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STATE-OF-THE-ART PAPER

Medical and Surgical Treatment of Acute Right Ventricular Failure

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Acute right ventricular (RV) failure is a frequent and serious clinical challenge in the intensive care unit. It is usually seen as a consequence of left ventricular failure, pulmonary embolism, pulmonary hypertension, sepsis, acute lung injury or after cardiothoracic surgery. The presence of acute RV failure not only carries substantial morbidity and mortality, but also complicates the use of commonly used treatment strategies in critically ill patients. In contrast to the left ventricle, the RV remains relatively understudied, and investigations of the treatment of isolated RV failure are rare and usually limited to nonrandomized observations. We searched PubMed for papers in the English language by using the search words right ventricle, right ventricular failure, pulmonary hypertension, sepsis, shock, acute lung injury, cardiothoracic surgery, mechanical ventilation, vasopressors, inotropes, and pulmonary vasodilators. These were used in various combinations. We read the abstracts of the relevant titles to confirm their relevance, and the full papers were then extracted. References from extracted papers were checked for any additional relevant papers. This review summarizes the general measures, ventilation strategies, vasoactive substances, and surgical as well as mechanical approaches that are currently used or actively investigated in the treatment of the acutely failing RV. (J Am Coll Cardiol 2010;56:1435–46) © 2010 by the American College of Cardiology Foundation

Right ventricular failure (RVF) in the intensive care unit (ICU) remains a formidable clinical challenge. Significant comorbidities and hemodynamic instability are often present, and common therapeutic interventions may have deleterious hemodynamic effects. The importance of the right ventricle (RV) is reflected in a recent publication from a National Heart, Lung, and Blood Institute working group, which suggested that studying the RV should be a priority in cardiovascular research (1). Pathogenesis, physiology, symptoms, and diagnosis of RVF have recently been reviewed in detail (2–5) and are beyond the scope of this review. We briefly review the causes, pathophysiology, and diagnosis of acute RVF in the ICU and focus on the general measures, vasoactive substances, and surgical and mechanical approaches used in the treatment of the acutely failing RV.

Etiology and Pathophysiology of Acute RVF

RVF results from any structural or functional process decreasing the ability of the RV to pump blood into the pulmonary circulation. Causes include alterations in pre-load and diastolic filling, decreases in inotropy, and increases in afterload (3) (Table 1). RV pre-load and diastolic filling affect myocardial fiber length and contractility via the Frank-Starling mechanism, and both increases as well as decreases in pre-load may negatively affect RV function (3). The most common etiologies of RVF in the ICU are left ventricular (LV) failure, RV ischemia, acute pulmonary embolism, pulmonary hypertension (PH), sepsis, acute lung injury, cardiac tamponade, and post-cardiothoracic surgery states. Arrhythmias and pericardial, congenital, and/or valvular heart disease may also contribute (3). Acute RVF is also observed during acute chest syndrome in patients with sickle cell disease (6). In the majority of these conditions, RV dysfunction prognosticates worse outcomes (5–8). The pathophysiology of acute RVF in critically ill patients is

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Abbreviations and Acronyms

BAS = balloon atrioseptostomy
CO = cardiac output
HPV = hypoxic pulmonary vasoconstriction
ICU = intensive care unit
iNO = inhaled nitric oxide
LV = left ventricular
LVAD = left ventricular assist device
PA = pulmonary artery
PAC = pulmonary artery catheter
PAH = pulmonary arterial hypertension
PAP = pulmonary artery pressure
PDE = phosphodiesterase
PH = pulmonary hypertension
PVR = pulmonary vascular resistance
RAP = right atrial pressure
RV = right ventricle
RVEF = right ventricular ejection fraction
RVF = right ventricular failure
V_T = tidal volume

complex and includes ischemia and/or arrhythmias, endotoxin- and cytokine-induced decreases in systolic and diastolic LV and RV function, as well as afterload increases from endothelial dysfunction, hypoxic pulmonary vasoconstriction (HPV), and pulmonary microthrombi and/or thromboemboli (1,5,8–11). LV dysfunction, either cytokine-induced or due to ischemia or nonischemic cardiomyopathies, induces RV dysfunction via afterload increase, and/or displacement of the interventricular septum toward the RV with subsequent impairment of RV filling (known as ventricular interdependence). Hypovolemia and inflammation-induced capillary leak alter RV function by decreasing pre-load (8,9,11). Important interactions between inflammation, sepsis, pulmonary endothelial dysfunction with associated PH, and RV and LV dysfunction have recently been reviewed (8). Proinflammatory cytokines like tumor necrosis factor-α directly suppress myocardial contractility (10). Heightened oxygen demands from increased heart rate, afterload, and wall tension, combined with decreased coronary perfusion from hypotension, result in subendocardial (1,2) and myocardial RV ischemia (8). Mechanical ventilation, certain drugs, and volume overload may further alter RV function (3,4,12,13). These pathogenetic entities (Fig. 1) provide the rationale for the treatment strategies outlined in this review.

Diagnosis of RVF in the ICU

Although no specific biomarker for RVF exists, serum chemistries aid in prognostication (Table 2) (14–20). Electrocardiography, although specific, lacks sensitivity (2,3,12). Once chest X-ray or CT demonstrates signs of RV dysfunction, RVF is usually advanced and associated with high mortality (Fig. 2).

Pulmonary artery catheters (PACs) and transthoracic or transesophageal echocardiography remain the most reliable methods to diagnose RVF and evaluate the treatment response in the ICU. Although PACs do not affect outcomes in acute lung injury (21), they provide crucial hemodynamic information in acute RVF, particularly when used in combination with echocardiographic parameters of RV function and indexes of tissue oxygenation. In addition to directly measuring pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure, PACs allow measurement and/or calculation of additional parameters like right atrial pressure (RAP), cardiac output (CO), mixed venous oxygen saturation, pulmonary vascular resistance (PVR), and RV stroke work index (Table 2) (22–27). PACs also allow evaluation of the response to pharmacologic therapies and drug titration to specific end points. Importantly, a decrease in PAP may reflect decreasing right ventricular ejection fraction (RVEF) and worsening RVF (28). Although a chronically hypertrophied RV usually tolerates a significantly elevated PAP, a RV without pre-existing hypertrophy will not be able to generate a systolic PAP >50 to 60 mm Hg.

The critical role of bedside echocardiography, especially when combined with specific markers of RV dysfunction, such as tricuspid annular plane systolic excursion index (29), tissue Doppler (30), and Tei index (31), cannot be overemphasized (Table 2) (3,32).

Whether newer predictors of fluid responsiveness (e.g., variations in pulse pressure, systolic blood pressure, or stroke volume) (33) can be of merit in isolated RVF needs further study. In studies of various forms of shock, these are promising new techniques for patients in sinus rhythm and on mechanical ventilation (33). Mechanical insufflation increases intrathoracic pressures, decreases RV pre-load, and increases RV afterload, resulting in diminished RV and LV stroke volumes. These changes are more pronounced in patients whose RV operates on the steep portion of the Starling curve, making dynamic changes in arterial waveform a sensitive indicator of RV pre-load dependence (33,34). Passive leg raising may better predict fluid responsiveness in patients with arrhythmias and spontaneous respirations (34). Cardiac magnetic resonance imaging is the most sensitive method to assess RV function (1–3,12); however, due to logistical issues, it is rarely used for critically ill patients.

Treatment of Acute RVF

Treatment strategies for acute RVF in the ICU are derived from the pathogenetic entities outlined previously. Major components include volume optimization, RV inotropy enhancement, and RV afterload reduction, the latter being achieved through multiple interventions (Fig. 3). These goals are achieved through careful volume management, vasopressor and/or inotrope therapy, selective pulmonary vasodilators, surgical and/or mechanical interventions, and, if possible, specific measures directed against the underlying etiology (Fig. 4).

