Treatment of right ventricular dysfunction and heart failure in pulmonary arterial hypertension

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Abstract: Right heart dysfunction and failure is the principal determinant of adverse outcomes in patients with pulmonary arterial hypertension (PAH). In addition to right ventricular (RV) dysfunction, systemic congestion, increased afterload and impaired myocardial contractility play an important role in the pathophysiology of RV failure. The behavior of the RV in response to the hemodynamic overload is primarily modulated by the ventricular interaction and its coupling to the pulmonary circulation. The presentation can be acute with hemodynamic instability and shock or chronic producing symptoms of systemic venous congestion and low cardiac output. The prognostic factors associated with poor outcomes in hospitalized patients include systemic hypotension, hyponatremia, severe tricuspid insufficiency, inotropic support use and the presence of pericardial effusion. Effective therapeutic management strategies involve identification and effective treatment of the triggering factors, improving cardiopulmonary hemodynamics by optimization of volume to improve diastolic ventricular interactions, improving contractility by use of inotropes, and reducing afterload by use of drugs targeting pulmonary circulation. The medical therapies approved for PAH act primarily on the pulmonary vasculature with secondary effects on the right ventricle. Mechanical circulatory support as a bridge to transplantation has also gained traction in medically refractory cases. The current review was undertaken to summarize recent insights into the evaluation and treatment of RV dysfunction and failure attributable to PAH.

Keywords: Right ventricular dysfunction; heart failure; pulmonary arterial hypertension (PAH)

Introduction

Pulmonary arterial hypertension (PAH) is a progressively fatal disease with a median survival of 7 years (1). The prognosis of the patients is closely linked to the right ventricle (RV) function and the ability of the RV to adapt to the progressive increase in afterload. The development of clinical symptoms is closely linked to the development of RV dysfunction. The development of clinical right heart failure is characterized by maladaptive RV remodeling and RV-pulmonary arterial uncoupling.

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The anatomy and physiology of the cardiopulmonary unit

Myofiber architecture of the RV

The RV is a thin-walled structure that is triangular from the side and crescentic in cross-section. Embryologically, the RV is derived from cardiac precursor cells in the anterior or second heart field (2). It is distinct from the left ventricle (LV) in its anatomic, electrical, and cellular configurations. Anatomically, the RV is composed of 3 distinct portions. The Inlet, trabeculated apex and the infundibulum or conus (outlet region) (3). The muscle fibers of RV myocardium are composed of 2 layers. The superficial layer arranged circumferentially in a direction parallel to the atrioventricular groove (AV) groove and continuity with the LV. The deep fibers aligned longitudinally from base to apex. The RV and LV are closely inter-related through the septum, shared epicardial circumferential myocytes, and the pericardium which forms the basis for the ventricular interdependence (4,5).

Myocardial mechanics of the RV

The RV has a distinctive, peristaltic like contraction pattern that starts from the inlet portion and ends at the infundibulum. The subepicardial layer of the inflow tract acts as an early pressure generator and deforms the RV circumferentially during isovolumic contraction. The subendocardial layers contribute to longitudinal shortening during the ejection phase and the interventricular septum accounts for a significant portion of the global RV function (6,7).

The mechanisms of RV pump function include (I) shortening of the longitudinal axis with traction of the tricuspid annulus towards the apex; (II) radial movement of the RV free wall (referred to as a bellows effect); (III) bulging of the interventricular septum into the RV during LV contraction, and (IV) stretching of the free wall over the septum (causing shortening in the anteroposterior direction). Longitudinal contraction is thought to contribute up 75% of RV contractility under physiological conditions, with a lesser contribution from radial contraction (8). It is unknown if these relative contributions change in disease conditions.

Defining right heart failure

The International Right Heart Failure Foundation Scientific Working Group proposed the following definition for right heart failure: "*a clinical syndrome due to an alteration of structure and/or function of the right heart circulatory system that leads to sub-optimal delivery of blood flow (high or low) to the pulmonary circulation and/ or elevated venous pressures at rest or with exercise*" (9). Exercise limitation, fatigue, and fluid retention are the cardinal manifestations of right heart failure. Right heart failure can also be defined by World Health Organization functional class IV symptoms with clinical signs of venous congestion with fluid retention and signs of decreased cardiac output (10).

