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Impact of Pharmacologic Interventions—Treating Endothelial Dysfunction and Group 2 Pulmonary Hypertension

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ABSTRACT

Pulmonary hypertension (PH) secondary to left heart disease (LHD) is a largely underappreciated therapeutic target. Except for a specific focus on PH consequences in patients with advanced heart failure (HF) receiving a left ventricular assist device or candidates for heart transplant, prevention and treatment of initial subclinical forms of PH are not considered a priority in the management of this chronic disease population. Nonetheless, there is recent growing evidence supporting a clinical and prognostic role of PH in the elderly populations and in HF with preserved ejection fraction (pEF). Although the prevalence of PH in these populations still remains largely unknown, there is a large potential for effective pharmacological approaches that might impact the natural history of HFpEF by targeting earlier stages. However, pharmacological studies performed to date with traditional pulmonary vasodilators (i.e. prostanoids and endothelin receptor blockers) in cohorts with HF and left-sided PH have not been positive, primarily because of concomitant systemic hypotension and hepatic toxicity. The encouraging preliminary data with more selective well-tolerated pulmonary vasodilators, such as phosphodiesterase type 5 inhibitors and guanylate cyclase stimulators/activators, however, suggest the need for new targets of pulmonary microvascular dysfunction and for treating PH-LHD at both early and later stages of the disease process.

Left-sided heart disease (LHD) is the most common cause of pulmonary hypertension (PH), classified according to the latest guidelines as Group 2 [1]. LHD-PH most frequently develops as a consequence of impaired left ventricular (LV) relaxation and distensibility properties. The elevated pressure in the pulmonary vasculature leads to a cascade of adverse anatomical and functional effects on the pulmonary capillaries, arterial and venous circulation, and right ventricular (RV) function. The magnitude of LHD-PH is an important determinant of morbidity and mortality, with a twofold higher risk of death in patients developing RV failure [2]. Clinicians are aware of the need to treat PH when RV pump failure develops and clinical deterioration is apparent. However, there may be potential advantages of

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Abbreviations and Acronyms

cGMP = cyclic guanylate cyclase

CHD = coronary heart disease

ET1 = endothelin 1

HF = heart failure

HR = heart rate

HTX = heart or cardiac transplantation

LV = left ventricle or ventricular

LVAD-LV = assist device

NO = nitrous or nitric oxide

PAP = pulmonary artery pressure

PCWP = pulmonary capillary wedge pressure

PDE = phosphodiesterase

pEF = preserved ejection fraction

PH = pulmonary or pulmonary artery hypertension

PVR = pulmonary vascular resistance

RAP = right atrial pressure

RV = right ventricle or ventricular

sGC = soluble guanylate cyclase

VHD = valvular heart disease

preventing PH as well as treating subclinical early stages of PH when capillary stress failure and endothelial lung dysfunction are already undermining factors. Prevention of PH would be ideal, considering epidemiological evidence from community-based studies showing the unfavorable impact of PH with aging both in the general population [3] and in patients with heart failure (HF)-preserved ejection fraction (pEF) [4]. While in recent years remarkable results have been obtained in the treatment of PH, no significant advancements have been seen in the treatment of Group 2 PH [5]. Based on these premises, evidence and general issues relevant to the therapeutic approach of LHD-PH at various stages will be discussed, placing special emphasis on the therapeutic opportunities that may hold promise for the future.

Therapeutic strategies in the treatment of LHD-PH

There are currently no consensus therapeutic strategies or algorithms for the treatment of Group 2 PH. The lack of robust evidence from trials led 'Guidelines' to provide only general recommendations [6]. Specifically, there are suggestions that well apply to the evolving stages of the disease such as treating comorbid disorders, optimizing volume status, and improving of left ventricular (LV) relaxation properties and are seen as mainstay interventions [6]. In advanced stages correction of valvular heart disease (VHD; primarily mitral insufficiency), LV assist devices (LVAD), and heart transplantation (HTX) are then indicated. It remains to be determined, however, whether or not pharmacological treatment of pulmonary vascular disease may be a conceivable goal that favorably impacts the course of the disease especially in the early/intermediate stages (Fig 1, [7]).

Current pharmacological therapies for HF, such as vasodilators and diuretics, may improve PH through a reduction in filling pressures. These agents lower the pulmonary vascular resistance (PVR) and can reduce functional mitral insufficiency. Neurohormonal antagonists such as angiotensin-system antagonists or β-blockers are less effective on the pulmonary circulation and have not been systematically evaluated in clinical trials. Trials investigating pulmonary vasodilator agents thus far have consistently failed to demonstrate a benefit in patients with HF suffering from severe systolic dysfunction and advanced neurohumoral activation. Although most of these therapies are effective in reducing pulmonary artery pressure (PAP), systemic hypotension and hepatic side effects complicate their use [5]. In addition, use of selective pulmonary vasodilators may trigger acute pulmonary edema in the presence of a non-compliant LV chamber [8]. Nonetheless, the validity of this conclusion has been recently questioned by the availability of newer selective agents that may optimally target endothelial pathways involved in the control of pulmonary vascular tone and permeability whose hemodynamic effects are described in the next sections.

Pharmacological therapies

Table 1 outlines major study findings of trials testing pulmonary vasodilator therapies in LHD-PH [9–24].

Prostanoids

Prostanoids are considered a cornerstone therapy for the treatment of precapillary PH. Preliminary observations obtained in left-sided PH with acute administration of intravenous prostacyclin documented a decrease in pulmonary capillary wedge pressure (PCWP) and PVR, and an increase in cardiac index. However, these positive effects coincided with a drop in systemic arterial pressure and resistance, and a rise in plasma concentrations of epinephrine, norepinephrine, renin, and aldosterone [25]. A few small non-randomized trials have shown a trend toward better outcomes with intermittent infusion of prostaglandin E1 [9]. Epoprostenol added to a maximal conventional treatment resulted in a significant improvement in 6-min walk distance [10]. In patients undergoing assessment for HTX, inhaled iloprost, a prostacyclin analogue, produced some improvement in PAP, PCWP, and PVR [26]. Despite these favorable signals, the use of prostaglandins in systolic HF in The Flolan International Randomized Trial (FIRST) [11] showed a strong trend toward decreased survival with intravenous epoprostenol and led to the trial premature termination. However, upon reviewing the randomized groups, the treatment group had a much higher PCWP and thus a reduced LV compliance. This likely resulted in a higher incidence of HF and fatal events. Some have suggested an unfavorable positive inotropic effect of epoprostenol, and perhaps a small dose of drug might have been more effective.

Endothelin-1 receptor blockers

Endothelin-1 (ET1) is one of the most potent endogenous vasoconstrictors. Concentrations in the pulmonary vasculature correlate with PVR [27]. In experimental settings,