General supportive ICU care. Infection prevention measures, thromboembolism and peptic ulcer prophylaxis, early nutritional support, glucose control, and (in stable mechanically ventilated patients) daily interruptions of sedation combined with spontaneous breathing trials should be applied to all patients with acute RVF. The optimal hemoglobin level for patients with acute RVF remains to be

Table 1 Causes of Acute RV Failure in the Intensive Care Unit

Left ventricular dysfunction	Most common cause of right heart failure RV co-involvement in structural or ischemic heart disease or indirect RV dysfunction due to ventricular interdependence, pulmonary venous congestion, and/or arrhythmias
RV ischemia (via negative effects on inotropy and/or relaxation or via arrhythmias)	RV infarction Relative RV ischemia secondary to RV pressure or volume overload
Afterload increase (endothelial dysfunction, vasoconstriction, and/or mechanical obstruction)	Pulmonary arterial hypertension and secondary forms of PH Hypoxic pulmonary vasoconstriction Post-cardiothoracic surgery (CABG, corrective surgery for CHD, heart/lung transplantation, pneumonectomy) Pulmonary embolus Pulmonary microthrombi (sepsis and acute lung injury) Pulmonary stenosis/RV outflow tract obstruction Acute chest syndrome in sickle cell disease Mechanical ventilation
Pre-load decrease (via effects on RV fiber length and contractility)	Hypovolemia/capillary leak Superior vena cava syndrome Tricuspid stenosis Cardiac tamponade (inhibition of diastolic filling) Mechanical ventilation
Intrinsic myocardial disease	Cardiomyopathies Arrhythmogenic RV dysplasia Sepsis (cytokine-induced myocardial depression)
Congenital and valvular heart disease	Ebstein's anomaly Tetralogy of Fallot Transposition of the great arteries Atrial septum defect Anomalous pulmonary venous return Tricuspid regurgitation Pulmonary regurgitation Mitral valve disease
Pericardial disease (via negative effects on diastolic filling)	Constrictive pericarditis
Arrhythmias	

CABG = coronary artery bypass grafting; CHD = congenital heart disease; PH = pulmonary hypertension; RV = right ventricular.

determined. Although ICU patients usually benefit from a conservative transfusion strategy (35), patients with shock or heart failure may require higher hemoglobin levels (36,37). This might be the case for patients with acute RVF as well. Clearly, significant anemia in the setting of decreased tissue oxygenation should be corrected. Sodium restriction (in volume overload states) and daily monitoring of body weight and volume status are indicated.

Treatments that attenuate HPV, optimize volume status, and target arrhythmias. Adequate oxygenation is of utmost importance to avoid afterload increases due to HPV. We therefore aim for oxygen saturations of ≥92%. As RV function is highly volume dependent, a careful balance between optimized pre-load and decreased afterload is essential. If pre-load is too low, RVEF will not be adequate. However, too much pre-load will cause the intraventricular septum to shift leftward, decrease LV output, and cause hypotension through ventricular interdependence, especially in the setting of high intrathoracic pressures or pericardial disease (2,8). Therefore, careful administration of fluid boluses, used in conjunction with noninvasive or invasive assessment of CO, is recommended. Vigorous fluid administration may be detrimental and should be discouraged (2). Diuretics are indicated for volume overload. Due to its potential for greater weight and fluid loss than intravenous diuretics, venovenous ultrafiltration is increasingly used for decompensated *left* heart failure (38). Whether this represents a feasible option in diuretic-resistant right heart failure needs further study. As the RV is extremely susceptible to alterations in cardiac rhythm and ventricular synchrony (39), restoration of sinus rhythm and/or atrioventricular synchrony makes sense, but few studies have focused on this matter in acute RVF specifically (2,3). Clearly, hemodynamically significant bradycardias or tachyarrhythmias should be corrected. Digoxin marginally improves CO in patients with severe PH in the short term (40). However, due to potential side effects and a narrow therapeutic window, routine use is discouraged (2,12). Beta-blocking agents and angiotensin-converting enzyme inhibitors improve RV hemodynamics in patients with biventricular failure and have theoretical benefits in isolated RVF (41,42), but their role in the latter is poorly studied.

Strategies that avoid negative effects of mechanical ventilation on RV pre-load and afterload. Due to potential adverse hemodynamic effects, mechanical ventilation needs to be administered with caution and expertise. Higher tidal volume (V_T) and positive end-expiratory pressure may increase PAP and RAP, worsen tricuspid regurgitation, and increase RV afterload (13). In addition, positive end-expiratory pressure may decrease pre-load by diminishing venous return. Therefore, the lowest V_T, plateau pressure, and positive end-expiratory pressure needed to provide adequate ventilation and oxygenation should be used (43,44). Lower V_T may also decrease cytokine-induced

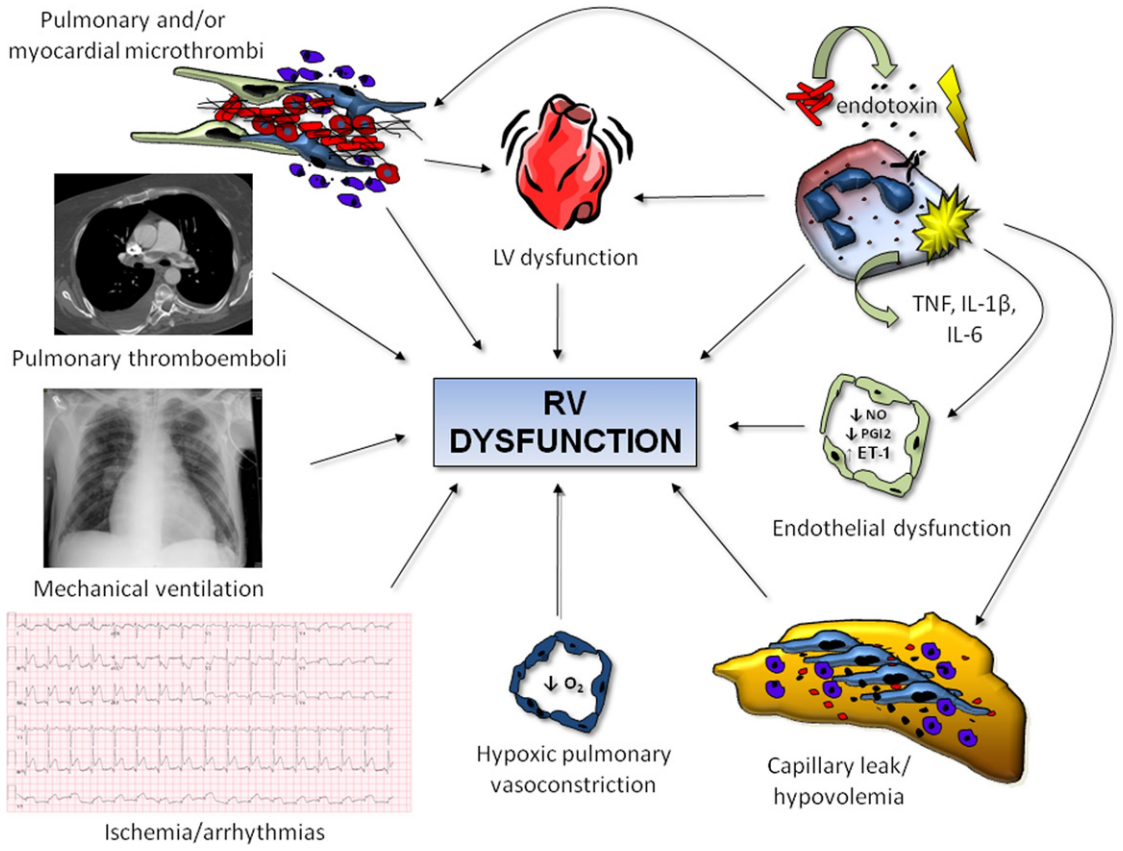

Figure 1 **Mechanisms of RV Dysfunction in Critically Ill Patients**

Right ventricular (RV) dysfunction occurs directly due to cardiodepressant effects of proinflammatory cytokines, cardiac microthrombi, and ischemia and/or arrhythmias or indirectly due to left ventricular (LV) dysfunction, afterload increases from endothelial dysfunction, hypoxic pulmonary vasoconstriction, pulmonary emboli, and/or pulmonary microthrombi, as well as pre-load decreases (induced or aggravated by capillary leak syndrome). Mechanical ventilation contributes to RV dysfunction by negatively affecting pre-load and/or afterload. Endotoxin and proinflammatory cytokines negatively affect RV function on several levels. ET = endothelin; IL = interleukin; NO = nitric oxide; O_2 = oxygen; PGI2 = prostacyclin; TNF = tumor necrosis factor.

endothelial dysfunction (43). However, because permissive hypercapnia can increase PAP and worsen RVF through vasoconstriction, excessive hypercapnia should be avoided (12,45). Hyperventilation, on the other hand, attenuates acidosis-induced vasoconstriction and decreases PAP (46). Hyperventilation can be used to lower PAP acutely, but should not be performed at the expense of a high V_T. Because increases in respiratory rate can cause dynamic hyperinflation and increased intrathoracic pressures, airway pressures and flow-time loops should be watched closely. Prone ventilation, although not affecting mortality in acute lung injury, may unload the RV through effects on airway pressure and improved alveolar ventilation (47). The effects of high-frequency oscillatory ventilation on RV function are poorly defined, although decreases in CO are described (48,49). Although transient improvements in oxygenation may also be achieved with recruitment maneuvers, these may cause decreased venous return and hypotension (50) and should therefore only be used with extreme caution when significant hypoxemia is present.

