Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 24, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.12.049

EDITORIAL COMMENT

Pulmonary Hypertension

A Stage for Ventricular Interdependence?*

Henry H. Hsia, MD, Francois Haddad, MD

Stanford, California

Once considered an uncommon disease, chronic thromboembolic pulmonary hypertension (CTEPH) is now recognized as a distinct clinical entity (1). Its pathophysiology may be related to recurrent embolic events, in situ thrombosis, effects of vasoconstrictive mediators, immune-related events, and ventricular remodeling (2–6). Changes in the microvascular arteriopathy, similar to those seen in other forms of pulmonary hypertension, may also account for progressive clinical decline (7).

See page 2193

Heart failure associated with chronic right ventricular (RV) pressure overload is a complex syndrome (8), with ventricular hypertrophy, dilatation, and systolic failure. At a cellular level, marked down-regulation of the α-myosin heavy chain (MHC) was observed with a reciprocal up-regulation of its less active beta-isoform (beta-MHC). Such shifts in cardiac myosin composition are associated with a decrease in contractility and have been seen in other pathologic conditions associated with myocardial failure (9–11). Significant RV dysfunction occurs with delayed activation and repolarization, with down-regulation of various potassium currents (I_{K1}, I_{to1}, and I_{Ks}) contributing to action potential duration (APD) prolongation in the RV (12,13). RV metabolism is also altered in the failing RV, demonstrated by an increase in glucose uptake (14). This has been the basis for an interesting field of research on metabolic modulation in right heart failure (15).

However, ventricular dysfunction in the setting of chronic RV pressure overload is not just limited to the RV. Interdependence between the RV and left ventricle (LV) was first described by P.I. Bernheim in 1910. The "Bernheim effect" described RV failure in patients with aortic stenosis, presumably due to the hypertrophied septum encroaching on the RV cavity (16). Similarly, RV dysfunction influencing LV hemodynamics in various clinical and experimental models has also been recognized. Such "reverse Bernheim effects" implies that RV pressure overload leads to leftward bowing of the interventricular septum during diastole, thereby causing decreased LV chamber size, compliance, and contractility (17–19). However, the impaired LV function in the setting of chronic RV pressure overload may not simply be the result of geometric effects of RV enlargement and LV chamber distortion by the Frank-Starling mechanism. Effects of RV remodeling, notably conduction slowing and AP prolongation, contribute to lengthening of the RV contraction duration and marked delay in RV peak myocardial shortening and, consequently, the onset of diastolic relaxation with respect to the septum and the LV, regardless of the presence of absence of right bundle branch block (20,21). Such interventricular mechanical asynchrony and RV-to-LV diastolic interventricular delay decrease LV filling and effective stroke volume. The abnormal LV diastolic and systolic function is therefore in large part due to low LV preload and underfilling rather than LV compression (17,20,22).

In clinical observations and animal studies of pulmonary hypertension, ventricular interdependence is further manifested by LV "atrophic" remodeling. Reductions in LV mass and expression of α-MHC were observed as a consequence of LV unloading (23). Similar atrophic LVs can also be observed in other conditions with chronic RV pressure overload, such as rheumatic mitral stenosis (24) and end-stage pulmonary emphysema (25), in which the LV is also underfilled. Normalization of RV function and LV diastolic filling after mitral valvuloplasty and orthotopic lung transplantation lead to significant increases in LV end-diastolic volume, stroke volume, and restoration of LV mass. Similarly, successful pulmonary thromboendarterectomy restores the LV mass in patients with CTEPH (23).

Mechanical unloading in vivo induced profound electrophysiologic changes similar to that observed in pressure overload induced hypertrophic phenotype (26). Whether electrophysiologic remodeling of the LV occurs in pressure overload-induced RV failure is unknown. In this issue of the *Journal*, Hardziyenka et al. (27) studied the LV electrophysiologic properties in rats with experimentally induced pulmonary hypertension. Electrocardiographic and echocardiographic recordings, coupled with epicardial mapping in Langendorff-perfused hearts, histology analysis, patch clamping, gene expression, and protein measurements of the LV in rats with pressure-induced RV failure were compared with controls. Moreover, intraoperative epicardial LV mapping was also performed in patients with CTEPH who underwent pulmonary endarterectomy.