Pathophysiology of right ventricular failure in PAH

The pathophysiology of RV failure involves a complex interplay of neurohormonal activation, inflammation, apoptosis, insufficient coronary perfusion, oxidative stress and metabolic shifts with a variable degree of fibrosis and hypertrophy (*Figure 1*). In situations like human immunodeficiency virus (HIV) associated PAH, infection/ inflammation of the myocardium and the intramural vessels has been shown to adversely affect the RV function as assessed by cardiac magnetic resonance imaging (15). The symptomatology, functional prognosis, and survival of patients with PAH depend on the ability of the RV to adapt to a progressive increase in afterload. This adaptation, often referred to as ventriculo-arterial coupling, is a measure of energy transfer assessed from the ratio between end-systolic elastance Ees (contractility) and arterial elastance Ea (afterload). The normal ratio is between 1.5 and 2.0 (16-18). RV adaptation is thought to represent a continuum, with true uncoupling occurring below a ratio of 0.7–0.8. The adaptive phase (homeometric adaptation) is characterized by an increase in contractility with preserved stroke volume, whereas maladaptation (heterometric adaptation) is characterized by a dilated ventricle and eventually decreased stroke volume. During the adaptive phase, functional status, exercise capacity, and resting cardiac output are relatively well preserved. During the maladaptive phase, ventriculoarterial uncoupling results in inadequate energy transfer from the myocardium to the pulmonary circulation and subsequent right heart failure (19-22).

Studies of isolated myocytes (obtained from human RV septal biopsies and autopsy samples) revealed disparate contractile function between subtypes of PAH. Myocytes from idiopathic PAH has shown increase contractility relative to controls, even in end-stage disease, whereas systemic sclerosis related-PAH show impaired contractile
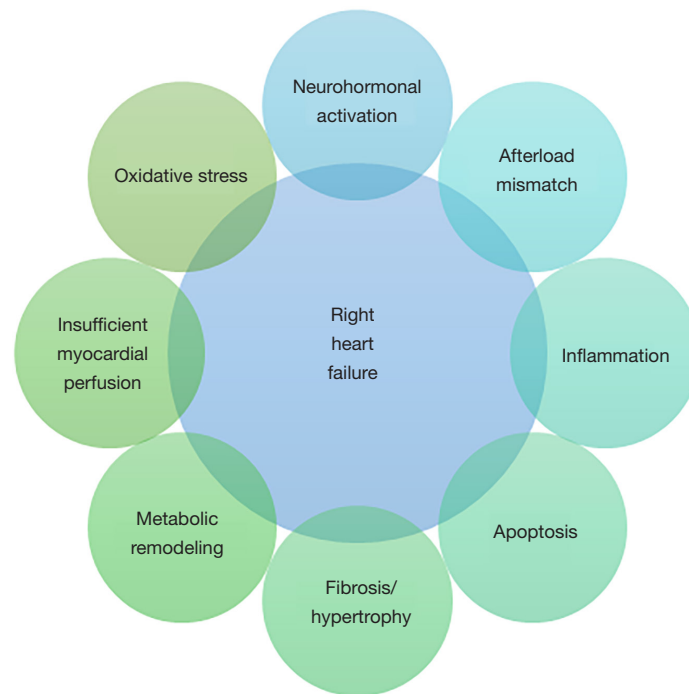
Figure 1 The Pathophysiology of Right Heart Failure (11-14).

function (11,23). Reduced RV contractile function has also been seen in animal models of ischemic LV dysfunction (12). Similar to the difference in contractile response, the RV adaptation to PAH has been evaluated in humans. Badagliacca *et al.* evaluated the morphologic adaptation of the RV in 60 patients with idiopathic PAH using echocardiography and cardiac magnetic resonance imaging. The study noted that concentric hypertrophy defined by RV mass/volume ratio >0.46 is a more favorable adaptation to increased afterload than the eccentric hypertrophy (mass/volume <0.46) (13). The authors also noted in patients with narrow QRS, RV dyssynchrony is associated with the eccentric hypertrophy pattern suggesting that the mechanical delay could be another factor that influences the RV pump function in PAH patients (14,24).