Strategies that improve RVEF, increase RV perfusion pressure, and minimize tachyarrhythmias and afterload. Inotropes improve cardiac contractility and CO by increasing cyclic adenosine monophosphate. Vasopressors increase RV perfusion pressure, thereby attenuating subendocardial ischemia. All inotropes concomitantly target the left ventricle (a desired effect in LV failure–induced RVF).

Dobutamine, the inotrope traditionally used in cardiac pump failure, works through β_1-receptor–mediated increases in myocardial contractility. Concomitant β_2 stimulation induces vasodilation and decreases afterload. In acute PH, low-dose dobutamine (2 to 5 μg/kg/min) increases CO and decreases PVR, whereas higher doses (5 to 10 μg/kg/min) only induce tachycardia and increase myocardial oxygen consumption without further improvements in PAP (12,51,52). In an animal model of acute RVF, dobutamine was superior to norepinephrine in improving RV function, likely due to superior inotropic properties and the absence of peripheral vasoconstriction (52). In acute and

Table 2 Overview of Serum Markers, Hemodynamic Parameters, and Echocardiographic Variables Used in the Diagnosis of Acute RV Failure in the Intensive Care Unit

BNP, NT-proBNP, troponin	Increase in LV dysfunction, renal failure, sepsis, but significant RV dysfunction less likely if values normal BNP predicts survival in acute RVF in PAH; increased levels (1,415 pg/ml vs. 628 pg/ml) associated with increased mortality (14) BNP >168 pg/ml identifies RV dysfunction in CTEPH patients with 88% sensitivity, 86% specificity (15) Risk stratification in patients with subtle RV dysfunction during acute, nonmassive PE (16,17)
Sodium	≤136 mmol/l predicts RVF and increased risk of death in PAH patients (18) Predicts survival in PAH patients with acute RVF; decreased levels associated with increased mortality (14)
Creatinine	Predicts survival in PAH patients with acute RVF; increased levels (1.5 mg/dl vs. 1.25 mg/dl) suggest increased mortality (14)
C-reactive protein	Predicts survival in PAH patients with acute RVF; increased levels (4 mg/dl vs. 1.2 mg/dl) associated with increased mortality (14)
Transaminases	Increase reflects hepatic congestion and/or hypoperfusion due to compromised LV function and forward failure Prognostic value not established
Growth differentiation factor-15	Stress responsive, transforming growth factor-beta–related myocardial cytokine Independent predictor of long-term mortality in acute PE; increased value of established prognostic markers (19) Risk stratification in PAH patients; increased levels associated with increase in markers of RV dysfunction (20)
Right atrial pressure, cardiac index	Strongest hemodynamic prognosticators in PAH (22); more accurate reflection of RV function than PAP Right atrial pressure ≥15 mm Hg, cardiac index ≤2 l/min/m^2 indication for transplantation referral in PAH (22)
PVR	Differentiates whether increased afterload is due to PAH, secondary PH, or hyperdynamic states (23) PVR >1,000–1,200 dynes·s·cm^{-5}: contraindication for atrial septal defect closure (24), balloon atrial septostomy in severe PAH (22), pulmonary endarterectomy in CTEPH (22)
Right ventricular stroke work index	Prognosticates RVF after LVAD placement and transplantation-free survival in dilated cardiomyopathy (25,26) Easily obtained via PAC; may allow for further prognostication in acute RVF, but further studies needed
Pulmonary artery impedance	Evaluates and integrates PVR and pulmonary artery elastance, flow, pulsatile pressure, and wave reflection (27) Superior and more complete method of RV afterload assessment than PVR alone (27)
RVEF, RA and RV volume, tricuspid regurgitation, ventricular septal shift, pericardial effusion	Established and readily available markers of RV dysfunction (3) Limited by marked pre-load dependence (3)
Right ventricular systolic pressure	Calculated from tricuspid regurgitant jet and RAP; cannot be obtained if no regurgitant jet identified Off by >10 mm Hg in almost 50% of measurements in PAH patients (32)
TAPSE, tissue Doppler, Tei index	More specific and less pre-load–dependent than traditional echocardiographic markers (29–31) Established prognostic value of TAPSE in PAH patients; significantly decreased survival if TAPSE <1.8 cm (29)

For a more detailed description of assessment of RV function, please see Haddad et al. (3). Several of the listed PAC- and echocardiography-derived parameters, as well as additional advanced measurements, can be determined by cardiac magnetic resonance imaging.

BNP = B-type natriuretic peptide; CTEPH = chronic thromboembolic pulmonary hypertension; LV = left ventricular; LVAD = left ventricular assist device; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PAC = pulmonary artery catheter; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PE = pulmonary embolism; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RA = right atrial; RV = right ventricular; RVF = right ventricular failure; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion.

chronic PH, the combination of dobutamine and inhaled nitric oxide (iNO) improved CO, decreased PVR, and increased the Pao_2/Fio_2 ratio (51,53). However, dobutamine may cause hypotension through peripheral β_2 stimulation, sometimes requiring the addition of a peripheral vasoconstrictor (e.g., norepinephrine) (12).

Milrinone, a selective phosphodiesterase (PDE)-3 inhibitor, also exerts inotropic and vasodilatory properties. Although decreasing PVR and increasing RVEF in acute and chronic PH, use is limited by systemic vasodilation and hypotension (54). Like dobutamine, milrinone can be combined with iNO to augment pulmonary vasodilation while minimizing hypotension and tachyarrhythmias (55). Inhaled milrinone minimizes hypotension but maintains beneficial effects on PVR and RVEF (56) and even attenuates pulmonary endothelial dysfunction (57). However, due to relatively selective PDE-5 expression in the lung and hypertrophied RV, PDE-5 inhibitors may be more effective and more pulmonary artery (PA) and RV specific than PDE-3 inhibitors (58,59).

Norepinephrine increases inotropy through β_1 agonism. Concomitant stimulation of α_1-receptors increases RV perfusion pressure and CO, as seen in a model of acute pulmonary embolism–induced RVF (60). Concerns about increases in PVR and PAP exist, but were not observed in that particular study. Norepinephrine may therefore be beneficial in hypotensive and tachycardic patients not tolerating dobutamine, but the latter remains the preferred inotrope for PH and/or acute RVF without significant hypotension (12,52).

Levosimendan sensitizes cardiac troponin C to the effects of intracellular calcium, thereby increasing contractility without increasing oxygen consumption. Levosimendan also has global vasodilatory and anti-ischemic properties that are mediated by activation of adenosine triphosphate-sensitive potassium channels in mitochondria of vascular smooth muscle cells (61) and by endothelin-1 inhibition (62). The drug increases CO, decreases PVR, and improves regional perfusion, together with a protective effect against endothelial dysfunction by inhibiting expression of soluble adhesion molecules (63). Levosimendan attenuates injury-induced RV and LV dysfunction and increases regional blood flow and global oxygen transport (64). Although sharing the vasodilatory effects of dobutamine and milrinone, it seems to have more specific pulmonary vasodilatory properties. Animal studies of RVF demonstrated decreased