The strength of this study resides in its multifaceted, well-designed experimental design. Echocardiographic evidence of RV failure was associated with diminished LV

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Cardiovascular Medicine Division, Stanford University, Stanford, California. Dr. Hsia has received support from Medtronic, Biosense-Webster, and St. Jude Medical. Dr. Haddad has reported that he has no relationships relevant to the contents of this paper to disclose.

stroke volume and ejection fraction. Epicardial mapping demonstrated significantly prolonged QT intervals and LV effective refractory periods (ERPs), along with markedly reduced longitudinal conduction velocity in both patients and animals with RV failure compared with controls.

To establish the cellular basis of ERP prolongation and conduction slowing, cellular electrophysiology studies were performed on isolated myocytes. LV myocytes from animals with RV failure exhibited significantly prolonged APDs. The mRNA expression of *Kcnip2*, which encodes a subunit of the transient outward potassium current (I_{to}) was significantly reduced, in accordance with the observed AP/ERP prolongations. In contrast, expression levels of other potassium, sodium, and calcium channels remained unchanged.

Morphometric measurements showed the LV myocytes were shorter and narrower compared with controls, consistent with atrophic changes with reduction of LV mass. The LV conduction slowing was not explained by impaired impulse formation, as resting membrane potential, AP amplitude/upstroke, and ionic currents were unaltered. Instead, impaired LV impulse transmission in RV failure was related to both the reduction in cell size (28) and impaired cell-to-cell impulse transmission. Quantification of the connexin (Cx)-43 protein expression indicated a 24% decrease in the LV of experimental animals with RV failure. Similarly, LVs of CTEPH patients also exhibited marked ERP prolongation and conduction slowing, compared with those without RV failure.

The current study highlights the much underappreciated RV influence on LV function. It represents an extension of previous investigations on the complex interactions between the ventricles and provides insight into the mechanism of LV remodeling. It is interesting that mechanical unloading produces a similar phenotype as that of hemodynamic overload. Down-regulation of the α-MHC was observed in both hypertrophic failing RV myocytes and shrinking LV myocytes in animal models of RV failure (11,23). LV electrophysiologic alterations induced by RV failure were similar to changes occurring in other forms of left heart failure (29,30). Despite an increase in the interstitial collagen deposition in the RV (but not in the LV), RV conduction velocities were increased compared with controls. This was associated with RV myocyte hypertrophy and a 30% increase in Cx-43 expression. Other investigators have demonstrated a greater degree of electrical abnormalities in the RV compared with the LV. Such heterogeneity in regional conduction velocities, prolongation of refractoriness, and abnormal dispersion of repolarization between ventricles favor the occurrence of early afterdepolarizations, and constitute the substrate for ventricular arrhythmias (11,31).

Clinical Implications

Pulmonary hypertension increases loading on the RV, which can lead to electrical, mechanical, and structural changes. It sets the stage for ventricular interdependence, resulting in LV unloading, dyssynchrony, and atrophic remodeling. Pulmonary thromboendarterectomy offers a potentially curative intervention for patients with CTEPH. Successful surgery improves lung perfusion and reduces pulmonary vascular resistance, and is associated with an acceptable perioperative mortality in experienced centers (3). RV afterload reduction results in recovery of RV systolic function and improved LV preload. Restoration of LV diastolic and systolic functions is associated with a normalization of LV mass (22,23,32,33). These findings suggest that atrophic LV remodeling may be reversible. Future investigations should focus on innovative treatments to minimize such secondary adaptation to abnormal LV unloading and mechanisms of "reverse remodeling."

Because interventricular delay in systolic contraction and diastolic relaxation occur in patients with CTEPH and other forms of RV pressure overload, pre-exciting the RV with RV pacing may provide resynchronization, minimize diastolic interventricular delay, improve LV filling and stroke volume (34). In addition to pulmonary hypertension, RV pacing may be a viable treatment for RV failure in congenital heart diseases (35–37). These studies offer proof-of-concept of using RV pacing for treatment of right heart failure. However, whether such RV resynchronization can prevent LV remodeling is unknown. Replication of the clinical observations with independent randomized trials to assess long-term benefits and mortality reduction are still required.

