparison to those with PVR of 3–5 WU. In addition, there is evidence showing that the risk of heart transplantation can be significantly reduced when PVR and TPG are lowered below 2.5 WU and 12 mmHg, respectively [28,29]. These data encouraged the use of PAH-specific therapies in patients with combined pre- and post-capillary PH. In patients with advanced left heart failure considered for advanced therapies it is important to discriminate between vasoreactive and non-vasoreactive PH. Hence most centers use provocative vasodilatory testing with nitric oxide, prostaglandins, adenosine, sodium nitroprusside or nitroglycerin [26,30,31].

Mechanical circulatory devices like LVAD have revolutionized the management of patients with combined pre- and post-capillary PH. An increasing number of patients who have elevated PVR are now referred for LVAD placement as a bridge to transplantation. Long-term mechanical support to the failing LV has shown to lower mean pulmonary artery pressures and PVR by significant unloading the LV and decreasing the hydrostatic pressure in the pulmonary veins that with time results in a reduction of the *trans*-pulmonary gradient [32–35]. Etz et al. [34] placed a non-pulsatile LVAD in patients with LV failure and PH refractory to medical management. Over a period of six months they noted a significant decrease in mean pulmonary artery pressures from 42 to 24 mmHg and PVR from 4.8 to 2.2 WU. All these patients subsequently underwent heart transplantation with no increase in their mean pulmonary artery pressures, PVR and TPG at 3 and 6-month follow-up. Alba et al. [35] reported that heart transplantation can be safely considered in patients with persistent PH receiving LVAD as a bridge to transplant.

Martin et al. [33] showed successful treatment of persistent PH with pulsatile LVAD in six patients, with reductions in PVR from a range of 4.4–6.5 WU to a range of 0.8–3.6 WU, over a period of three to six months. In a case series by Gallagher et al. [36], individuals receiving LVAD had a significant reduction in PVR and improvement in RV ejection fraction, improvements that were sustained after heart transplantation. Importantly, four patients who otherwise would not have been considered candidates for heart transplantation due to elevated PVR, underwent successful heart transplantation after LVAD support. A prospective study in 63 patients by Smedira et al. [37] showed a significant decrease in PVR from 5 to 3.7 WU and mean pulmonary pressure from 41 to 30 mmHg after LVAD implantation (HeartMate, Thermo Cardiosystems, Inc, Woburn, MA). In this study, the survival was >90% after heart transplantation in subjects with PH, defined as mean pulmonary artery pressure >30 mm Hg and/or PVR >4 WU [37].

There is sufficient evidence to support that in patients with PH due to heart failure with reduced ejection fraction, LVAD (both pulsatile and continuous flow) accomplish an enduring reduction in PVR and pulmonary artery pressures. In fact, LVAD as bridge to cardiac transplantation in patients with PH has made heart transplantation a feasible option [38,39]. The hemodynamic benefits in PVR and mean pulmonary artery pressures are commonly seen within six months after LVAD placement, without significant improvement thereafter [40]. At the time of this writing, there are no data comparing survival in patients with PH due to LV dysfunction who received or did not receive LVAD therapy [41].

Studies assessing the impact of the type of LVAD (continuous versus pulsatile flow) on pulmonary hemodynamics showed mixed results. Ozturk et al. [42] compared the effect of continuous and pulsatile flow LVAD in patients with "persistent" PH. Patients who received continuous flow devices had a significantly greater decrease in systolic pulmonary artery pressures but no significant difference in tricuspid annular plane systolic excursion (TAPSE). Garcia et al. [43] showed no difference in hemodynamics between continuous and pulsatile flow LVAD in patients with end-stage LV heart failure. Nevertheless, patients who received pulsatile flow devices had a more pronounced reduction in PVR. Klotz et al. [44]