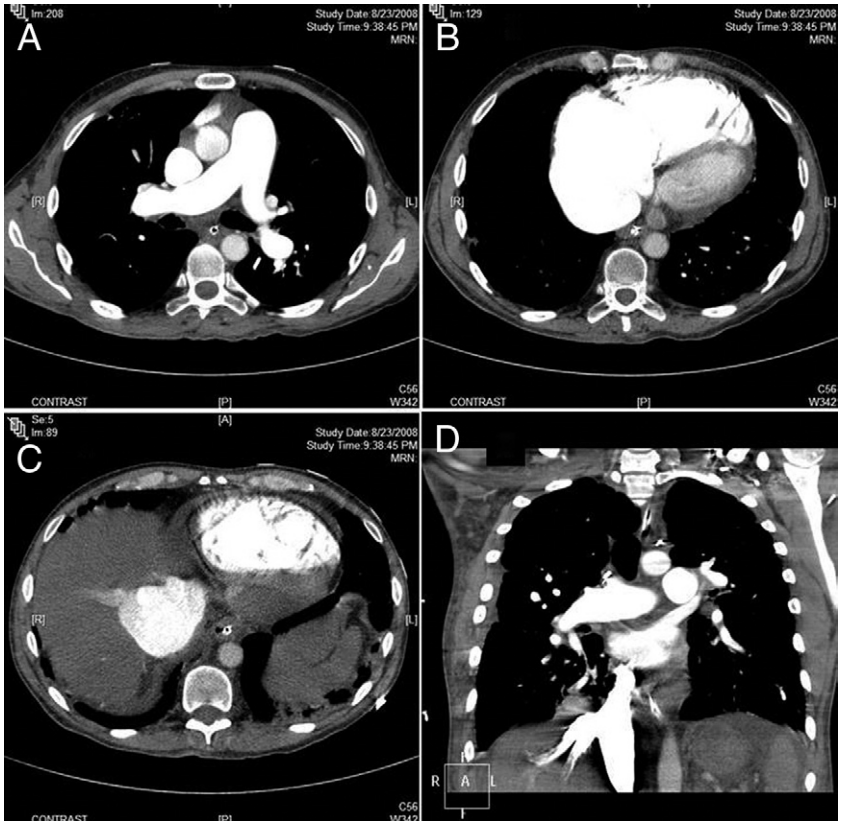

Figure 2 **Computed Tomography Imaging of RVF**

(A to C) A 55-year-old male patient with idiopathic pulmonary arterial hypertension presenting with right ventricular failure (RVF) due to acute respiratory distress syndrome from aspiration pneumonia. Computed tomography shows dilated pulmonary arteries **(A)**, massive right atrial and right ventricular dilation **(B)**, and retrograde flow of contrast into the inferior vena cava **(C)**. **(D)** A 56-year-old man with fibrocystic sarcoid presenting with RVF due to acute hypercarbic and hypoxic respiratory failure from community-acquired pneumonia. Retrograde flow of contrast into the inferior vena cava and hepatic veins is demonstrated. These findings suggest advanced RVF and high mortality.

afterload and increased RV contractility with levosimendan superior to those of dobutamine (65,66). However, use can be limited by hypotension and arrhythmias (especially with bolus dosing) (67), and further studies in acute RVF are needed before its use can be recommended. Levosimendan is currently approved for use in Europe, but not in the U.S. **Strategies that decrease RV afterload by attenuating cytokine production, endothelial dysfunction, HPV, and microthrombi and that may directly improve RVEF.** Because the RV poorly tolerates afterload increases and because PH is a common cause of RVF, pulmonary vasodilators represent cornerstones of RVF treatment. All systemically administered pulmonary vasodilators can cause hypotension and need to be initiated cautiously.

iNO mediates pulmonary vasodilation by increasing cyclic guanosine monophosphate. Rapid inactivation by hemoglobin in the pulmonary capillaries prevents systemic vasodilation. Effects are limited to ventilated areas of the lung, therefore attenuating HPV, decreasing PAP and PVR, and improving oxygenation without increasing intrapulmonary shunt fraction (unlike systemically administered pulmonary vasodilators, which may aggravate hypoxemia in patients with lung disease) (68,69). In addition, iNO decreases inflammatory cytokine production (12,70,71). In 26 ICU patients with acute RVF, 14 patients experienced significant increases in CO and oxygenation as well as decreases in PVR with iNO (35 ppm) (72). iNO use for PH and/or RVF in patients undergoing orthotopic heart or lung transplantation was associated with lower mortality compared with its use in cardiac surgery or medical patients with hypoxemia (73). Improvements in PVR and RV dysfunction were confirmed in another study of heart transplant recipients (74) and in patients with PH after mitral valve replacement (75). Use of iNO is limited by potential methemoglobinemia, production of reactive nitrogen species, and rebound PH after rapid discontinuation (12,70,76). iNO may be of particular benefit when combined with inodilators (dobutamine or milrinone) (77).

Prostacyclins activate cyclic adenosine monophosphate, resulting in pulmonary and systemic vasodilation and inhibition of platelet aggregation. Although improving end points in pulmonary arterial hypertension (PAH) (78), prospective data on critically ill patients with acute RVF are

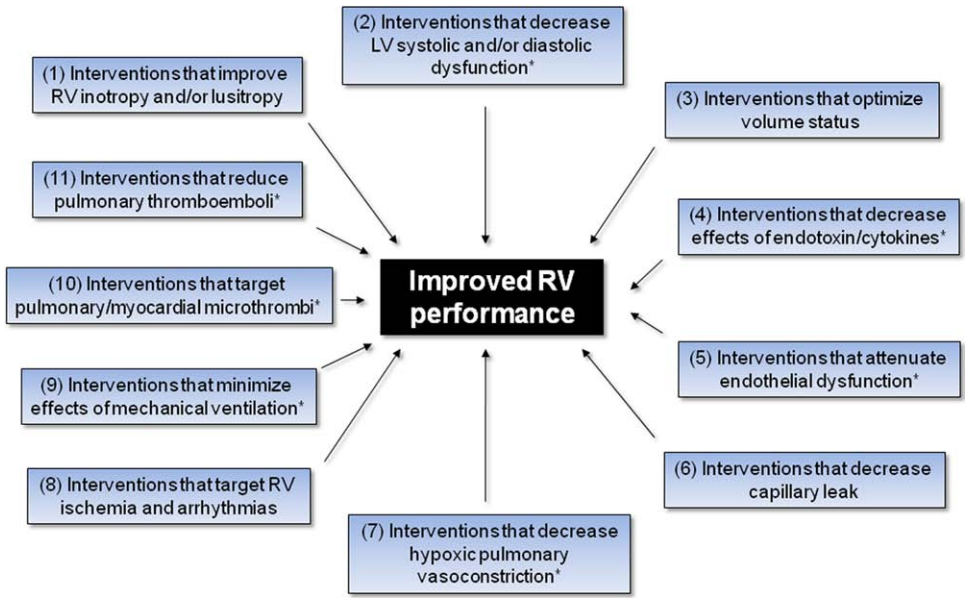

Figure 3 **Categorization of Therapeutic Interventions Aimed at Improving RV Function in the Intensive Care Unit**

Interventions marked with an **asterisk** directly or indirectly decrease right ventricular (RV) afterload. LV = left ventricular.

sparse. The short half-life (3 to 6 min) and its potent effects make epoprostenol the preferred prostacyclin in the ICU. Initiated at 1 to 2 ng/kg/min, the drug is increased by 0.5 to 1 ng/kg/min every 15 to 30 min. A more cautious approach is often warranted in critically ill patients with significant comorbidities, hypoxemia, and/or labile hemodynamics. Epoprostenol decreases PAP and PVR and increases CO, but its use is limited by dose-dependent side effects (e.g., hypotension, gastrointestinal symptoms, headaches) (79). It should be avoided in respiratory failure, shock, and LV dysfunction. Similar to iNO, abrupt discontinuation may lead to rebound PH and even death (79,80). Nebulized or inhaled prostacyclins forgo systemic side effects, representing an attractive alternative to iNO. No special equipment is required for administration or toxicity monitoring. In heart transplant and lung transplant recipients with PH, refractory hypoxemia, and RV dysfunction, inhaled prostacyclin decreased PAP and CVP and improved cardiac index and mixed venous oxygen saturation similar to iNO (81). Inhaled iloprost for RVF is supported by experimental (82) and clinical data. Iloprost improves PH and RV function in patients undergoing mitral valve surgery, cardiopulmonary bypass, or heart transplantation (83–85) and may be more potent than iNO (86). Treprostinil decreases PAP and PVR (87), but its use in the ICU is limited by a longer half-life than that of epoprostenol. In unstable patients, intravenous or inhalational administration is preferred over the subcutaneous route because the latter may be limited by unpredictable absorption. Inhaled treprostinil (15 or 30 μg) additively decreased PVR and PAP and increased CO when added to sildenafil in a recent open-label trial in PH patients (88).

