Trying to succeed when the right ventricle fails

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Purpose of review

Compared with the left ventricle, studies of right ventricular failure as a distinct clinical entity have lagged behind. Evolving appreciation of the prognostic significance of right ventricular dysfunction in the heart failure population and advances in noninvasive imaging have provided the impetus for recent investigation into the assessment and management of right ventricular failure.

Recent findings

Pulmonary hypertension and attendant right ventricular dysfunction are prevalent in patients with systolic and diastolic heart failure and are associated with poor survival. Simple echocardiographic and MRI indices of right ventricular function relate to prognosis and may also be useful in following response to therapy. Management of acute and chronic right ventricular failure is largely empiric and is focused on treating the underlying cause along with judicious use of diuretics and inotropes. The use of left ventricular assist devices to help treat pulmonary hypertension in heart failure is an emerging strategy in transplant-eligible patients.

Summary

Right ventricular failure is clinically significant and merits further dedicated study. Parameters of right ventricular dysfunction can be assessed noninvasively. An approach to the management of acute and chronic right ventricular failure should take into consideration novel pharmacologic and device-based therapies.

Keywords

heart failure, pulmonary hypertension, right ventricle, ventricular assist devices

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Introduction

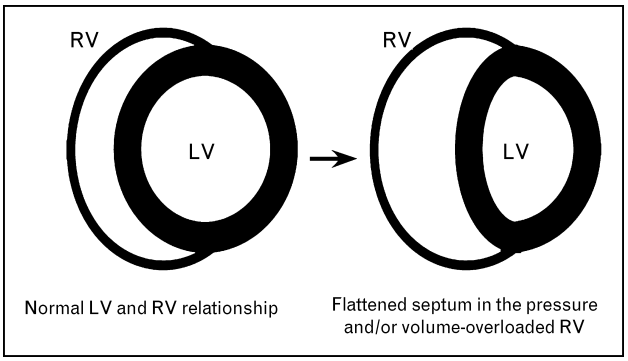
The importance of right ventricular (RV) function in pulmonary vascular disease, left-sided heart disease and congenital heart disease is gaining increasing appreciation. However, despite recent advances in imaging and assessment, the pathophysiology of RV failure is incompletely understood, and RV-specific therapies remain elusive or unexplored. In contrast to left ventricular failure, there has been a paucity of research on RV failure as a distinct and separate entity *per se*; historically, the guiding principles for assessing and managing RV dysfunction have been extrapolated from studies of the left ventricle (LV) [1–3]. However, further insight into the fundamental anatomical and functional differences between the two ventricles as well as their physiologic interdependence highlights the inadequacy of this approach. This review will discuss the importance of RV failure especially as it relates to LV failure and will outline the role of different empiric therapies and evolving treatment strategies.

Defining the issue

Right heart failure may be broadly defined as the inability of the right ventricle to maintain adequate circulation through the pulmonary vascular bed at normal central venous pressures. This process is often insidious and chronic as the RV is subjected to unfavorable loading conditions over time [i.e. pulmonary arterial hypertension (PAH)], or can occur acutely with precipitous hemodynamic deterioration and end-organ injury [i.e. massive pulmonary embolus with acute cor pulmonale, RV infarction, postcardiac transplant RV failure and RV failure following left ventricular assist device (LVAD) implantation].

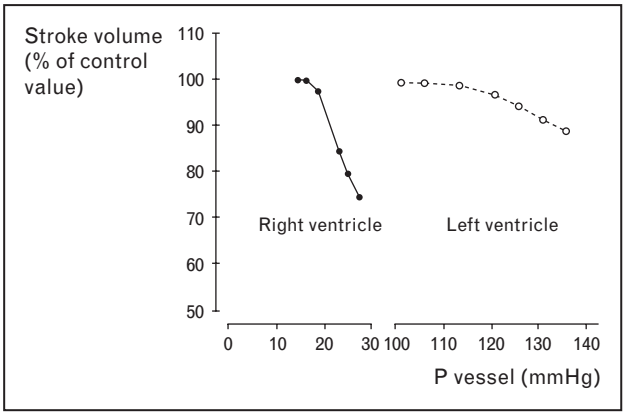
Adverse changes in right-sided afterload, preload or right ventricular contractility can result in RV decompensation, first characterized in 1974 [4] as a state of low cardiac output with elevated right-sided (right atrial and central venous) filling pressures. In isolated RV failure, pulmonary capillary wedge pressure (PCWP) and left-sided

