



REVIEW PAPER

Right Ventricular Failure in Patients With Preserved Ejection Fraction and Diastolic Dysfunction: An Underrecognized Clinical Entity

AUTHOR

Pulmonary hypertension is frequently seen in patients with chronic heart failure (HF) and may be associated with increased morbidity and mortality. It is now known that HF with preserved left ventricular (LV) ejection fraction (EF) is present in approximately half of patients with acute decompensated HF (ADHF).^{1,2} Elevated pulmonary artery pressures have been shown to be an independent predictor of cardiac transplant³ and to be associated with an increased risk of death and hospitalization in patients with dilated cardiomyopathy.⁴ Pulmonary hypertension leads to right ventricular (RV) systolic failure, which has been shown to be a stronger predictor of mortality than the gold standard $\text{VO}_{2\text{max}}$ in patients with advanced systolic HF.⁵ Although underrecognized, RV systolic failure may occur with HF with preserved LVEF (also referred to as diastolic HF) through the mechanisms outlined in Figure 1.

Pathophysiology

Diastolic Dysfunction. The pathophysiology of LV diastolic dysfunction is at least in part related to impaired ventricular relaxation and compliance and has been discussed in depth elsewhere.⁶ Contributing factors include increased stiffness of the aortic tree as well as an increase in intravascular volume as it occurs with renal failure.⁷ The degree of impairment can be quantified by calculating the time constant of isovolumic relaxation (τ) from a high-fidelity LV pressure tracing or by various echocardiographic

It is well recognized that patients with severe left ventricular (LV) systolic dysfunction develop pulmonary venous hypertension or postcapillary pulmonary hypertension, which leads to an increase in pulmonary vascular resistance (PVR) and right ventricular (RV) systolic failure. It is often underrecognized, however, that patients with heart failure with preserved LV ejection fraction and diastolic dysfunction may also develop postcapillary pulmonary hypertension with elevated PVR leading to RV systolic failure. This form of biventricular failure is a result of diastolic failure on the left in patients with preserved LV ejection fraction and systolic failure on the right. At this time, there are no randomized trials or guidelines addressing the management of patients with diastolic heart failure with and without resultant RV failure. The authors review the pathophysiology, clinical presentation, and suggested treatment of this underrecognized clinical entity. (CHF. 2007;13:164-169) ©2007 Le Jacq

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Manuscript received February 9, 2007; revised March 16, 2007;
accepted April 16, 2007

parameters (mitral inflow velocities, color M-mode of mitral flow propagation, pulmonary vein flow, and tissue Doppler of mitral annulus). Persistent diastolic dysfunction may lead to pulmonary hypertension.

Pulmonary Hypertension: Not Just An Increase in Pulmonary Capillary Wedge Pressure. Pulmonary hypertension is defined by a mean pulmonary artery pressure >25 mm Hg at rest or >30 mm Hg with exercise. This can be suggested by finding an elevated RV systolic pressure using Doppler echocardiography. Differentiating precapil-

lary pulmonary hypertension (pulmonary capillary wedge pressure [PCWP] ≤ 15 mm Hg with a transpulmonary gradient >5 mm Hg) from postcapillary pulmonary hypertension (PCWP ≥ 18 mm Hg), however, currently requires right heart catheterization.

Mean pulmonary artery pressure (mPAP) is equal to right-sided cardiac output (Q) multiplied by pulmonary vascular resistance (PVR), added to pulmonary venous pressure. In clinical practice, the pulmonary venous pressure can be approximated by the PCWP (mPAP = (Q • PVR) + PCWP).

Thus, abnormal increases in either the volume of pulmonary blood flow, PVR, or PCWP will lead to pulmonary arterial hypertension and subsequent RV pressure overload.