Endothelin receptor antagonists block endothelin-A and -B receptors in vascular smooth muscle and endothelial cells, attenuating endothelin's vasoconstrictive, proliferative, and proinflammatory effects (78). Although increasing CO and decreasing PAP in PH patients, endothelin receptor antagonist use in the ICU is limited by relatively long half-lives (5 h for bosentan) and potential hepatotoxicity (78,89), the latter occurring less frequently with selective endothelin-A receptor antagonists (90).

PDE-5 inhibitors block degradation of cyclic guanosine monophosphate. They decrease PAP and increase CO in both acute and chronic PH and may be particularly beneficial for HPV (58,70,91,92). In isolated PA rings, sildenafil, vardenafil, and tadalafil caused dose-dependent PA relaxation and inhibited phenylephrine-induced PA contraction, but only tadalafil inhibited HPV and decreased hypoxia-induced up-regulation of proinflammatory cytokines (93). Few studies investigated PDE-5 inhibitors in ICU patients. In 8 patients undergoing mitral valve repair or LV assist device (LVAD) placement, sildenafil decreased PAP and PVR and facilitated weaning of inhaled and intravenous pulmonary vasodilators while only minimally decreasing systemic blood pressure (94). Sildenafil and zaprinast may act synergistically with iNO (92,95,96) or iloprost (97) and decrease rebound PH after iNO withdrawal (98). In LVAD patients, sildenafil facilitated weaning from iNO and inotropes and provided additional decreases in PAP (99). Sildenafil or its analogues decrease PVR, maintain systemic vascular resistance, and improve myocardial perfusion after coronary artery bypass grafting (100,101). Sildenafil also has unique lusitropic and/or ino-

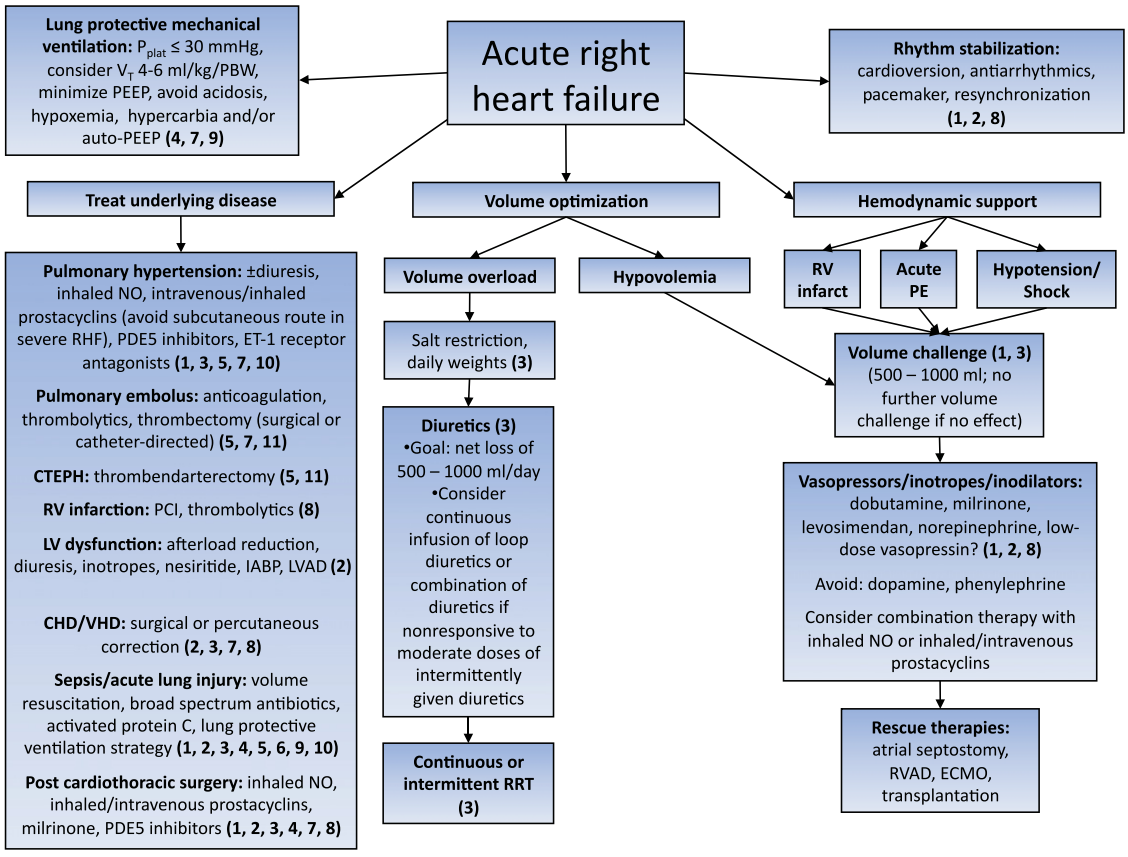

Figure 4 **Treatment of Acute Right Ventricular Failure in the Intensive Care Unit**

Numbers in parentheses refer to the treatment categories outlined in Figure 3. In addition to the strategies depicted in the figure, general measures such as oxygen administration, nutritional support, and prophylactic measures should be applied. Modified from Haddad et al. (2). CHD/VHD = congenital/valvular heart disease; CTEPH = chronic thromboembolic pulmonary hypertension; ECMO = extracorporeal membrane oxygenation; ET-1 = endothelin-1; IABP = intra-aortic balloon pump; LV = left ventricle; LVAD/RVAD = left/right ventricular assist device; NO = nitric oxide; PCI = percutaneous coronary intervention; PDE5 = phosphodiesterase 5; PE = pulmonary embolism; PEEP = positive end-expiratory pressure; P_{plat} = plateau pressure; PBW = predicted body weight; RRT = renal replacement therapy; V_T = tidal volume.

tropic effects in the hypertrophied RV (102), the latter being exerted through PDE-3 inhibition (milrinone-like effect) (59). Furthermore, sildenafil decreases RV mass in PAH patients (102,103). The drug also improves pulmonary hemodynamics and exercise capacity in patients with systolic LV dysfunction (104). Hemodynamic effects of sildenafil occur after 15 to 30 min, with peak effects after 30 to 60 min, and a half-life of 4 h. An association between sildenafil and severe thrombocytopenia was recently reported in a patient with advanced PH (105).

Surgical and interventional therapies. These are indicated for patients with potentially reversible RVF unresponsive to or intolerant of medical therapy or for those with disease progression despite maximal medical therapy. Surgical or percutaneous correction is also used in RVF due to valvular or congenital heart disease. Pre-operative optimization of filling pressures is crucial, and periprocedural inotropic support may be necessary. All interventions should be performed before irreversible end-organ injury develops. Furthermore, surgical or mechanical support is unlikely to benefit those with advanced RV dysfunction and/or massively elevated PVR. For example, pulmonary endarterectomy for chronic thromboembolic PH is not recommended for patients with a pre-operative PVR >1,000 to 1,200 dynes·s·cm^{-5} (22). Balloon atrial septostomy (BAS) is contraindicated in severe RVF and should not be offered to patients with RAP ≥20 mm Hg, significant hypoxemia (<90% on room air), and/or PVR index ≥4,400 dynes·s·cm^{-5}/m^2 (12,22,106–109). Caution is indicated when repair of an atrial septal defect is planned in the setting of RV dysfunction (24). PVR >1,200 dynes·s·cm^{-5} has traditionally been accepted as a contraindication for surgical closure. However, pre-operative pulmonary vasodilator therapy may sufficiently improve hemodynamics to allow for surgical correction (110).

In RVF due to chronic thromboembolic PH, pulmonary thrombendarterectomy improves New York Heart Association functional class, exercise tolerance, and survival (22,111). The best outcomes are achieved in patients with proximal angiographic PA obstruction and absent or min-

imal small vessel disease and if the post-operative PVR can be decreased to <500 dynes·s·cm^{-5} (111). Surgical embolectomy is used for *acute* massive pulmonary embolism when thrombolysis fails or is contraindicated (112). Percutaneous mechanical approaches with or without intrapulmonary thrombolytics can be used in this setting, but comparisons of this approach with medical or surgical thrombolysis are sparse (112).

BAS represents a surgical right-to-left-shunt used to "unload" the RV. The associated decrease in oxygenation is outweighed by increased oxygen delivery and mediated by increased CO (107,113). BAS is used as a bridge to lung transplantation or as a palliative measure in refractory PH, but is contraindicated with concomitant LV failure (22). Spontaneous decreases in orifice size necessitating repeat BAS are not uncommon (113).