RV diastolic dysfunction:

Numerous recent studies have detailed the presence of RV diastolic dysfunction in the setting of PAH (25,26). The change in RV diastolic dysfunction may precede changes in the contractility in response to pressure overload as previously noted (27,28). The curvilinear diastolic pressure-volume relationship can be determined through multi-beat pressure-volume loops and is the optimal method to describe diastolic function. Echocardiography or cardiac magnetic resonance imaging measuring RV relaxation velocities have been proposed as a way to measure RV diastolic function, but these are load-dependent and prone to error measurement. Using a single-beat surrogate to compare 21 IPAH (20 women with an average age 45 years) and 7 controls, Rain *et al.* found significantly increased RV diastolic stiffness (β) in patients with IPAH and increased passive tension at a single myocyte level. The study also noted that the RV diastolic stiffness was significantly and inversely correlated with lower stroke volume [β –2.92 (95% CI for β –4.34 to –1.50, P=0.001)], 6–minute walk distance [β –11.8 (95% CI for β –20.0 to –3.9, P=0.009)] and closely correlated to RA pressure [β 1.01 (95% CI for β 0.52 to 1.51, P=0.001)], than the systolic properties (20). In a retrospective study by Trip *et al.*, RV diastolic stiffness was linked to clinical progression in treatment naïve patients and to those on treatment (29). Despite marked differences in resting and reserve systolic function (30), RV diastolic stiffness appears similarly impaired in IPAH and systemic sclerosis related PAH (19). These elegant studies have paved the way to increasing understanding of the role of RV diastolic dysfunction in the pathophysiology of PAH. However, its role in clinical practice is yet to be well defined at this time due to its lack of reproducibility

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and accessibility. It is important to note that although the diastolic properties are impaired as noted above, the RV findings predominantly reflect end stage systolic dysfunction (dilated RV with elevated RVEDP) and the increase in the right atrial pressure is mainly due to the tricuspid regurgitation and RV systolic dysfunction.

Left ventricular diastolic dysfunction and postcapillary pulmonary hypertension

In patients with left ventricular diastolic dysfunction, post-capillary pulmonary hypertension occurs in response to a passive increase in pulmonary pressures that results from loss of left atrial and ventricular compliance (31,32). Co-morbidities like atrial fibrillation, older age, obesity, and uncontrolled hypertension also contribute to the development of the PH (33,34). A pre-capillary component may also develop, which is associated with worse outcomes and more severe hemodynamic perturbations (35). This increase in RV afterload leads to the activation of neurohormonal and molecular pathways (36). Initially, RV diastolic impairments are evident with preserved or enhanced contractility (37). This adaptive response is associated with right ventricular hypertrophy in approximately 45% of patients with post-capillary PH (38). In the progressive stage, the RV contractility is already at maximum and with progressive increases in afterload, RV-PA uncoupling occurs (39-41). Human myocyte studies are yet to be performed to determine the contribution of contractile impairments. Additionally, in the setting of diastolic ventricular interaction and pericardial constraint, right ventricular dilation may even begin to compromise LV filling. At this phase, heart rate increases to maintain cardiac output. The increased heart rate leads to increased wall stress and oxygen demand. Long-standing high metabolic demand leads to right heart failure as the RV is unable to maintain cardiac output. In heart failure with preserved ejection fraction, the contractile impairment and the afterload mismatch will eventually lead to the development of RVD and failure (42-44). In a study of 1,454 patients with heart failure (n=399 enrolled by retrospective chart review and 219 by prospective enrollment) by Gerges *et al.* the overall prevalence of combined pre and post-capillary pulmonary hypertension (CPcPH) was noted to be 12% in the HF cohort. The study noted that the measures of the RV-PA coupling were lower when compared to isolated post capillary PH and idiopathic PAH. Additionally, CpcPH was associated with reduced median survival (54 *vs.* 102 months)

when compared to patients with post capillary PH alone (45).

Ventricular-ventricular interactions and LV impairment

The ventricles share myocardial fibers and the interventricular septum. Approximately 30–60% of RV systolic performance can be attributed to LV contraction (3,46). This systolic interaction is explained by the mechanical entrainment effect and as well as the LV contribution to coronary blood flow (and its role in maintaining systemic blood pressure) (25). With severe RV dilation and dysfunction, diastolic ventricular interdependence is exaggerated, which reduces the effective LV distending pressure (true LV preload), LV contractility and cardiac output. Given the above-mentioned dependence on LV contractility, RV contractility may therefore also decline. Evidence of chronic LV underfilling and perhaps the development of associated LV atrophy comes from observations after lung transplantation where the LV cannot accommodate a normal preload (47,48).

More details on non-invasive imaging of RV dysfunction has been discussed elsewhere in this special issue (49).

Coronary malperfusion/ischemia in advanced PAH

Under normal conditions, the right coronary artery is perfused during systole and diastole, in contrast to the LV which receives most of its perfusion during diastole. As the RV remodels in response to chronically elevated afterload, the elevation in RV wall tension and transmural pressure reduces perfusion pressure such that blood flow occurs predominantly during diastole. Malperfusion of the right coronary artery then leads to RV ischemia and an increased risk of arrhythmias and can rapidly precipitate right ventricular failure (50-52).