Figure 1 Septal shift and exaggerated ventricular interdependence in right ventricular dysfunction



Because the RV is constrained by the pericardium (not shown), pathologically increased right ventricular filling pressures are transmitted to the interventricular septum, which shifts towards the LV and distorts the normal geometric relationship between the ventricles. This may mechanically disadvantage the RV and adversely affect left ventricular diastolic filling. LV, left ventricle; RV, right ventricle. Adapted from [3].

Figure 2 Effect of increased afterload on right ventricular versus left ventricular function



Increased pulmonary artery pressures and RV afterload cause a marked reduction in right-sided stroke volume and cardiac output. By comparison, LV performance is less sensitive to increased systemic arterial pressure and afterload. LV, left ventricular; RV, right ventricular. Adapted from [5].

filling pressures are low, and pulmonary edema is absent. Chronic RV failure, with longstanding elevation of central venous pressures, can lead to atrial arrhythmias, peripheral edema, ascites and congestive dysfunction of the liver, kidneys and gut. Persistent low cardiac output due to an underfilled LV can precipitate classic symptoms of exercise intolerance and end-organ hypoperfusion. The clinical situation may be further exacerbated as LV diastolic filling becomes compromised through the mechanism of ventricular interdependence in which the RV is 'constrained' by the pericardium, and increased right-sided pressures cause the interventricular septum to shift and impinge on the LV cavity and left ventricular filling (Fig. 1).

Considerations in pulmonary hypertension

As shown in Fig. 2, RV function is very sensitive to alterations in afterload [5,6], and RV failure is often seen in the setting of pulmonary hypertension in which increased pulmonary vascular resistance (PVR) is the primary hemodynamic problem [7]. Ultimately, progressive RV dysfunction in this setting may lead to diminishing right-sided cardiac output and a decline in pulmonary artery pressures; hence, the diagnosis of RV failure in the setting of chronic pulmonary hypertension does not require pulmonary artery pressures to remain elevated. It may, therefore, be useful to consider the RV and pulmonary arteries together as a single, functional, interrelated unit [2].

The most recent classification of pulmonary hypertension centers on the underlying pathophysiologic process and response to therapy [7,8]. Table 1 outlines this current classification scheme. A detailed description of the different types of pulmonary hypertension is beyond the scope of this review; however, a distinction is made between PAH characterized by resting mean pulmonary artery pressure of more than 25 mmHg, PVR of more than 3 Wood units and PCWP of less than 15 mmHg, and pulmonary hypertension due to left-sided heart disease characterized by elevated left atrial pressures. Irrespective of the cause, right ventricular failure often represents the final common pathway portending a poor prognosis and may be a potential target for therapeutic intervention.

Table 1 Classification of pulmonary hypertension

Category	Examples
PAH	Idiopathic
	Familial
	Congenital systemic pulmonary shunts, connective tissue disease
	HIV
	Toxins
Pulmonary hypertension with left heart disease	Left-sided atrial or ventricular disease (LV systolic or diastolic dysfunction)
	Left-sided valvular heart disease
Pulmonary hypertension associated with lung disease/hypoxia	Chronic obstructive lung disease
	Interstitial lung disease
	Sleep-disordered breathing
Pulmonary hypertension due to chronic thrombotic or embolic disease or both	Thromboembolic obstruction of pulmonary arteries
	Nonthrombotic obstruction of pulmonary arteries
Miscellaneous	Sarcoidosis
	Histiocytosis X

LV, left ventricular; PAH, pulmonary arterial hypertension. Adapted from [8].