Mechanical circulatory support is usually used as a bridge to heart, lung, or heart-lung transplantation. LVADs can be used to treat RVF due to LV failure. LVADs lower pre-heart transplantation PAP, which may improve long-term post-transplantation survival (114,115). However, because LVADs may potentially worsen pre-existing or even result in new-onset RVF (due to changes in RV geometry and flow/pressure dynamics after LV unloading), their use needs to be evaluated on a case-by-case basis (4,116,117). Recent data indicate improved outcomes with continuous-flow LVADs used in a subgroup of patients with concomitant RVF (118). Biventricular VADs may be used if concomitant RV dysfunction is present. Right VADs may be indicated for isolated RVF. As with many surgical procedures, timing is of crucial importance, and VADs should be placed in patients with cardiogenic shock or progressive hemodynamic deterioration despite inotropic therapy before irreversible end-organ failure develops (119). However, isolated right VADs may be insufficient or even deleterious in cases of increased afterload, and extracorporeal membrane oxygenation may be more effective in unloading the RV (120). Extracorporeal membrane oxygenation may be considered for patients with potentially reversible RVF due to severe hypoxemic respiratory failure and/or PH in whom conventional support is failing (121), but randomized, controlled trials are needed.

Heart, lung, or combined heart-lung transplantation is the last resort for end-stage RVF. In patients with PAH, RVF (RAP >15 mm Hg and/or cardiac index <2.0 l/min/m^2) indicates poor prognosis and warrants transplantation referral (22). However, due to the resilient nature of the RV, even patients with severe RVF due to PAH can be considered for isolated lung transplantation with successful outcomes (65% to 75% 1-year-survival rate) (2,122).

Conclusions and Future Directions

The RV, although commonly affected in multiple conditions treated in the ICU, remains understudied and much less well understood than the left ventricle. Investigations of the treatment of isolated RVF are rare and limited to nonrandomized observations. In addition to specific therapies directed against the underlying cause of RVF, supportive measures and judicious volume management, and the use of selective pulmonary vasodilators in conjunction with inotropes seem most promising. The combination of iNO with dobutamine is best supported by current evidence, with evolving data supporting the use of inhaled prostacyclins. PDE-5 inhibitors seem to have selective actions on the RV. Mechanical or surgical interventions are used as primary treatment for distinct conditions or as rescue therapy.

Future directions should include therapies specifically targeting the diseased RV. Examples include metabolic modulators aimed at reversing mitochondrial dysfunction (123). Stem cells are being investigated in ischemic and PAH-related RVF (4,124–126). Tyrosine kinase inhibitors show promise in severe PAH with RVF (127). Future research should consider sex-based differences in RV function. Multiple studies demonstrate female protection in acute and chronic forms of *left* ventricular injury (128,129). Recent data indicate a similar pattern with regard to *right* ventricular function (130). This is of interest as healthy, cardiovascular disease–free women have a higher RVEF than their male counterparts (131). A better understanding of the molecular mechanisms protecting the female RV in health and disease may therefore allow future therapeutic interventions that ultimately benefit patients from either sex.

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REFERENCES

1. Voelkel NF, Quaife RA, Leinwand LA, et al. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. Circulation 2006;114:1883–91.
2. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II. Circulation 2008;117:1717–31.
3. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I. Circulation 2008;117:1436–48.
4. Markel TA, Wairiuko G, Lahm T, et al. The right heart and its distinct mechanisms of development, function, and failure. J Surg Res 2007;146:304–13.
5. Bogaard HJ, Abe K, Vonk Noordegraaf A, Voelkel NF. The right ventricle under pressure: cellular and molecular mechanisms of right-heart failure in pulmonary hypertension. Chest 2009;135:794–804.
6. Mekontso Dessap A, Leon R, Habibi A, et al. Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease. Am J Respir Crit Care Med 2008;177:646–53.

7. Konstantinides S. Clinical practice. Acute pulmonary embolism. N Engl J Med 2008;359:2804–13.
8. Chan CM, Klinger JR. The right ventricle in sepsis. Clin Chest Med 2008;29:661–76, ix.
9. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348:138–50.
10. Meldrum DR. Tumor necrosis factor in the heart. Am J Physiol 1998;274:R577–95.
11. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 1977;296:476–80.
12. Zamanian RT, Haddad F, Doyle RL, Weinacker AB. Management strategies for patients with pulmonary hypertension in the intensive care unit. Crit Care Med 2007;35:2037–50.
13. Jardin F, Vieillard-Baron A. Right ventricular function and positive pressure ventilation in clinical practice: from hemodynamic subsets to respirator settings. Intensive Care Med 2003;29:1426–34.
14. Sztrymf B, Souza R, Bertoletti L, et al. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. Eur Respir J 2010;35:1286–93.
15. Reesink HJ, Tulevski II, Marcus JT, et al. Brain natriuretic peptide as noninvasive marker of the severity of right ventricular dysfunction in chronic thromboembolic pulmonary hypertension. Ann Thorac Surg 2007;84:537–43.
16. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007;116:427–33.
17. Lega JC, Lacasse Y, Lakhal L, Provencher S. Natriuretic peptides and troponins in pulmonary embolism: a meta-analysis. Thorax 2009;64:869–75.
18. Forfia PR, Mathai SC, Fisher MR, et al. Hyponatremia predicts right heart failure and poor survival in pulmonary arterial hypertension. Am J Respir Crit Care Med 2008;177:1364–9.
19. Lankeit M, Kempf T, Dellas C, et al. Growth differentiation factor-15 for prognostic assessment of patients with acute pulmonary embolism. Am J Respir Crit Care Med 2008;177:1018–25.
20. Nickel N, Kempf T, Tapken H, et al. Growth differentiation factor-15 in idiopathic pulmonary arterial hypertension. Am J Respir Crit Care Med 2008;178:534–41.
21. Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 2006;354:2213–24.
22. Keogh AM, Mayer E, Benza RL, et al. Interventional and surgical modalities of treatment in pulmonary hypertension. J Am Coll Cardiol 2009;54:S67–77.
23. Hoeper MM, Barbera JA, Channick RN, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009;54:S85–96.
24. Steele PM, Fuster V, Cohen M, Ritter DG, McGoon DC. Isolated atrial septal defect with pulmonary vascular obstructive disease—long-term follow-up and prediction of outcome after surgical correction. Circulation 1987;76:1037–42.
25. Fitzpatrick JR 3rd, Frederick JR, Hsu VM, et al. Risk score derived from pre-operative data analysis predicts the need for biventricular mechanical circulatory support. J Heart Lung Transplant 2008;27:1286–92.
26. La Vecchia L, Varotto L, Zanolla L, Spadaro GL, Fontanelli A. Right ventricular function predicts transplant-free survival in idiopathic dilated cardiomyopathy. J Cardiovasc Med (Hagerstown) 2006;7:706–10.
27. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55–66.
28. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part one. Am J Respir Crit Care Med 1994;150:833–52.
29. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 2006;174:1034–41.
30. Meluzin J, Spinarova L, Bakala J, et al. Pulsed Doppler tissue imaging of the velocity of tricuspid annular systolic motion; a new, rapid, and non-invasive method of evaluating right ventricular systolic function. Eur Heart J 2001;22:340–8.
31. Tei C, Dujardin KS, Hodge DO, et al. Doppler echocardiographic index for assessment of global right ventricular function. J Am Soc Echocardiogr 1996;9:838–47.
32. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009;179:615–21.
33. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 2009;37:2642–7.
34. Monnet X, Rienzo M, Osman D, et al. Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med 2006;34:1402–7.
35. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340:409–17.
36. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.
37. Groenveld HF, Januzzi JL, Damman K, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. J Am Coll Cardiol 2008;52:818–27.
38. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007;49:675–83.
39. Goldstein JA, Harada A, Yagi Y, Barzilai B, Cox JL. Hemodynamic importance of systolic ventricular interaction, augmented right atrial contractility and atrioventricular synchrony in acute right ventricular dysfunction. J Am Coll Cardiol 1990;16:181–9.
40. Rich S, Seidlitz M, Dodin E, et al. The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. Chest 1998;114:787–92.
41. Massie B, Kramer BL, Topic N, Henderson SG. Hemodynamic and radionuclide effects of acute captopril therapy for heart failure: changes in left and right ventricular volumes and function at rest and during exercise. Circulation 1982;65:1374–81.
42. Quaife RA, Christian PE, Gilbert EM, Datz FL, Volkman K, Bristow MR. Effects of carvedilol on right ventricular function in chronic heart failure. Am J Cardiol 1998;81:247–50.
43. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342:1301–8.
44. Vieillard-Baron A, Jardin F. Why protect the right ventricle in patients with acute respiratory distress syndrome? Curr Opin Crit Care 2003;9:15–21.
45. Balanos GM, Talbot NP, Dorrington KL, Robbins PA. Human pulmonary vascular response to 4 h of hypercapnia and hypocapnia measured using Doppler echocardiography. J Appl Physiol 2003;94:1543–51.
46. Bindslev L, Jolin-Carlsson A, Santesson J, Gottlieb I. Hypoxic pulmonary vasoconstriction in man: effects of hyperventilation. Acta Anaesthesiol Scand 1985;29:547–51.
47. Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. Chest 2007;132:1440–6.
48. David M, von Bardeleben RS, Weiler N, et al. Cardiac function and haemodynamics during transition to high-frequency oscillatory ventilation. Eur J Anaesthesiol 2004;21:944–52.
49. Roosens CD, Ama R, Leather HA, et al. Hemodynamic effects of different lung-protective ventilation strategies in closed-chest pigs with normal lungs. Crit Care Med 2006;34:2990–6.
50. Fan E, Wilcox ME, Brower RG, et al. Recruitment maneuvers for acute lung injury: a systematic review. Am J Respir Crit Care Med 2008;178:1156–63.
51. Vizza CD, Rocca GD, Roma AD, et al. Acute hemodynamic effects of inhaled nitric oxide, dobutamine and a combination of the two in patients with mild to moderate secondary pulmonary hypertension. Crit Care 2001;5:355–61.
52. Kerbaul F, Rondelet B, Motte S, et al. Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. Crit Care Med 2004;32:1035–40.