Diagnostic testing and principles of ICU monitoring

The initial evaluation of suspected RV failure should include basic laboratories (e.g., electrolytes, blood counts, renal function), chest X-ray, electrocardiogram, and transthoracic echocardiography. Invasive hemodynamic monitoring allows continuous monitoring of cardiac output, central venous oxygen saturation (a marker of peripheral perfusion), and estimation of fluid status by

measurement of filling pressures. Rapid identification and timely management of warning signs of imminent death such as declining central venous oxygenation, the elevation of lactate or liver enzymes, and a decline in urine output are critical. Supplemental oxygen should be provided to all patients with hypoxemia to maintain oxygen saturation >90%. In hypercapnic patients, non-invasive ventilation can be considered weighing the risks and benefits as positive pressure ventilation may further impair RV function (53,54). Intubation should be avoided if possible due to the risk of cardiovascular collapse as described below. In situations where intubation is unavoidable, preservation of systemic blood pressure is key (55,56).

Goals of therapy

(I)   Treatment of triggering factors contributing to decompensation;
(II) Fluid management;
(III) Optimize cardiac function;
(IV) Initiation or escalation of targeted PAH therapy;
(V)   Extracorporeal life support (ECLS);
(VI) Lung transplantation.

Recommendations specific to the diagnosis and treatment of RV dysfunction and failure in congenital heart disease (CHD) are outlined elsewhere in this special issue (57).

Identification and management of triggering factors

The initial evaluation of a patient with acute right ventricular failure requires the identification of a potentially reversible cause (58,59). Known triggers precipitate decompensation (*Table 1*, *Figure 2*) in approximately 20–40% of patients. Infection, dysrhythmias, development of pulmonary embolus, unanticipated withdrawal of PAH specific therapy, and dietary indiscretion are some common triggers (61,62).

Infection

Infection leading to clinical decompensation is frequently encountered in clinical practice (62). Infection is often poorly tolerated hemodynamically and a strong predictor of mortality (63). Common sources of infection include indwelling catheters and translocation of gut bacteria in conditions of low cardiac output with associated systemic venous congestion (62,64).

Atrial arrhythmias

Atrial arrhythmias including atrial fibrillation and atrial flutter may precipitate RV failure. The altered structural and electrophysiological properties of the enlarged right atrium due to hypervolemia and chronic hypoxia altering the atrial substrate have been implicated as mechanisms for the development of atrial arrhythmias. Atrial fibrillation in the setting of RV dysfunction, when the heart rate is high, the reduction in the diastolic filling time influences the ventricular filling further raising right atrial pressure (65,66). Beta-blockers and calcium channel blockers should be avoided due to negative inotropic effects (67). Medical management with antiarrhythmic drug therapy (e.g., amiodarone) or radiofrequency ablation has been used with varying success (68,69). Rapid restoration of sinus rhythm with electrical cardioversion should be considered despite varying degrees of success in achieving and maintaining sinus rhythm (68,70,71).

Preload optimization

Under normal physiologic conditions, the right atrial pressure is low from the high compliance of the RV. Systemic venous return is unimpeded and cardiac output is preserved. As RV remodeling progresses, sodium and water retention ensue, leading to systemic congestion. In cases of decompensation, patients often receive fluids due to hypotension at the time of presentation. Fluid administration often leads to an increase in right-sided filling pressure, shift of the interventricular septum to the left, and an increase in tricuspid regurgitation. The goals of management involve optimization of RV preload will reduce systemic congestion, tricuspid insufficiency, and deleterious ventricular interdependence. Effective preload reduction through diuresis will diminish ventricular interdependence and improve both RV and LV function, including response to inotropic stimulation (*Figure 2*) (72).

Diuretics remain the mainstay of therapy to relieve congestion. The intensity of diuretic therapy needs varies based on coexistent renal disease. In some clinical situations where congestion leads to impaired drug absorption and visceral edema, large doses of loop diuretics or combination of loop diuretics and thiazides may be needed to augment diuresis via sequential nephron blockade. In some cases, congestion may be refractory of medical therapy and require ultrafiltration. Sodium restriction is a common clinical

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Table 1 Factors precipitating clinical decompensation