Acute and chronic right ventricular failure: impact of the problem in left heart disease

The most common underlying cause of pulmonary hypertension and RV failure is concomitant left-sided heart disease [1]. Although the exact prevalence is poorly defined [9], pulmonary hypertension is common in heart failure patients and is associated with a poor prognosis in ischemic and nonischemic cardiomyopathy [9–11,12•].

Pulmonary hypertension in left ventricular dysfunction

Although previous work has been limited to patients with poor left ventricular systolic function, Kjaergaard *et al.* [12•] recently evaluated the prognostic significance of elevated pulmonary pressures in a broad spectrum of heart failure patients enrolled in the EchoCardiography and Heart Outcome Study (ECHOS) [13]. Approximately 25% of the 388 patients in this cohort had preserved left ventricular function. Pulmonary artery pressure was found to be an independent predictor of overall mortality. In both low ejection fraction and preserved ejection fraction subgroups, patients with pulmonary systolic pressure at least 39 mmHg had significantly worse survival [12•]. Although others have observed pulmonary hypertension and RV failure in patients with preserved left ventricular ejection fraction (LVEF) [14], this is the first study to demonstrate the prognostic importance of elevated pulmonary artery pressures in a contemporary heart failure population that includes both systolic and diastolic heart failure patients.

Concomitant right ventricular and left ventricular dysfunction

By extension, RV dysfunction itself is a powerful and independent predictor of short and long-term survival in chronic LV systolic failure [10,15–18]. In studies [10,16,18] of selected patients with ischemic or nonischemic cardiomyopathy, RV dysfunction, usually defined by right ventricular ejection fraction (RVEF) of less than 0.35, has been observed in more than 50%. Ghio *et al.* [10] demonstrated the independent and additive effects of RV dysfunction and pulmonary hypertension in a low LVEF heart failure cohort. They also observed an inverse relation between RVEF and mean pulmonary artery pressures, suggesting that persistent elevation of pulmonary pressures is pathophysiologically important, and that RV dysfunction is not simply an epiphenomenon of the left ventricular cardiomyopathic process [10]. Javaheri *et al.* [19•] assessed the prognostic significance of sleep-disordered breathing in patients with systolic heart failure. In a multivariable analysis, central sleep apnea and RV dysfunction were independent predictors of long-term mortality, suggesting that sleep apnea is linked to right ventricular dysfunction through chronic elevation of pulmonary artery pressures [19•].

Right ventricular failure after left ventricular assist device implantation

Acute RV dysfunction after LVAD implantation for end-stage heart failure is an increasingly important issue. The incidence of significant RV failure, typically defined as inotrope support for more than 14 days, inhaled nitric oxide (iNO) for at least 48 h or need for right ventricular assist device (RVAD), is approximately 30–40% and is associated with a perioperative mortality of nearly 40% [20••,21,22]. A recent preoperative risk score for RV failure post-LVAD implantation found that preoperative vasopressor requirements and elevated serum aspartate aminotransferase, bilirubin and creatinine were independent predictors of RV failure [20••]. This study implies that the end-organ effects of RV dysfunction add prognostic value beyond hemodynamic measurements taken in isolation. Moreover, anticipation and aggressive measures to manage the RV in this situation are warranted given the impact of RV failure on perioperative mortality.

Towards better assessment of right ventricular structure and function

Because management of RV failure is largely empiric, an understanding of the unique anatomy and physiology of the RV is essential. The RV is a thin-walled complex three-dimensional structure designed for circulating high volumes in a low-resistance system. Compared with the LV, the bellows-like action of RV contraction against the interventricular septum generates less stroke work, and measures of RV performance are more load-dependent [3,6]. Although RV function is greatly affected by changes in afterload [5], chronic volume overload conditions such as atrial septal defects and tricuspid and pulmonary regurgitation are well tolerated, as is the Fontan circuit in which the RV is noncontributory. The RV ultimately fails, however, when PVR and right ventricular afterload increase [3,23].