53. Bradford KK, Deb B, Pearl RG. Combination therapy with inhaled nitric oxide and intravenous dobutamine during pulmonary hypertension in the rabbit. J Cardiovasc Pharmacol 2000;36:146–51.
54. Chen EP, Bittner HB, Davis RD Jr., Van Trigt P 3rd. Milrinone improves pulmonary hemodynamics and right ventricular function in chronic pulmonary hypertension. Ann Thorac Surg 1997;63:814–21.
55. Khazin V, Kaufman Y, Zabeeda D, et al. Milrinone and nitric oxide: combined effect on pulmonary artery pressures after cardiopulmonary bypass in children. J Cardiothorac Vasc Anesth 2004;18:156–9.
56. Hentschel T, Yin N, Riad A, et al. Inhalation of the phosphodiesterase-3 inhibitor milrinone attenuates pulmonary hypertension in a rat model of congestive heart failure. Anesthesiology 2007;106:124–31.
57. Lamarche Y, Malo O, Thorin E, et al. Inhaled but not intravenous milrinone prevents pulmonary endothelial dysfunction after cardiopulmonary bypass. J Thorac Cardiovasc Surg 2005;130:83–92.
58. Tsai BM, Wang M, Pitcher JM, Kher A, Crisostomo P, Meldrum DR. Zaprinast attenuates hypoxic pulmonary artery injury and causes less aortic relaxation than milrinone. Shock 2005;24:417–20.
59. Nagendran J, Archer SL, Soliman D, et al. Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility. Circulation 2007;116:238–48.
60. Angle MR, Molloy DW, Penner B, Jones D, Prewitt RM. The cardiopulmonary and renal hemodynamic effects of norepinephrine in canine pulmonary embolism. Chest 1989;95:1333–7.
61. Kopustinskiene DM, Pollesello P, Saris NE. Levosimendan is a mitochondrial K(ATP) channel opener. Eur J Pharmacol 2001;428:311–4.
62. Gruhn N, Nielsen-Kudsk JE, Theilgaard S, Bang L, Olesen SP, Aldershvile J. Coronary vasorelaxant effect of levosimendan, a new inodilator with calcium-sensitizing properties. J Cardiovasc Pharmacol 1998;31:741–9.
63. Parissis JT, Karavidas A, Bistola V, et al. Effects of levosimendan on flow-mediated vasodilation and soluble adhesion molecules in patients with advanced chronic heart failure. Atherosclerosis 2008;197:278–82.
64. Morelli A, Teboul JL, Maggiore SM, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. Crit Care Med 2006;34:2287–93.
65. Kerbaul F, Rondelet B, Demester JP, et al. Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure. Crit Care Med 2006;34:2814–9.
66. Missant C, Rex S, Segers P, Wouters PF. Levosimendan improves right ventriculovascular coupling in a porcine model of right ventricular dysfunction. Crit Care Med 2007;35:707–15.
67. Kota B, Prasad AS, Economides C, Singh BN. Levosimendan and calcium sensitization of the contractile proteins in cardiac muscle: impact on heart failure. J Cardiovasc Pharmacol Ther 2008;13:269–78.
68. Rossaint R, Gerlach H, Schmidt-Ruhnke H, et al. Efficacy of inhaled nitric oxide in patients with severe ARDS. Chest 1995;107:1107–15.
69. Kaisers U, Busch T, Deja M, Donaubauer B, Falke KJ. Selective pulmonary vasodilation in acute respiratory distress syndrome. Crit Care Med 2003;31:S337–42.
70. Morell ED, Tsai BM, Criostomo PR, Hammoud ZT, Meldrum DR. Experimental therapies for hypoxia induced pulmonary hypertension during acute lung injury. Shock 2006;25:214–26.
71. Meldrum DR, Shames BD, Meng X, et al. Nitric oxide downregulates lung macrophage inflammatory cytokine production. Ann Thorac Surg 1998;66:313–7.
72. Bhorade S, Christenson J, O'Connor M, Lavoie A, Pohlman A, Hall JB. Response to inhaled nitric oxide in patients with acute right heart syndrome. Am J Respir Crit Care Med 1999;159:571–9.
73. George I, Xydas S, Topkara VK, et al. Clinical indication for use and outcomes after inhaled nitric oxide therapy. Ann Thorac Surg 2006;82:2161–9.
74. Ardehali A, Hughes K, Sadeghi A, et al. Inhaled nitric oxide for pulmonary hypertension after heart transplantation. Transplantation 2001;72:638–41.
75. Fattouch K, Sbraga F, Bianco G, et al. Inhaled prostacyclin, nitric oxide, and nitroprusside in pulmonary hypertension after mitral valve replacement. J Card Surg 2005;20:171–6.
76. Christenson J, Lavoie A, O'Connor M, Bhorade S, Pohlman A, Hall JB. The incidence and pathogenesis of cardiopulmonary deterioration after abrupt withdrawal of inhaled nitric oxide. Am J Respir Crit Care Med 2000;161:1443–9.
77. Solina A, Papp D, Ginsberg S, et al. A comparison of inhaled nitric oxide and milrinone for the treatment of pulmonary hypertension in adult cardiac surgery patients. J Cardiothorac Vasc Anesth 2000;14:12–7.
78. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest 2007;131:1917–28.
79. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;334:296–302.
80. Badesch DB, Abman SH, Ahearn GS, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:35S–62S.
81. Khan TA, Schnickel G, Ross D, et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. J Thorac Cardiovasc Surg 2009;138:1417–24.
82. Rex S, Missant C, Claus P, Buhre W, Wouters PF. Effects of inhaled iloprost on right ventricular contractility, right ventriculo-vascular coupling and ventricular interdependence: a randomized placebo-controlled trial in an experimental model of acute pulmonary hypertension. Crit Care 2008;12:R113.
83. Rex S, Schaelte G, Metzelder S, et al. Inhaled iloprost to control pulmonary artery hypertension in patients undergoing mitral valve surgery: a prospective, randomized-controlled trial. Acta Anaesthesiol Scand 2008;52:65–72.
84. De Wet CJ, Affleck DG, Jacobsohn E, et al. Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery. J Thorac Cardiovasc Surg 2004;127:1058–67.
85. Theodoraki K, Rellia P, Thanopoulos A, et al. Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass. Can J Anaesth 2002;49:963–7.
86. Winterhalter M, Simon A, Fischer S, et al. Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: a prospective randomized trial. J Cardiothorac Vasc Anesth 2008;22:406–13.
87. Gomberg-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. Eur Respir J 2008;31:891–901.
88. Voswinckel R, Reichenberger F, Enke B, et al. Acute effects of the combination of sildenafil and inhaled treprostinil on haemodynamics and gas exchange in pulmonary hypertension. Pulm Pharmacol Ther 2008;21:824–32.
89. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896–903.
90. McGoon MD, Frost AE, Oudiz RJ, et al. Ambrisentan therapy in patients with pulmonary arterial hypertension who discontinued bosentan or sitaxsentan due to liver function test abnormalities. Chest 2009;135:122–9.
91. Sebkhi A, Strange JW, Phillips SC, Wharton J, Wilkins MR. Phosphodiesterase type 5 as a target for the treatment of hypoxia-induced pulmonary hypertension. Circulation 2003;107:3230–5.
92. Lepore JJ, Maroo A, Pereira NL, et al. Effect of sildenafil on the acute pulmonary vasodilator response to inhaled nitric oxide in adults with primary pulmonary hypertension. Am J Cardiol 2002;90:677–80.
93. Tsai BM, Turrentine MW, Sheridan BC, et al. Differential effects of phosphodiesterase-5 inhibitors on hypoxic pulmonary vasoconstriction and pulmonary artery cytokine expression. Ann Thorac Surg 2006;81:272–8.
94. Trachte AL, Lobato EB, Urdaneta F, et al. Oral sildenafil reduces pulmonary hypertension after cardiac surgery. Ann Thorac Surg 2005;79:194–7, discussion 194–7.
95. Lepore JJ, Maroo A, Bigatello LM, et al. Hemodynamic effects of sildenafil in patients with congestive heart failure and pulmonary hypertension: combined administration with inhaled nitric oxide. Chest 2005;127:1647–53.