Triggers	Diagnosis	Management strategies
Infection	Chest X-ray	Antibiotics
	Blood culture	Antibacterial/antifungal depending on the source
	Urinalysis	
Dysrhythmia		
Atrial	Electrocardiogram	Antiarrhythmic drug therapy
Ventricular	Event monitor	Ablation
Dietary Indiscretion	Clinical history	Sodium restriction to less than 2 grams
		Fluid restriction to less than 2 L per day
Ischemia		
Pulmonary embolism	D-Dimer	Anticoagulation
	CT angiogram	
	Brain natriuretic peptide	
Myocardial infarction	Troponin	
Hypoxemia/hypercarbia	Pulse oximetry	Maintain oxygenation
	Arterial blood gas	Avoid hypercarbia
		Maintain Peak Plateau pressure to less than 30 cm H_2O
		Maintain Tidal Volume 6–8 mL/kg/min
Hyper/hypothyroidism	Thyroid stimulating hormone	Thyroid supplementation
	Free T4	Radioactive Iodine (RAI)
Iron Deficiency anemia (60)	Serum iron	Oral or IV Iron supplementation
	Total iron binding capacity	
	Ferritin	
Unanticipated PAH therapy withdrawal	Clinical history	Resume treatment

practice, although no large-scale studies have demonstrated benefit from this approach (73,74).

Afterload reduction

An important mechanism to improve function in the pressure overloaded RV is to lower afterload. Reduction in RV afterload has been shown to improve cardiac function (75). The beneficial effect is through a multitude of mechanisms. (I) Reduction in RV wall tension; (II) reduced myocardial oxygen consumption (III) improved coronary macrovascular and microvascular perfusion (IV) increase in RV stroke volume 5. Improved LV filling through a reduction in RV septal shift. In patients presenting with decompensated RV failure with elevated right atrial pressure and depressed cardiac index, the use of intravenous prostacyclin analog is typically the first choice because of its rapid onset, titratability, magnitude of afterload reduction and reduction in mortality (76). In patients with newly diagnosed PAH and right heart failure, initiation of triple therapy with a prostacyclin analogue, endothelin receptor antagonist and phosphodiesterase inhibitor in combination has been shown to improve outcomes (77). In a retrospective study of 21 patients with severe idiopathic PAH who are treatment naïve upfront combination therapy with 3 agents is associated with decrease in right atrial pressure from 13±3 to 5±2 mmHg, mean pulmonary artery pressure from 60±9 to 42±5 mmHg and pulmonary vascular resistance from
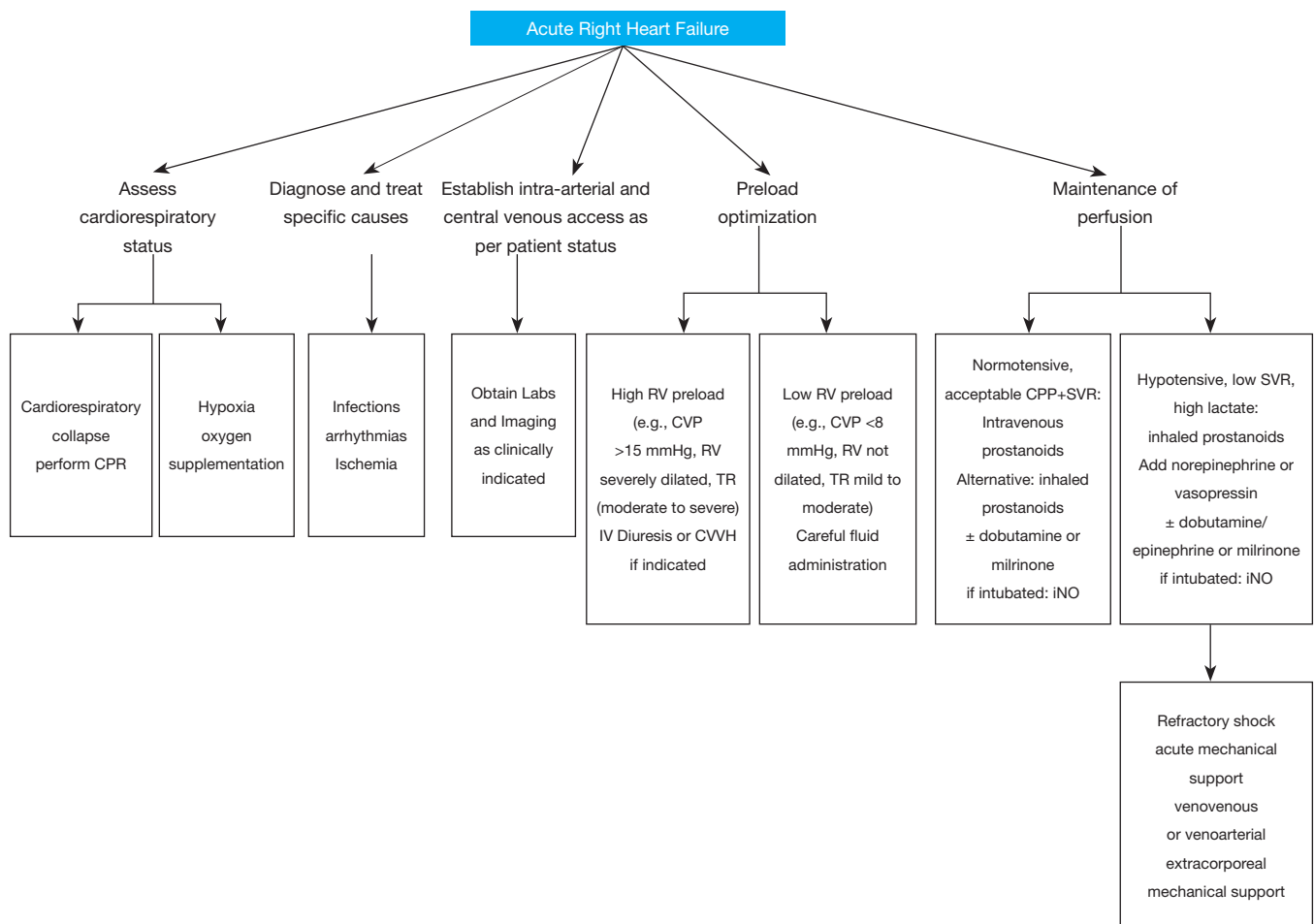
Figure 2 Algorithmic Management of acute right heart failure.