Reprints requests and correspondence: Dr. Henry H. Hsia, Cardiac Electrophysiology & Arrhythmia Service, Stanford University, 300 Pasteur Drive, H2146, Stanford, California 94305-5233. E-mail: hhsia@stanford.edu.

REFERENCES

1. Piazza G, Goldhaber S. Chronic thromboembolic pulmonary hypertension. N Engl J Med 2011;364:351–60.
2. Fedullo P, Rubin L, Kerr K, Auger W, Channick R. The natural history of acute and chronic thromboembolic disease: the search for the missing link. Eur Respir J 2000;15:435–7.
3. Fedullo P, Auger W, Kerr K, Kim N. Chronic thromboembolic pulmonary hypertension. Semin Respir Crit Care Med 2003;24:274–85.
4. Kim H, Yung G, Marsh J, et al. Pulmonary vascular remodeling distal to pulmonary artery ligation is accompanied by upregulation of endothelin receptors and nitric oxide synthase. Exp Lung Res 2000;26:287–301.
5. Reesink H, Meijer R, Lutter R, Boomsma F, Jansen H, Kloek J, Bresser P. Hemodynamic and clinical correlates of endothelin-1 in chronic thromboembolic pulmonary hypertension. Circ J 2006;70:1058–63.
6. Usui S, Yao A, Hatano M, Kohmoto O, Takahashi T, Nagai R, Kinugawa K. Upregulated neurohumoral factors are associated with left ventricular remodeling and poor prognosis in rats with monocrotaline-induced pulmonary arterial hypertension. Circ J 2006;70:1208 –15.
7. Moser K, Bloor C. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 1993;103:685–92.