In patients with chronic LV diastolic dysfunction, as is the case with patients who have chronic LV systolic dysfunction, there is an elevation of PCWP resulting in an increase in pulmonary venous pressure. These patients also have an increase in PVR due to dysregulation of vascular smooth muscle and structural remodeling.⁸ The elevated PVR in patients with pulmonary venous hypertension contains a predominately “reactive,” or readily reversible, component and a “fixed,” or not readily reversible, component (Figure 1). The reactive component is readily reversible because of pulmonary vascular endothelial dysfunction involving alterations in levels of nitric oxide and endothelin.

Endothelin, a potent arterial and venous vasoconstrictor, binds to the endothelin receptor on smooth muscle cells, which leads to vasoconstriction of pulmonary arteries and veins.⁹ In addition to its direct vasoconstrictive properties, endothelin can exert long-term effects on vascular smooth muscle cell proliferation and phenotype, increasing collagen synthesis that leads to intimal fibrosis, which contributes to pathologic pulmonary vascular remodeling.^{10,11} This component of pulmonary hypertension secondary to chronic LV dysfunction is generally referred to as fixed because it does not rapidly respond to vasodilator treatment but may resolve over months to years.

Increased PVR, in addition to elevated pulmonary venous pressure, reflects an increase in mPAP, which is a major determinant of RV afterload and therefore RV output.

The key determinants of pulmonary venous hypertension in patients with LV dysfunction have been the focus of several recent investigations. It had been previously thought that the degree of LV systolic dysfunction has a strong correlation with the severity

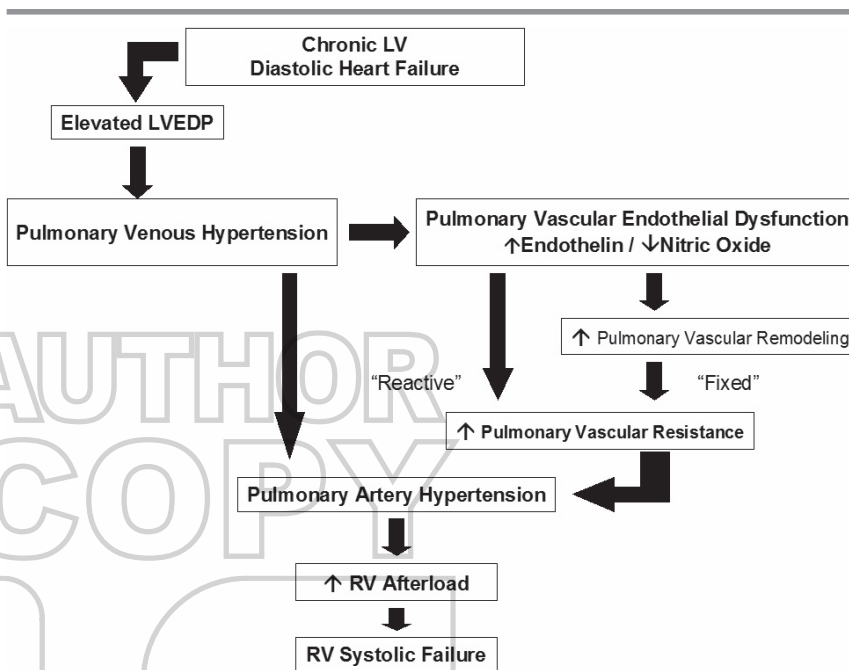


Figure 1. Proposed relationship between left ventricular (LV) diastolic dysfunction, pulmonary venous hypertension, and pulmonary artery hypertension. LVEDP indicates LV end-diastolic pressure; and RV, right ventricular.

of pulmonary hypertension. It was shown that pulmonary hypertension in patients with LV dysfunction is not independently related to the degree of LV systolic dysfunction, but is strongly associated with diastolic dysfunction (shorter mitral valve deceleration time).¹² These findings were confirmed in a study that compared invasive measurements in patients with postcapillary pulmonary hypertension, and the results demonstrated that patients with pulmonary hypertension had more diastolic abnormalities and had a poor correlation with systolic LV indices. Patients with the greatest impairment of diastolic function had the highest pulmonary artery pressure.¹³ These studies suggest that the degree of diastolic dysfunction may correlate better with pulmonary hypertension and thus RV function.