16.4±4.4 to 5.5±1.3 Wood units (74). Prostacyclin analogs are generally administered by continuous intravenous infusion. However, such therapy places a considerable burden on the patients and is associated with side effects such as site pain and bloodstream infections. The emerging use of fully implantable pumps such as the gas driven LENUS Pro pump (implanted in the abdominal wall connected to the tunnel catheter and terminating in the right atrium) improves the subject comfort with a favorable safety profile (78,79). Adjunctive use of corticosteroids and cyclophosphamide in addition to pulmonary vasodilators may improve outcomes in PAH secondary to systemic lupus erythematosus (80).

Augment contractility

In patients presenting with low output RV failure, inotropic

therapy may be needed to improve cardiac output and restore ventriculo-arterial coupling without increasing RV afterload. Inotropes like dobutamine, milrinone, and levosimendan (*Table 2*) have been used in various preclinical and clinical studies (*Figure 2*) (81,82). β1 adrenergic agonist remains the inotropic agents of choice in most practices. Milrinone, a phosphodiesterase inhibitor and "inodilator" increases myocardial contractility, reduces systemic afterload, and reduces pulmonary vascular resistance (83). However, its use may be limited due to systemic vasodilation and resultant hypotension. Levosimendan was found to be more effective than dobutamine in animal models of right heart failure by optimizing hemodynamics and restoring RV-PA coupling (81,84-87). In a small placebo-controlled pilot study of 24 patients (Levosimendan n=15; placebo, n=9) that included patients with PAH, the

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Table 2 Overview of inotropes and vasopressors

Drug	C.O	PVR	SVR	Heart Rate
Dobutamine	↑↑	↓	↓	↑
Milrinone	↑↑	↓	↓	
Levosimendan	↑↑	↓	↓	
Dopamine	↑	↑	↑	↑↑
Epinephrine	↑↑	↑/↓	↑↑	↑↑
Norepinephrine	↑	↑	↑↑	↑
Vasopressin	↑/↓	↑/↓	↑↑	

use of Levosimendan was associated with a mean decrease of 12%±9% in pulmonary vascular resistance and a change in mean pulmonary arterial pressure was a decrease of 14%±4% at 24 hours when compared to placebo (88). Similar results were noted in a prospective single arm study performed in 9 patients with idiopathic PAH and associated right heart failure (89). Future larger studies are needed to determine the safety and efficacy in levosimendan in this patients with PAH who experience higher morbidity and mortality (90).