Noninvasive markers of right ventricular function

Given the relative complexity of RV structure and function, there has been great interest in imaging the RV and assessing various prognostically important parameters. The valsartan in acute myocardial infarction trial (VALIANT) echocardiographic (ECHO) study assessed right ventricular function in postmyocardial infarction (MI) heart failure patients using two-dimensional right ventricular fractional area change (RVFAC) [24•]. Higher rates of RV dysfunction after MI were observed than had previously been reported, and this was associated with a significantly increased risk of death, heart failure and stroke, independent of LV function [24•]. In chronic heart failure patients, blunted RV tissue Doppler systolic velocity emerged as a novel predictor of cardiac death or heart failure hospitalization, suggesting

that this may be a more sensitive marker of RV dysfunction than conventional parameters, including RVEF or RVFAC [25].

MRI imaging, currently the gold standard for assessment of RV dimensions and volumes [2,26,27], offers tremendous potential for evaluating RV function and perfusion [2]. MRI assessment of RV isovolumic relaxation time, a marker of RV diastolic function, has correlated well with PVR, and improved following afterload reduction with sildenafil [28•]. This suggests that RV diastolic function and response to therapy can be assessed quantitatively and noninvasively. RV volumes calculated from multislice computed tomography (CT) scan imaging have shown excellent correlation with MRI imaging, providing an alternative modality for evaluating RV anatomy and function [29].

Managing chronic right ventricular dysfunction

Although no specific therapies exist for chronic RV failure, treatment is generally based on identifying and correcting the underlying physiologic derangements. Appropriate therapy for left-sided heart disease should theoretically ameliorate chronically elevated PCWP and RV dysfunction; however, data directly supporting this are lacking. Carvedilol has been shown to increase both RVEF and LVEF compared with placebo in small studies [30,31] of systolic heart failure patients. A randomized controlled trial of darbepoetin α, a recombinant erythropoietin analogue, in 32 patients with heart failure also demonstrated improvements in LVEF and RVEF compared with placebo over 3 months [32].

Diuretics are standard therapy for conditions of volume overload. Despite the lack of evidence supporting their use in RV failure, a combination of loop diuretics, spironolactone and thiazides may be used to manage peripheral edema, ascites and end-organ congestion. Appropriate diuresis may have salutary effects on RV loading conditions without negatively impacting left ventricular preload and cardiac output. A pilot study [33] comparing the hemodynamic effects of loop diuretics found that torsemide effectively lowered central venous pressure and PCWP, improved cardiac output and had less neurohormonal activation than furosemide. These novel findings need to be confirmed in large-scale studies, but underscore the need to include pulmonary vascular and RV functional parameters in physiologic studies of heart failure.

Can therapies for pulmonary arterial hypertension be extrapolated to heart failure patients?

In addition to chronically elevated filling pressures in 'postcapillary' pulmonary hypertension due to left heart disease, many heart failure patients have superimposed elevations in PVR with a relatively fixed component of pulmonary hypertension due to an abnormal pulmonary arterial vasoconstrictor response and structural remodeling [9,34,35]. Conceptually, then, therapies for idiopathic PAH may be effective for some patients with pulmonary hypertension due to LV dysfunction. There are a number of issues with this approach. For example, PAH trials of prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase inhibitors have not looked at long-term morbidity and mortality outcomes germane to the heart failure population. As well, available literature on prostacyclins and endothelin receptor antagonists in patients with advanced heart failure suggests an adverse effect on short-term mortality and worsening heart failure [36–38]. In the endothelin antagonist bosentan for lowering cardiac events in heart failure (ENABLE) study [38], the endothelin receptor antagonist bosentan showed no effect on mortality, but was associated with an increased risk of hospitalization for heart failure in patients with LV systolic dysfunction.