RV Failure. Persistent pulmonary hypertension can lead to RV failure from pressure overload. The right ventricle hypertrophies in response to chronic elevation in pulmonary artery pressure, generating much higher peak systolic pressures than the unstrained

right ventricle. This leads to a reduction in wall stress for any given intracavitary pressure. As hypertrophy progresses, the mechanical characteristics of the right ventricle become similar to those of the left ventricle. It is able to maintain systolic function in the face of heightened pulmonary artery pressure but requires higher filling pressures to maintain preload and forward flow. The right ventricle is more afterload-sensitive than the left ventricle, which can augment contractility in the face of pressure overload when compared with the right ventricle. With time, RV hypertrophy may be unable to maintain a normal level of systolic stress and leads to RV dilatation with diminished contractile performance. RV dilatation with HF may be associated with a resultant drop in flow; thus, pulmonary arterial pressures when measured at this time may be relatively low despite persistent elevation in PVR. RV dilatation is accelerated by tricuspid regurgitation, which tends to thwart the compensatory Frank-Starling mechanism.¹⁴

The hallmark of right-sided HF is edema. Its formation requires both

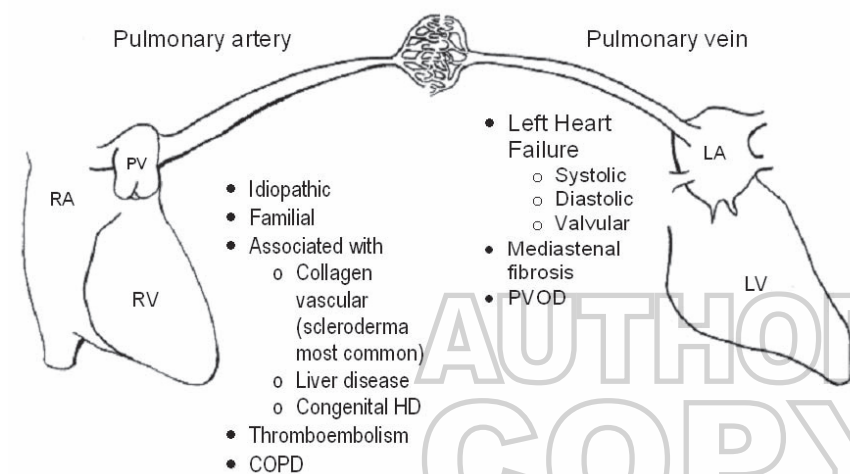


Figure 2. An anatomic overview of precapillary or pulmonary arterial hypertension (left) and postcapillary or pulmonary venous hypertension (right). Abbreviations: PV, pulmonary valve; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; HD, heart disease; COPD, chronic obstructive pulmonary disease; and PVOD, pulmonary veno-occlusive disease.

elevation of central venous pressures and a stimulus for renal sodium and water retention. It is thought that reduced forward cardiac output and perturbation of neuroendocrine activity leads to renal sodium retention.¹⁵ Moreover, in the setting of right-sided HF, increased renin secretion leading to enhanced vasoconstriction and sodium retention is accentuated by augmented adrenergic activity.¹⁶ Simply stated, a hyperrenin, hyperaldosterone state exists in patients with right-sided HF and contributes substantially to sodium retention and edema formation.

In addition to peripheral edema and ascites, edema of the visceral organs contributes to alterations in hepatic, pancreatic (interstitial pancreatitis), renal, and intestinal function. Pleural effusions develop because of impediment to parietal pleural drainage.

Diagnosis of RV Failure

Symptoms. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and peripheral edema.¹⁷ Although patients with RV failure often complain of dyspnea due to

elevated filling pressures and low cardiac output, the absence of pulmonary congestion on chest radiography because of an increase in pulmonary vascular resistance may lead to misdiagnosis and treatment delays. In addition, patients may present with a dull ache in the right upper quadrant or epigastrium from congestive hepatomegaly with ascites and peripheral edema. In some cases, patients may present with abdominal pain and diarrhea from bowel edema due to decreased reabsorption of water in the colon. These atypical symptoms may lead to misdiagnoses and delays in optimal treatment.

