Chronic Right Heart Failure
Expanding Prevalence and Challenges in Outpatient Management

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KEYWORDS

• Chronic right heart failure • Right heart failure (RHF) • Right ventricular failure (RVF)
• Pulmonary arterial hypertension (PAH) • Chronic thromboembolic pulmonary hypertension (CTEPH)
• Right ventricular assist devices (RVAD)

KEY POINTS

- Chronic right heart failure management generally follows a 3-pronged approach: reducing afterload, optimizing preload, and increasing contractility.
- The best evidence available in right heart failure management lies in afterload reduction in the setting of pulmonary arterial hypertension.
- Robust clinical data to guide preload optimization in right heart failure are lacking.
- Developments in targeted therapy for right heart failure have been slow.
- Management of chronic right heart failure relies on adapting therapies for left ventricular heart failure to the right, which may not be appropriate at times.

INTRODUCTION

Right heart failure (RHF) is a clinical syndrome caused by anatomic and/or physiologic right heart dysfunction resulting in suboptimal stroke volume to supply the pulmonary circulation.[1–3] RHF has a very poor prognosis.[4,5] Early studies showed that survival in patients with congestive left ventricular (LV) failure with New York Heart Association functional classes II through IV symptoms was inversely related to right ventricular (RV) ejection fraction.[4,6]

The exact prevalence of RHF is unknown, but its underlying causes are common and include LV failure, pulmonary vascular disease, parenchymal lung disease, RV infarction, and arrhythmia.[7] Many advances over the last 2 decades have improved our understanding of the distinct RV anatomy, physiology, and pathobiology.[8,9] With more effective therapies,[1,10] patients with acute RHF are surviving to hospital discharge and so live with chronic RHF. Herein, we review the management of RHF in the ambulatory setting and its numerous challenges.

GENERAL OVERVIEW OF RIGHT HEART FAILURE MANAGEMENT

RHF management generally follows a 3-pronged approach: reducing afterload, optimizing preload, and increasing contractility.[11] The best evidence in the treatment of RHF is in afterload reduction, specifically in the setting of pulmonary arterial hypertension (PAH).

Afterload Reduction

The hemodynamic characterization of PAH is a mean pulmonary arterial pressure of 25 mm Hg or greater at rest, a pulmonary wedge pressure

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of 15 mm Hg or less, and a pulmonary vascular resistance (PVR) of 3 Wood units or greater.[12] Although there are many causes of PAH, the final common pathways, pathobiology, and histopathology are similar.[13] Pulmonary arterioles exhibit increased vessel wall fibrosis, medial wall thickening, and intimal proliferation. Endothelial dysfunction results in decreased production of vasodilatory endopeptides (nitric oxide [NO] and prostacyclin) and increased endothelin and thromboxane production, favoring vasoconstriction, thrombosis, and endothelial cell proliferation.[14] As a result, patients with PAH have increased PVR, increased RV afterload, and consequent maladaptive hypertrophy and eventually RHF if left untreated. Vascular-targeted therapies have therefore been developed to specifically target the molecular pathways that increase PVR. Pharmacotherapy advances over the last 2 decades have increased median survival from 2.8 years to approximately 8 years after diagnosis.[15]

Supplemental oxygen

Apart from vascular pharmacotherapy, hypoxemia should be corrected with supplemental oxygen if present, because pulmonary hypoxia is a potent pulmonary vasoconstrictor that can contribute to increased afterload and RV workload. Oxygen supplementation has been shown to decrease PVR.[16]

Prostacyclin pathway agonists

Epoprostenol, a prostacyclin analogue and a short-acting potent vasodilator and inhibitor of platelet aggregation, was the first approved drug for PAH.[17] In a multicenter open-label randomized controlled trial (RCT) (n = 81), epoprostenol increased quality of life, exercise capacity, hemodynamics, and survival.[17] Epoprostenol is reserved for patients with severe PAH (World Health Organization [WHO] functional class III or VI)[18] and can be used first line in WHO functional class III patients with advanced disease and high-risk features.[18] Challenges with epoprostenol include intravenous administration, which can be complex, instability at room temperature necessitating ice packs for storage, catheter-related infection, catheter-related thrombosis, a short half-life necessitating continuous infusion, and rebound PAH in some interrupted cases.[13] Thermostable epoprostenol has been developed and obviates the need for ice packing, thereby improving convenience for patients.[19]

Treprostinil, another prostacyclin analogue, benefits from a longer half-life, stability at room temperature, and multiple routes of administration (intravenous, oral, subcutaneous, and inhaled).[13] A double-blind placebo-controlled RCT (n = 470) showed that subcutaneous treprostinil improved hemodynamics, symptoms, quality of life, and 6-minute walk distance (6MWD).[20] Intravenous treprostinil is well-tolerated and provides similar hemodynamic improvements to epoprostenol.[21–23] Treprostinil can be used as first-line therapy for severe PAH (WHO functional class III or VI).[18] However, a significant limiting factor of subcutaneous treprostinil is pain at the infusion site.[20]

Inhaled treprostinil is efficacious as an add-on therapy. Combination therapy with bosentan or sildenafil improves 6MWD and quality of life in patients with PAH.[24] In contrast, monotherapy with oral treprostinil has been shown to improve exercise capacity in patients with PAH, but not when used in combination with sildenafil or bosentan.[25–27] A major limitation of these 3 trials evaluating oral treprostinil was the relatively low dose achieved, limiting its efficacy.[28]

Iloprost, another prostacyclin analogue, is approved by the US Food and Drug Administration (FDA) as inhaled therapy for PAH. It has a half-life of 20 to 25 minutes without an active metabolite so it requires frequent administration six to nine times a day.[13] The AIR RCT (n = 203) found that inhaled iloprost improved WHO functional class and 6MWD in WHO functional class II or III patients.[29] In combination, iloprost shows conflicting results.[30,31]

Selexipag, an orally administered selective prostacyclin receptor agonist, benefits WHO functional class II and III patients with PAH. The GRIPHON RCT (n = 1156) showed that selexipag decreased hospitalizations (14% vs 19%; $P<.003$) and slowed disease progression compared with placebo.[32]

Endothelin receptor antagonists

Endothelin-1 is a vasoactive peptide found at high concentrations in the lungs of patients with PAH. Endothelin-1 acts through 2 receptors: ET-A receptors, which are primarily found on pulmonary vascular smooth muscle cells and are vasoconstrictive and promote smooth muscle proliferation; and ET-B receptors, which are primarily located on endothelial cells and act to clear endothelin.[33]

Bosentan is a nonselective, orally administered ERA that has been shown in patients with PAH to slow disease progression, improve 6MWD (in 1 study by an average of 44 m; $P<.001$), and improve WHO functional class.[34,35] Bosentan therapy is associated with elevation of transaminases[36] and CYP2C9 and CYP3A4 induction, leading to interactions with commonly used medications including sildenafil, oral contraceptives, warfarin, and antiretrovirals.[37]