96. Nagamine J, Hill LL, Pearl RG. Combined therapy with zaprinast and inhaled nitric oxide abolishes hypoxic pulmonary hypertension. Crit Care Med 2000;28:2420–4.
97. Ghofrani HA, Wiedemann R, Rose F, et al. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. Ann Intern Med 2002;136:515–22.
98. Atz AM, Wessel DL. Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. Anesthesiology 1999;91:307–10.
99. Klodell CT Jr., Morey TE, Lobato EB, et al. Effect of sildenafil on pulmonary artery pressure, systemic pressure, and nitric oxide utilization in patients with left ventricular assist devices. Ann Thorac Surg 2007;83:68–71, discussion 71.
100. Fung E, Fiscus RR, Yim AP, Angelini GD, Arifi AA. The potential use of type-5 phosphodiesterase inhibitors in coronary artery bypass graft surgery. Chest 2005;128:3065–73.
101. Urdaneta F, Lobato E, Beaver T, et al. Treating pulmonary hypertension post cardiopulmonary bypass in pigs: milrinone vs. sildenafil analog. Perfusion 2008;23:117–25.
102. Michelakis E, Tymchak W, Lien D, Webster L, Hashimoto K, Archer S. Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. Circulation 2002;105:2398–403.
103. Wilkins MR, Paul GA, Strange JW, et al. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. Am J Respir Crit Care Med 2005;171:1292–7.
104. Lewis GD, Shah R, Shahzad K, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation 2007;116:1555–62.
105. Philip A, Ramchandani S, Dorrance K, Dorrance C. Sildenafil-induced thrombocytopenia. Ann Intern Med 2008;149:437–9.
106. Rothman A, Sklansky MS, Lucas VW, et al. Atrial septostomy as a bridge to lung transplantation in patients with severe pulmonary hypertension. Am J Cardiol 1999;84:682–6.
107. Reichenberger F, Pepke-Zaba J, McNeil K, Parameshwar J, Shapiro LM. Atrial septostomy in the treatment of severe pulmonary arterial hypertension. Thorax 2003;58:797–800.
108. Sandoval J, Gaspar J, Pulido T, et al. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. J Am Coll Cardiol 1998;32:297–304.
109. Olsson JK, Zamanian RT, Feinstein JA, Doyle RL. Surgical and interventional therapies for pulmonary arterial hypertension. Semin Respir Crit Care Med 2005;26:417–28.
110. Hoetzenecker K, Ankersmit HJ, Bonderman D, et al. Atrial septal defect repair after a 10-month treatment with bosentan in a patient with severe pulmonary arterial hypertension: a case report. J Thorac Cardiovasc Surg 2009;137:760–1.
111. Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg 2003;76:1457–62, discussion 1462–4.
112. Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ. Executive summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:71S–109S.
113. Kurzyna M, Dabrowski M, Bielecki D, et al. Atrial septostomy in treatment of end-stage right heart failure in patients with pulmonary hypertension. Chest 2007;131:977–83.
114. Liden H, Haraldsson A, Ricksten SE, Kjellman U, Wiklund L. Does pretransplant left ventricular assist device therapy improve results after heart transplantation in patients with elevated pulmonary vascular resistance? Eur J Cardiothorac Surg 2009;35:1029–34.
115. Zimpfer D, Zrunek P, Sandner S, et al. Post-transplant survival after lowering fixed pulmonary hypertension using left ventricular assist devices. Eur J Cardiothorac Surg 2007;31:698–702.
116. Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol 2008;51:2163–72.
117. Dang NC, Topkara VK, Mercando M, et al. Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure. J Heart Lung Transplant 2006;25:1–6.
118. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241–51.
119. Wilson SR, Mudge GH Jr., Stewart GC, Givertz MM. Evaluation for a ventricular assist device: selecting the appropriate candidate. Circulation 2009;119:2225–32.
120. Berman M, Tsui S, Vuylsteke A, Klein A, Jenkins DP. Life-threatening right ventricular failure in pulmonary hypertension: RVAD or ECMO? J Heart Lung Transplant 2008;27:1188–9.
121. Conrad SA, Rycus PT, Dalton H. Extracorporeal Life Support Registry Report 2004. ASAIO J 2005;51:4–10.
122. Mendeloff EN, Meyers BF, Sundt TM, et al. Lung transplantation for pulmonary vascular disease. Ann Thorac Surg 2002;73:209–17, discussion 217–9.
123. Nagendran J, Gurtu V, Fu DZ, et al. A dynamic and chamber-specific mitochondrial remodeling in right ventricular hypertrophy can be therapeutically targeted. J Thorac Cardiovasc Surg 2008;136:168–78, 178.e1–3.
124. Wairiuko GM, Crisostomo PR, Wang M, et al. Stem cells improve right ventricular functional recovery after acute pressure overload and ischemia reperfusion injury. J Surg Res 2007;141:241–6.
125. Crisostomo PR, Abarbanell AM, Wang M, Lahm T, Wang Y, Meldrum DR. Embryonic stem cells attenuate myocardial dysfunction and inflammation after surgical global ischemia via paracrine actions. Am J Physiol Heart Circ Physiol 2008;295:H1726–35.
126. Zhao YD, Courtman DW, Deng Y, Kugathasan L, Zhang Q, Stewart DJ. Rescue of monocrotaline-induced pulmonary arterial hypertension using bone marrow-derived endothelial-like progenitor cells: efficacy of combined cell and eNOS gene therapy in established disease. Circ Res 2005;96:442–50.
127. Ghofrani HA, Seeger W, Grimminger F. Imatinib for the treatment of pulmonary arterial hypertension. N Engl J Med 2005;353:1412–3.
128. Wang M, Crisostomo PR, Markel TA, Wang Y, Meldrum DR. Mechanisms of sex differences in TNFR2-mediated cardioprotection. Circulation 2008;118:S38–45.
129. Sun J, Picht E, Ginsburg KS, Bers DM, Steenbergen C, Murphy E. Hypercontractile female hearts exhibit increased S-nitrosylation of the L-type Ca2+ channel alpha1 subunit and reduced ischemia/reperfusion injury. Circ Res 2006;98:403–11.
130. Kawut SM, Al-Naamani N, Agerstrand C, et al. Determinants of right ventricular ejection fraction in pulmonary arterial hypertension. Chest 2009;135:752–9.
131. Tandri H, Daya SK, Nasir K, et al. Normal reference values for the adult right ventricle by magnetic resonance imaging. Am J Cardiol 2006;98:1660–4.

Key Words: acute lung injury ■ inotropes ■ pulmonary hypertension ■ sepsis ■ shock ■ vasodilators ■ vasopressors.

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