Physical Examination. Physical examination reveals elevated jugular venous pressure with hepatojugular reflex, an RV S3 gallop, an RV lift, a murmur of tricuspid regurgitation, Kussmaul's sign, and peripheral edema (which can include scrotal and presacral edema). Severe right-sided HF may be associated with a pulsatile, enlarged liver secondary to severe tricuspid regurgitation and ascites. Hypotension is often present in late stages secondary to decreased cardiac output in patients with more advanced right-sided HF.

Laboratory Analysis. Laboratory analyses are characterized by elevations in serum transaminase, alkaline phosphatase, and bilirubin secondary to chronic hepatic dysfunction from edema, ischemia, and impediment to venous return. The elevation in bilirubin is predominately indirect, indicating a deficiency in conjugation. These findings can be confused with acute viral hepatitis or chronic primary liver disease until it is appreciated that central venous pressure is elevated. Other laboratory findings commonly seen are hyponatremia from increased antidiuretic hormone release, elevated pancreatic enzymes, renal insufficiency from decreased cardiac output, and low serum protein and albumin levels due to lymphatic obstruction with resultant protein-losing enteropathy.

Transthoracic echocardiography typically demonstrates right atrial dilatation, RV dilatation and hypokinesis. When due to diastolic dysfunction, left atrial enlargement is seen (Figure 3). Color Doppler flow identifies varying degrees of tricuspid regurgitation. Paradoxical septal motion consisting of septal movement toward the RV during systole, rather than its normal motion toward the center of the LV cavity secondary to pressure overload is commonly seen.

Brain Natriuretic Peptide Testing.

Plasma brain natriuretic peptide (BNP) has been shown to increase in proportion to the extent of RV dysfunction in patients with precapillary pulmonary hypertension.¹⁸ Although it has not been demonstrated, one can expect similar results in patients with postcapillary pulmonary hypertension and RV failure. The analysis is complicated by the presence of LV diastolic BNP together with RV production of BNP, as it occurs when RV failure is present. The more muscular left ventricle produces more BNP in this setting. Although it cannot be used to differentiate LV diastolic HF with and without RV failure, serial measurements may be helpful in addition to physical examination findings to identify patients with decompensation.

Differential Diagnosis. Other potential etiologies of RV failure that should be considered include intrinsic renal disease, constrictive pericarditis, primary restrictive cardiomyopathy, and radiation heart disease. The most important masquerader is the patient with RV systolic failure due to precapillary pulmonary artery hypertension (Figure 2). On Doppler echocardiography, these patients may have abnormal mitral inflow patterns phasic with respiration due to ventricular interdependence.¹⁹ In these patients, however, the primary problem is obliterative changes in the pulmonary artery leading to plexogenic arteriopathy. Distinguishing between these similar clinical entities is crucial because treatments for precapillary pulmonary hypertension, such as use of endothelin receptor antagonists and epoprostenol, have shown to be of no benefit and may even be harmful in patients with postcapillary pulmonary hypertension.^{20–22}

Treatment

Treatment of biventricular failure (LV diastolic/RV systolic) is dependent on the severity of RV failure at the time of presentation. From our experience, we propose that patients with RV failure can be classified into 3 stages. This staging classification and the treatments proposed are based on the authors' experience and are not established.

Stage I RV Failure: Postcapillary Pulmonary Hypertension Without Volume Overload. Stage I patients have diastolic dysfunction, severe pulmonary hypertension, and RV enlargement with compensatory hypertrophy but have not developed significant volume overload.