Maintain right ventricular perfusion

Many patients may present with low systemic vascular resistance or it may decrease during therapy. This is often accompanied by the development of multiorgan failure and RV ischemia. A primary goal of increasing systemic vascular resistance is to restore perfusion pressure. Restoration of perfusion pressure will increase LV afterload, LV contractility and thus RV contractility. This eventually facilitates diuresis. The use of vasopressors such as norepinephrine, phenylephrine, or vasopressin to increase systemic vascular resistance and thus augmenting aortic root pressure has been used with varying success as they reduce RV ischemia (*Table 2*, *Figure 2*) (58,86,91). The use of norepinephrine has been shown to restore normal perfusion pressure and, in some cases, also improve right ventricular function and right ventricular-pulmonary arterial coupling (92,93).

Management of pericardial effusion in PAH

The development of pericardial effusion in a patient with PAH signifies poor prognosis. Its presence signifies an element of right heart failure as it is associated with higher right atrial pressure than those without the effusion.

Currently there are no guidelines, but available evidence suggests conservative management for those with small to moderate effusions and treatment of large effusions is controversial. The European executive summary in 2004 suggested that treatment of pericardial effusion in the setting of tamponade is recommended (94,95).

Ventilation strategies in PAH

Pathophysiological insults such as apnea and hypoventilation, fluctuating blood pressure, increased sympathetic activity arising from fluid shifts, changes in preload, hypoxia, and hypercarbia exacerbate PVR, which can worsen RV failure (96,97). Oxygen is a potent pulmonary vasodilator and high flow oxygen has been shown to increase cardiac index and reduce PVR in patients with pulmonary hypertension (98). Intubation and mechanical ventilation should be avoided when possible because they increase RV afterload and decrease right ventricular stroke volume which may precipitate a cardiovascular collapse (96,97). When intubation is unavoidable, maintaining peak plateau pressures to less than 30 cmH_2O, tidal volume at 6–8 mL/kg/min and auto-PEEP are essential to minimize the adverse effects on RV afterload and contractile function (99).

Pulmonary artery denervation

The sympathetic nervous system and the activation of renin-angiotensin axis contribute to the development and progression of PAH (100-102). In the PADN-1 study, 21 patients with idiopathic PAH, 13 patients received pulmonary artery denervation procedure and 8 served as controls. Pulmonary artery denervation has been shown to improve functional capacity in the form of significant improvement in 6 min walk distance (324±21 to 491±38 m,

P<0.006) and hemodynamics in patients not responding to medical therapy (103). It is important to note that data on the efficacy of pulmonary artery denervation are lacking in patients with acute RV failure. Existing evidence suggests the beneficial effects of pulmonary artery denervation in improving hemodynamics, cardiac function and in attenuating progressive remodeling of the pulmonary arteries and RV (104). The ongoing randomized multicentered sham-controlled study (Safety and Efficacy of Pulmonary Artery Denervation in Patients with Pulmonary Arterial Hypertension (PADN-CFDA) which aims to enroll 128 patients will provide more definitive safety and effectiveness data (NCT03282266).

Atrial septostomy

The first atrial septostomy as a treatment for PAH was performed by Rich and Lam in 1983 (105). The intervention involved creating a hole between the right and left atria thereby allowing shunting of blood from right to left and thus reducing wall stress. The shunting of blood leads to a decrease in arterial oxygen saturation and also increases in left ventricular preload and cardiac output. The procedure typically reserved for select patients with right ventricular failure and syncope (106,107). In a recent systematic review and meta-analysis of 16 studies comprising 204 patients by Khan et al, atrial septostomy led to a statistically significant reduction in right atrial pressure and an increase in cardiac index. The pooled incidence of short (<30 days) and long term (>30 days) procedural related mortality was noted to be 14.6 and 37.7% (108). The procedure is limited by systemic arterial oxygen desaturation, the potential for paradoxical embolic events and procedure-related mortality.

Mechanical support of the failing RV

Despite maximal medical management, right heart failure can be irreversible. The use of mechanical circulatory support is gaining traction due to its ability to reduce right ventricular preload and afterload while providing pump function. These changes also lead to a reduction in tricuspid regurgitation and improvement in left ventricular filling due to less septal bowing. The exact timing of initiation of mechanical support is a matter of debate. In conditions of medically refractory cases of right heart failure, it is important to involve a multidisciplinary team including cardiologists, pulmonologists, cardiac surgery and intensivists to determine the need for mechanical

support. The most important consideration during the evaluation should include patients bridging potential to a more durable therapy such as lung transplantation (109). Contraindications to mechanical circulatory support include the inability of the patient to be on anticoagulation, irreversible neurologic injury, and futile cases in which the patient is not eligible for transplant. The field of mechanical support witnessed major advances in the last decade. Improvement in a pump design with less thrombosis and heating issues, newer oxygenator designs that can be used for long periods with lower resistance, development of pumpless oxygenators, heparin-coated tubing circuits requiring less systemic heparinization have allowed for increased utilization of mechanical circulatory support (110,111). Recently, the ARIA Pulmonary Balloon Pump with first-in-man experience (United States Patent 9039925) has been designated as Breakthrough Device by the FDA to reduce RV afterload by increasing pulmonary artery compliance.