8. Bogaard H, Abe K, Vonk Noordegraaf A, Voelkel N. The right ventricle under pressure: cellular and molecular mechanisms of right-heart failure in pulmonary hypertension. Chest 2009:135:794–804.
9. Nakao K, Minobe W, Roden R, Bristow M, Leinwand L. Myosin heavy chain gene expression in human heart failure. J Clin Invest 1997:100:2362–70.
10. Lowes B, Minobe W, Abraham W, et al. Changes in gene expression in the intact human heart: down-regulation of alpha-myosin heavy chain in hypertrophied, failing ventricular myocardium. J Clin Invest 1997:1009:2315–24.
11. Benoist D, Stones R, Drinkhill M, Bernus O, White E. Arrhythmogenic substrate in hearts of rats with monocrotaline-induced pulmonary hypertension and right ventricular hypertrophy. Am J Physiol Heart Circ Physiol 2011:300:H2230–7.
12. Chen P, Moser K, Dembitsky W, et al. Epicardial activation and repolarization patterns in patients with right ventricular hypertrophy. Circulation 1991:83:104–18.
13. Li G, Lau C, Leung T, Nattel S. Ionic current abnormalities associated with prolonged action potentials in cardiomyocytes from diseased human right ventricles. Heart Rhythm 2004;4:460–8.
14. Oikawa M, Kagaya Y, Otani H, et al. Increased [18F]fluorodeoxyglucose accumulation in right ventricular free wall in patients with pulmonary hypertension and the effect of epoprostenol. J Am Coll Cardiol 2005;45:1849–55.
15. Haddad F, Ashley E, Michelakis ED. New insights for the diagnosis and management of right ventricular failure, from molecular imaging to targeted right ventricular therapy. Curr Opin Cardiol 2010:25:131–40.
16. Bernheim P. De l'asystolie veineuse dans l'hypertrophie du coeur gauche par stenose concomitante du ventricule droit. Rev Med 1910:30:785–801.
17. Lazar J, Flores A, Grandis D, Orie J, Schulman D. Effects of chronic right ventricular pressure overload on left ventricular diastolic function. Am J Cardiol 1993:72:1179–82.
18. Marcus J, Vonk Noordegraaf A, Roeleveld R, Postmus P, Heethaar R, Van Rossum A, Boonstra A. Impaired left ventricular filling due to right ventricular pressure overload in primary pulmonary hypertension: noninvasive monitoring using MRI. Chest 2001:119:1761–5.
19. Alpert J. The effect of right ventricular dysfunction on left ventricular form and function. Chest 2001:119:1632–3.
20. Marcus J, Gan C, Zwanenburg J, Boonstra A, Allaart C, Götte M, Vonk-Noordegraaf A. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. J Am Coll Cardiol 2008;19:750–7.
21. Hardziyenka M, Campian M, Bouma B, et al. Thromboembolic pulmonary hypertension is associated with activation delay and action potential prolongation in right ventricle. Circ Arrhythmia Electrophysiol 2009:2:555–61.
22. Gurudevan S, Malouf P, Auger W, et al. Abnormal left ventricular diastolic filling in chronic thromboembolic pulmonary hypertension: true diastolic dysfunction or left ventricular underfilling? J Am Coll Cardiol 2007;49:1334–9.
23. Hardziyenka M, Campian M, Reesink H, et al. Right ventricular failure following chronic pressure overload is associated with reduction in left ventricular mass: evidence for atrophic remodeling. J Am Coll Cardiol 2011:57:921–8.
24. Tischler M, Sutton M, Bittl J, Parker J. Effects of percutaneous mitral valvuloplasty on left ventricular mass and volume. Am J Cardiol, 1991:68:940–4.
25. Rensing B, McDougall J, Breen J, Vigneswaran W, McGregor C, Rumberger J. Right and left ventricular remodeling after orthotopic single lung transplantation for end-stage emphysema. J Heart Lung Transplant 1997:16:926–33.
26. Schwoerer A, Melnychenko I, Goltz D, et al. Unloaded rat hearts in vivo express a hypertrophic phenotype of cardiac repolarization. J Mol Cell Cardiol 2008:45:633–41.
27. Hardziyenka M, Campian ME, Verkerk AO, et al. Electrophysiologic remodeling of the left ventricle in pressure overload-induced right ventricular failure. J Am Coll Cardiol 2012;59:2193–202.
28. Wiegerinck R, Verkerk A, Belterman C, et al. Larger cell size in rabbits with heart failure increases myocardial conduction velocity and QRS duration. Circulation 2006;113:806–13.
29. Akar F, Rosenbaum D. Transmural electrophysiological heterogeneities underlying arrhythmogenesis in heart failure. Circ Res 2003:93:638–45.
30. Akar F, Spragg D, Tunin R, Kass D, Tomaselli G. Mechanisms underlying conduction slowing and arrhythmogenesis in nonischemic dilated cardiomyopathy. Circ Res 2004:95:717–25.
31. Li G, Lau C, Leung T, Nattel S. Ionic current abnormalities associated with prolonged action potentials in cardiomyocytes from diseased human right ventricles. Heart Rhythm 2004:1:460–8.
32. Menzel T, Wagner S, Kramm T, Mohr-Kahaly S, Mayer E, Braeuninger S, Meyer J. Pathophysiology of impaired right and left ventricular function in chronic embolic pulmonary hypertension: changes after pulmonary thromboendarterectomy. Chest 2000;118:897–903.
33. Reesink H, Marcus J, Tulevski I, et al. Reverse right ventricular remodeling after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension: utility of magnetic resonance imaging to demonstrate restoration of the right ventricle. J Thorac Cardiovasc Surg 2007:133:58–64.
34. Hardziyenka M, Surie S, de Groot J, et al. Right ventricular pacing improves haemodynamics in right ventricular failure from pressure overload: an open observational proof-of-principle study in patients with chronic thromboembolic pulmonary hypertension. Europace 2011:13:1753–9.
35. Dubin A, Feinstein J, Reddy V, Hanley F, Van Hare G, Rosenthal D. Electrical resynchronization: a novel therapy for the failing right ventricle. Circulation 2003;107:2287–9.
36. Dubin A, Janousek J, Rhee E, et al. Resynchronization therapy in pediatric and congenital heart disease patients: an international multicenter study. J Am Coll Cardiol 2005;46;2277–83.
37. Dubin A, Rosenthal D. Right ventricular resynchronization: moving beyond proof of concept. Heart Rhythm 2009;6:857–9.

Key Words: electrophysiologic remodeling ■ pulmonary hypertension ■ right ventricular failure.