In contrast, sildenafil, the prototypical phosphodiesterase inhibitor approved for PAH, has generated appreciable interest with respect to its potential efficacy in other types of pulmonary hypertension. Emerging data indicate a possible hemodynamic, functional and quality of life benefit in patients with chronic thromboembolic pulmonary hypertension [39], idiopathic pulmonary fibrosis [40] and left-sided heart failure [41••,42]. Early studies [43,44] of sildenafil in heart failure patients with pulmonary hypertension demonstrated an improvement in exercise capacity following a single dose. A randomized trial of 34 patients found that sildenafil use in this population increased RVEF, cardiac output and exercise tolerance and was associated with better quality of life [41••]. Although improvements in RV function in this study were attributed to observed reductions in PVR, Nagendran *et al.* [45••] have shown that phosphodiesterase inhibition with sildenafil may result in augmented RV contractility, providing evidence for a right ventricular-specific inotrope effect.

Mechanical solutions for pulmonary hypertension due to left heart disease

In end-stage heart failure, irreversible pulmonary hypertension remains a contraindication to transplantation as it imposes an unacceptable risk of death from postoperative RV failure [46,47]; the only treatment option, historically, has been heart–lung transplantation. Although sildenafil and other selective pulmonary vasodilators offer some promise of improving hemodynamics sufficiently to allow transplantation [42], experience with LVADs as a bridge to transplant eligibility for patients with severe pulmonary hypertension is growing. Amelioration of 'fixed' pulmonary hypertension with

LVADs has been described in a number of cases [35], including 26 patients successfully bridged to transplantation with outcomes similar to those transplanted without antecedent pulmonary hypertension [48]. Patel *et al.* [49•] also retrospectively assessed the incidence of RV dysfunction following implantation of the pulsatile HeartMate I LVADs (Thoratec Corp., Pleasanton, California, USA) versus the axial-flow HeartMate II devices. In this study, both yielded comparable reductions in pulmonary pressures, although postoperative RV failure was common, occurring in 35% of pulsatile and 41% of axial-flow devices. This suggests that different approaches for unloading the LV have similar potential to mechanically disadvantage the RV, despite favorable effects on pulmonary hypertension and RV afterload.

Acute decompensated right ventricular failure

Management of patients with acute decompensated RV failure is largely empiric and targeted towards treating underlying precipitants while optimizing conditions of RV preload, afterload and contractility.

Optimal preload

Irrespective of the cause of RV failure, adequate RV preload may help maintain cardiac output via the Frank–Starling mechanism. Excessive volume loading in this setting can be detrimental, however, as pericardial constraint may adversely affect left ventricular diastolic filling via ventricular interdependence. Congestive hepatopathy, renal venous hypertension and gut edema lead to progressive end-organ dysfunction, and elevated right atrial pressures can precipitate supraventricular arrhythmias that further exacerbate the problem. Pulmonary artery catheterization may help guide resuscitative efforts; if the syndrome of RV failure persists and right-sided filling pressures remain above 12–15 mmHg, diuresis, inotrope therapy and aggressive afterload reduction are usually required [50], and renal replacement therapy may become necessary.

Improving right ventricular contractility

Optimizing myocardial oxygen supply–demand balance mandates aggressive treatment of underlying ischemia [23]. In the face of persistently low cardiac output, dual chamber (right atrium and RV) pacing may be helpful in maintaining adequate heart rate or restoring atrioventricular synchrony or both. Inotropes, including epinephrine, milrinone and dobutamine, are frequently needed to augment contractility; however, milrinone and dobutamine may worsen systemic hypotension, requiring the addition of vasopressors [23,50,51]. Newer inotropes such as levosimendan have demonstrated improvements in parameters of RV function in animal models and early human studies [52,53]; however, their routine use in decompensated RV failure requires further investigation.