Although there is a lack of randomized trials addressing diastolic HF, some feel that neurohormonal blockade should be the focus of treatment as in systolic HF.²³ The underlying problem in approximately 80% of hospitalized patients with diastolic HF is increase in LV mass and hypertension.²⁴ Furthermore, patients with new

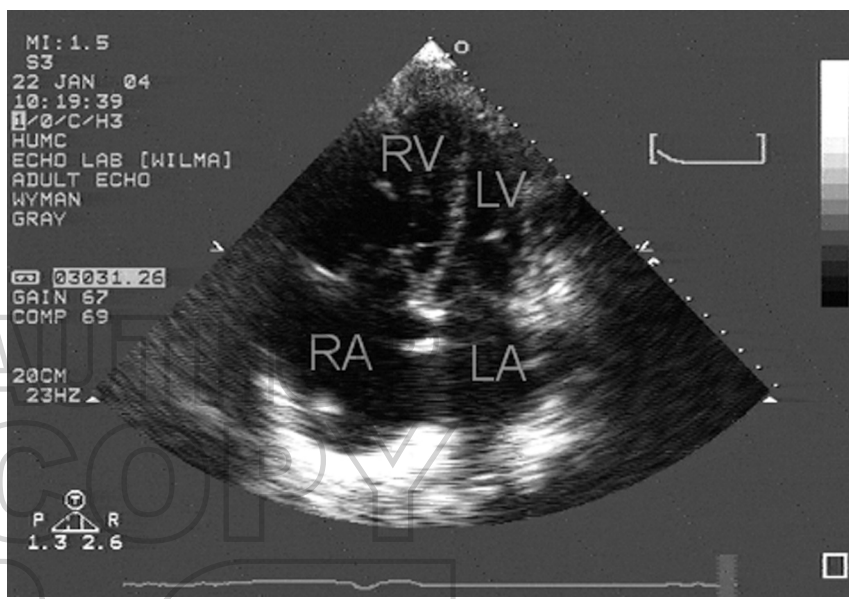


Figure 3. Transthoracic echocardiogram in the apical 4-chamber view demonstrates typical finding of right ventricular failure due to diastolic dysfunction. Abbreviations: RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

or persistent LV hypertrophy develop HF at a significantly higher rate than patients in whom LV hypertrophy regression occurs.²⁵ Reversing LV hypertrophy is best achieved by inhibition of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) compared with adrenergic blockade with β -blockers. In the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial,²⁶ losartan was associated with greater LV hypertrophy regression than was atenolol in patients with LV hypertrophy at baseline. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial²⁷ provides the best outcomes data supporting the use of ARBs in patients with diastolic HF. The study randomized slightly more than 3000 patients with symptomatic HF and LVEF >40% to either candesartan or placebo in addition to the present therapy. The candesartan group had a significant reduction in number of hospitalizations, but cardiovascular mortality was similar in both groups.²⁷

The Heart Failure Society of America (HFSA) 2006 Comprehensive Heart Failure Practice guidelines state that ACE inhibitors and ARBs should be considered in patients with HF and preserved LVEF.²⁸

Further RAAS blockade with an aldosterone antagonist (eplerenone) has been shown to have an additive effect in reducing LV mass when combined with an ACE inhibitor and may therefore be important in the management of patients with diastolic HF.²⁹ Further studies are required to better define its role.

Stage II RV Failure: Postcapillary Pulmonary Hypertension With Volume Overload. Stage II patients have diastolic dysfunction, elevated pulmonary artery pressures, RV dilatation, and significant fluid overload and may be diuretic-resistant.

General measures should aim to reduce RV systolic load with ACE inhibitors, aldosterone antagonists, digoxin, and diuretics to minimize the peripheral edema. Patients often become resistant to standard therapy with oral diuretics and develop marked azotemia while remaining edematous,

however. These patients are often admitted with ADHF for aggressive diuresis with intravenous diuretics.

In patients with ADHF who have evidence of fluid overload or worsening renal function with diuretic therapy, the HFSA guidelines state that intravenous vasodilator therapy with nitroglycerin, nitroprusside, or nesiritide may be added in the absence of systemic hypotension.²⁸ The combination of intravenous vasodilator and intravenous diuretic therapy often leads to profound diuresis without adversely affecting renal function. There is a paucity of clinical trials to define optimal therapy in patients with ADHF and they have predominately enrolled patients with a reduced LVEF.