Extracorporeal Membrane Oxygenation (ECMO) and ECLS

ECLS may be considered as a bridge to lung transplantation or as a bridge to recovery in treatment naïve or non-optimized patients (*Figure 2*) (111). Modes of support include Venovenous Extracorporeal membrane oxygenation (VV-ECMO) or Venoarterial Extracorporeal membrane oxygenation (VA-ECMO). In cases where oxygenation is a limiting factor VV-ECMO is used. In patients with RV failure from PAH in whom pump function is compromised VA-ECMO is used for support. Alternative modes of support include Arteriovenous Nova lung and Pulmonary Artery-Left Atrium Novalung, Hechingen, Germany. These are pumpless devices with a low resistance diffusion membrane. They are primarily useful to remove carbon dioxide but are limited in their ability to provide oxygenation support due to restricted blood flow through the device from low cardiac output or small cannula sizes. In patients following lung transplantation, pulmonary vascular resistance improves rapidly and leads to an increase in cardiac output and left ventricular filling. In such a situation the LV may not handle the high normal cardiac output that occurs in the immediate post-operative period. In a study of 50 patients (23 *vs.* 17 *vs.* 13) with severe PAH who received bilateral lung transplant with post-operative ECMO use compared to patients who received heart-lung transplant and bilateral lung transplant and without post-

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operative ECMO support, the use of ECMO has been used to reduce the development of grade III primary graft dysfunction as noted by reduction in primary graft scores and improvement in 90 day survival (100% *vs.* 82 *vs.* 85%) (110,112-114).

Right ventricular assist devices (RVAD)

RVAD serves to unload the RV leading to favorable supply-demand profile. The use of RVAD in patients with PAH is not considered an ideal treatment strategy as it does not address pressure overload which is the main pathophysiologic mechanism that leads to RV failure. At this time the use of RVAD in PAH is limited to case reports (115). Different types of RVAD exist at this time. They can be surgically or percutaneously implanted. They divert blood from Inferior vena cava or Right atrium to Pulmonary artery or left atrium bypassing the RV. The CentriMag pump (St. Jude, Minneapolis, Minnesota), or Impella RP catheter (Abiomed Inc, Danvers, MA) is such a type of device. Use of RVADs may also be limited by the risk of pulmonary edema in patients with concomitant LV diastolic dysfunction. This associated increase in pulmonary and capillary pressures may also predispose to pulmonary hemorrhage. The role of partial support devices and lower flow rates is physiologically intriguing but requires further study (116).

Lung transplantation and heart-lung transplantation in PAH

Bilateral lung transplantation remains the mainstay of therapy in cases of medically refractory right heart failure in PAH. Patients who are at high risk are recommended to be considered for lung transplantation. The European Respiratory Society pulmonary hypertension 2015 guidelines categorize patients as high risk if the mortality exceeds 10% on the current treatment over 1 year (73,112,117-121). In an effort to decrease the death rate on the transplant waiting list, a lung allocation score has been implemented in the United States in May 2005 and subsequently revised in 2015 (122). The revised score allowed modifications to the existing variables and added relative weight to the variables used to predict the mortality risk (123). The allocation score ranges from 0 to 100 and it is calculated for each registered candidate age >12 years. The higher score corresponds to higher chances of receiving an organ. It is important to recognize that the LAS may

not reflect the severity of PAH (124-126). Approximately 1.5% of patients receive lung transplants for IPAH between January 1995 to June 2018 (127). Patients who received lung transplants between 1990 and 2013 for PAH, the 3-month mortality is reported to be 23%. In the same era, the patients who survived to 1 year, the conditional median survival was noted to be 10 years (128).

Conclusions

The development of right heart failure is associated with poor clinical outcomes in patients with PAH. Available therapies are largely supportive and do not directly target the right heart remodeling and failure. The use of extracorporeal membrane oxygenation as a bridge to transplantation has improved survival for selected patients. There remains a considerable need for studies that provide an improved understanding of the pathophysiological mechanisms involved in right heart remodeling.

Acknowledgments

Footnote

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