Optimal right ventricular afterload

Minimizing positive intrathoracic pressure in ventilated patients and managing concomitant left ventricular dysfunction may have beneficial effects on RV afterload. In addition to these general measures, administering pulmonary artery vasodilators may be useful in the management of RV failure. In patients with RV infarction and cardiogenic shock, iNO has been shown to improve hemodynamic measures [54]. Inhaled prostacyclin analogues, iNO and oral sildenafil have all been used to successfully manage pulmonary hypertension and RV failure following cardiac surgery [55,56]. It remains to be seen whether broader applicability of these therapies to other patients with RV dysfunction will yield improvements in physiologic and clinical outcomes.

Conclusion

Compared with the LV, studies of RV *per se* have lagged behind, with a general paucity of data to inform clinical decision-making. With the evolution of noninvasive imaging and greater insight into the prognostic significance of RV dysfunction, there are new opportunities to enrich our assessment and treatment of patients across a spectrum of cardiovascular disease. An approach to the management of acute and chronic RV failure should take into consideration novel pharmacologic and device-based therapies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 264–267).

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; 114:1883–1891.

2 Nagendran J, Michelakis E. MRI: one-stop shop for the comprehensive assessment of pulmonary arterial hypertension? Chest 2007; 132:2–5.

3 Greyson CR. Pathophysiology of right ventricular failure. Crit Care Med 2008; 36 (1 Suppl):S57–S65.

4 Cohn JN, Guiha NH, Broder MI, *et al.* Right ventricular infarction: clinical and hemodynamic features. Am J Cardiol 1974; 33:209–214.

5 Chin KM, Kim NH, Rubin LJ. The right ventricle in pulmonary hypertension. Coron Art Dis 2005; 16:13–18.

6 Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I. Anatomy, physiology, aging and functional assessment of the right ventricle. Circulation 2008; 117:1436–1448.

7 Chin KM, Rubin LJ. Pulmonary arterial hypertension. J Am Coll Cardiol 2008; 51:1527–1538.

8 Simmonneau G, Galie N, Rubin LJ, *et al.* Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004; 43 (Suppl 1):5S–12S.

9 Oudiz RJ. Pulmonary hypertension associated with left-sided heart disease. Clin Chest Med 2007; 28:233–241.

10 Ghio S, Gavazzi A, Campana C, *et al.* Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001; 37:183–188.

11 Abramson SV, Burke JF, Kelly JJ, *et al.* Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. Ann Intern Med 1992; 116:888–895.

12 Kjaergaard J, Akkan D, Iverson KK, *et al.* Prognostic importance of pulmonary
• hypertension in patients with heart failure. Am J Cardiol 2007; 99:1146–1150.

This echocardiographic study describes the prognostic impact of pulmonary hypertension in a contemporary heart failure population. Increased pulmonary artery pressures were associated with increased mortality in patients with left ventricular systolic and diastolic heart failure.

13 Torp-Pedersen C, Carlsen J, Dacoronias D, *et al.* A double blind randomized trial of CHF1035, a prejunctional stimulator of DA2-dopaminergic and alpha2-adrenergic receptor, in patients with congestive heart failure. Eur J Heart Fail 2005; 4 (Suppl 1):89.

14 Zakir RM, Al-Dehneh A, Maher J, *et al.* Right ventricular failure in patients with preserved ejection fraction and diastolic dysfunction: an underrecognized clinical entity. Congest Heart Fail 2007; 13:164–169.

15 Polak JF, Holman L, Wynne J, Colucci WS. Right ventricular ejection fraction: an indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease. J Am Coll Cardiol 1983; 2:217–224.

16 De Groote P, Millaire A, Foucher-Hossein C, *et al.* Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. J Am Coll Cardiol 1998; 32:948–954.

17 Juilliere Y, Barbier G, Feldmann L, *et al.* Additional predictive value of both left and right ventricular ejection fractions on long-term survival in idiopathic dilated cardiomyopathy. Eur Heart J 1997; 18:276–280.