The largest randomized trial in patients with ADHF that included patients with preserved LVEF was the Vasodilatation in the Management of Acute CHF (VMAC) trial.³⁰ It was a randomized, double-blind, placebo- and active-controlled trial in which 489 patients (65 with preserved systolic function) were treated with intravenous nesiritide, nitroglycerin, or placebo. Among patients with preserved LV systolic function, nesiritide significantly reduced PCWP throughout the 3-hour study period, while nitroglycerin did not.³¹

There is also evidence from HF registries and small nonrandomized trials to suggest that nesiritide may be beneficial in patients with ADHF with preserved LV systolic function with or without concomitant RV failure.

ADHERE (the Acute Decompensated Heart Failure National Registry) is a database of patients hospitalized with a primary diagnosis of acute decompensated HF that allows for retrospective analyses of clinical characteristics, treatments, and clinical outcomes. Of the 4175 nesiritide-treated patients, 1008 (24%) had preserved systolic function and experienced similar symptom

relief, diuresis, and reduction of length of hospitalization to those with systolic dysfunction (Scios Inc, Mountain View, CA, data on file).

Similar results were noted in a retrospective analysis that included 37 patients who had significant volume overload unresponsive to standard diuretics and vasodilators, a baseline LVEF of 55%±7%, evidence of diastolic dysfunction by Doppler echocardiography and elevated LV filling pressures. Nesiritide was administered for a mean duration of 69±45 hours and resulted in profound diuresis and symptomatic relief while preserving serum creatinine levels.³¹

Similar results have been noted in 2 retrospective analyses of 5 and 10 patients with decompensated right-sided HF and preserved systolic function (EF >50%). Nesiritide administration resulted in “profound diuresis” with a neutral effect on renal function in the first study and a significant improvement in the second study.^{32,33}

In addition to being a potent vasodilator, nesiritide has been shown to have lusitropic effects manifested by improved isovolumic relaxation time (decrease, τ) and improved transmitral Doppler flow profiles.^{34,35} Nesiritide has also been demonstrated to significantly reduce pulmonary artery pressures and thus RV systolic load in patients with postcapillary pulmonary hypertension secondary to both LV systolic and LV diastolic dysfunction.^{36–38} These effects may be responsible for the benefits seen in this patient population; however, data from registries and small retrospective analyses should be viewed with caution.

Oral diuretic therapy alone for chronic maintenance therapy should be avoided, as there is little clinical benefit and it may lead to adverse renal effects. These patients may benefit from the addition of high-dose aldosterone antagonist in conjunction with

optimal medical therapy (ACE inhibitors, ARBs, and low-dose β -blockers). This combination appears to effectively maintain volume status without adversely affecting renal function.

Stage III RV Failure: RV Systolic Failure With Attenuated PA Pressures.

In more advanced RV failure (stage III) manifested by RV dilatation and hypokinesis with attenuated pulmonary artery pressures, management with vasodilator therapy may become difficult because of significant hypotension. The attenuated pulmonary pressures may allow for effective diuresis with intravenous loop diuretics alone. These patients often have severe RV systolic failure and require inotropic support to improve RV cardiac output, however. With improved cardiac output and correlative increases in blood pressure, low-dose ACE inhibitors and high-dose aldosterone antagonists are adjunctive. In patients with advanced RV failure, β -blocker therapy may not be possible because of its potential negative inotropic and chronotropic effects, which may lead to a decrease in right ventricle-dependent cardiac output. Continuous intravenous inotropic support may be necessary to maintain euvoledmia and avoid frequent hospitalizations.

Conclusions

The clinical entity of LV diastolic and RV systolic HF often remains underdiagnosed, which leads to delays in treatment with possible adverse outcomes. LV diastolic dysfunction should be considered as an etiology of pulmonary hypertension in the setting of elevated PCWP (postcapillary pulmonary hypertension) and as cause of RV systolic failure. The treatments discussed herein are dependent on the stage of RV failure and warrant further clinical studies to better define ideal treatment strategies.

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