18 Di Salvo TG, Mathier M, Semigran MJ, Dec WG. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. J Am Coll Cardiol 1995; 25:1143–1153.

19 Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ven-
• tricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol 2007; 49:2028–2034.

In this prospective cohort study of systolic heart failure patients, central sleep apnea, low diastolic blood pressure and right ventricular dysfunction were independently associated with poor survival.

20 Cowger Matthews J, Koelling TM, Pagani FD, Aaronson KD. The right
•• ventricular risk score. A preoperative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol 2008; 51:2163–2172.

The authors derive a preoperative risk score to predict the onset of right ventricular failure following LVAD implantation. They also demonstrate the association between high postoperative right ventricular failure risk and short-term mortality. If validated, this tool can be helpful in the selection of patients for LVAD versus biventricular assist device support.

21 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.

22 Kavarana MN, Pessin-Minsley MS, Urtecho J, *et al.* Right ventricular dysfunction and organ failure in left ventricular assist device recipients: a continuing problem. Ann Thorac Surg 2002; 73:745–750.

23 Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II. Pathophysiology, clinical importance, and management of right ventricular failure. Circulation 2008; 117:1717–1731.

24 Anavekar NS, Skali H, Bourgoun M, *et al.* Usefulness of right ventricular
• fractional area change to predict death, heart failure, and stroke following myocardial infarction (from the VALIANT ECHO study). Am J Cardiol 2008; 101:607–612.

In this echocardiographic substudy of the VALIANT trial, worsening right ventricular fractional area change was associated with an increased risk of death, heart failure and stroke. This simple measure of right ventricular function adds prognostically useful information to the assessment of heart failure patients.

25 Dokainish H, Sengupta R, Patel R, Lakkis N. Usefulness of right ventricular tissue Doppler imaging to predict outcome in left ventricular heart failure independent of left ventricular diastolic function. Am J Cardiol 2007; 99:961–965.

26 Tandri H, Daya SK, Nasir K, *et al.* Normal reference values for the adult right ventricle by magnetic resonance imaging. Am J Cardiol 2006; 98:1660–1664.

27 Alfakih K, Plein S, Thiele H, *et al.* Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. J Magn Reson Imaging 2003; 17:323–329.

28 Gan CTJ, Holverda S, Marcus JT, *et al.* Right ventricular diastolic dysfunction
• and the acute effects of sildenafil in pulmonary artery hypertension patients. Chest 2007; 132:11–17.

MRI indices of right ventricular diastolic dysfunction correlated with severity of underlying pulmonary hypertension. The dynamic nature of these indices in response to treatment with sildenafil suggests the utility of MRI imaging in monitoring disease progression and response to therapy.

29 Plumhans C, Muhlenbruch G, Rapaee A, *et al.* Asessment of global right ventricular function on 64-MDCT compared with MRI. Am J Roentgenol 2008; 190:1358–1361.

30 Tatli E, Kurum T, Aktoz M, Buyuklu M. Effects of carvedilol on right ventricular ejection fraction and cytokines levels in patients with systolic heart failure. Int J Cardiol 2008; 125:273–276.

31 Quaife RA, Christian PE, Gilbert EM, *et al.* Effects of carvedilol on right ventricular function in chronic heart failure. Am J Cardiol 1998; 81:247–250.

32 Parissis JT, Kourea K, Panou F, *et al.* Effects of darbepoetin α on right and left ventricular systolic and diastolic function in anemic patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am Heart J 2008; 155:751e.e1–751e.e7.

33 von Dossow V, Spies C, Schenk H, *et al.* Secondary pulmonary hypertension. Hemodynamic effects of torsemide versus furosemide. Clin Drug Invest 2008; 28:17–26.

34 Moreas DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. Circulation 2000; 102:1718–1723.

35 Haddad H, Elabbassi W, Moustafa S, *et al.* Left ventricular assist device as bridge to heart transplantation in congestive heart failure with pulmonary hypertension. ASAIO J 2005; 51:456–460.

36 Califf RM, Adams KF, McKenna WJ, *et al.* A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997; 134: 44–54.

37 Packer M, McMurray J, Massie BM, *et al.* Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. J Cardiac Fail 2005; 11:12–20.

38 Kalra PR, Moon JCC, Coats AJS. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for nonselective endothelin antagonism in heart failure? Int J Cardiol 2002; 85:195–197.

39 Suntharalingam J, Treacy CM, Doughty NJ, *et al.* Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. Chest 2008; 134:229–236.

40 Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest 2007; 131:641–643.

41 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; 116:1555–1562.

In this trial, sildenafil improved exercise tolerance and quality of life in patients with pulmonary hypertension due to left heart disease. Sildenafil holds promise in managing patients with symptomatic heart failure complicated by persistently elevated pulmonary artery pressures.

42 Jabbour A, Keogh A, Hayward C, Macdonald P. Chronic sildenafil lowers transpulmonary gradient and improves cardiac output allowing successful heart transplantation. Eur J Heart Fail 2007; 9:674–677.

43 Lewis GD, Lachmann J, Camuso J, *et al.* Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation 2007; 115:59–66.

44 Guazzi M, Tumminello G, Di Marco F, *et al.* The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure. J Am Coll Cardiol 2004; 12:2339–2348.

45 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: 238–248.

Inhibition of phosphodiesterase-5 with sildenafil may have a direct effect on right ventricular inotropic function in disease states, suggesting that the benefits of this class of medication may be mediated by reducing right ventricular afterload and improving right ventricular contractility.

46 Chen JM, Levin HR, Michler RE, *et al.* Reevaluating the significance of pulmonary hypertension before cardiac transplantation: determination of optimal thresholds and quantification of the effect of reversibility on perioperative mortality. J Thorac Cardiovasc Surg 1997; 114:627–634.

47 Butler J, Stankewicz MA, Wu J, *et al.* Pretransplant reversible pulmonary hypertension predicts higher risk for mortality after cardiac transplantation. J Heart Lung Transplant 2005; 24:170–177.

48 Zimpfer D, Zrunek P, Sandner S, *et al.* Posttransplant survival after lowering fixed pulmonary hypertension using left ventricular assist devices. Eur J Cardiothorac Surg 2007; 31:698–702.

49 Patel ND, Weiss ES, Schaffer J, *et al.* Right heart dysfunction after left
• ventricular assist device implantation: a comparison of the pulsatile HeartMate I and axial-flow HeartMate II devices. Ann Thorac Surg 2008; 86:832–840.

This study demonstrated that right ventricular failure post-LVAD implantation remains clinically challenging, and that the incidence of postoperative right ventricular dysfunction is comparable between newer generation axial flow devices and standard pulsatile flow LVADs.

50 Piazza G, Goldhaber SZ. The acutely decompensated right ventricle. Pathways for diagnosis and management. Chest 2005; 128:1836–1852.

51 Zamanian RT, Haddad F, Doyle R, Weinacker AB. Management strategies for patients with pulmonary hypertension in the intensive care unit. Crit Care Med 2007; 35:2037–2050.

52 Kerbaul F, Gariboldi V, Giorgi R, *et al.* Effects of levosimendan on acute pulmonary embolism-induced right ventricular failure. Crit Care Med 2007; 35:1948–1954.

53 Duygu H, Ozerkan F, Zoghi M, *et al.* Effect of levosimendan on right ventricular systolic and diastolic functions in patients with ischaemic heart failure. Int J Clin Pract 2007; 62:228–233.

54 Inglessis I, Shin JT, Lepore JJ, *et al.* Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock. J Am Coll Cardiol 2004; 44:793–798.

55 Trachte AL, Lobato EB, Urdaneta F, *et al.* Oral sildenafil reduces pulmonary hypertension after cardiac surgery. Ann Thorac Surg 2005; 779:194–197.

56 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 Cardiothor Vasc Anesthes 2008; 22:406–413.