JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2014 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 1, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.04.027

EDITORIAL COMMENT

Left Ventricular Atrophy in Pulmonary Arterial Hypertension

A Sinister Dexter Conundrum*

Markus Meyer, MD

In response to external demands, the myocardium undergoes adaptive changes. This process has been termed cardiac plasticity, and changes at the macroscopic and cellular levels under various environmental conditions have been documented (1). The most basic response to increased volume or pressure loading is an increase in cardiac muscle mass (2). Within this context, concentric left ventricular hypertrophy is the most prevalent and best understood cardiac adaptation, and many of the pathways triggered by pathological hemodynamic and neurohumoral stimuli have been identified (3). The mechanisms that lead to right ventricular hypertrophy in response to pulmonary arterial hypertension (PAH) have undergone less research, but similar basic concepts probably apply. However, in the right ventricle, this adaptive change is frequently associated with eccentric remodeling and contractile dysfunction, especially in patients with congenital heart disease, in whom the development of PAH is often preceded by a chronic volume load.

SEE PAGE 28

Ventricular interdependence, which is mandated by a serial circulatory system, pericardial restraints, and the shared myocardium of the septum, affects left ventricular geometry and function. In severe pulmonary hypertension, this is manifest as a flattened ventricular septum, which gives the left ventricle its characteristic D shape. But there are other more subtle changes in left ventricular geometry. In patients with severe pulmonary hypertension, the left ventricle often appears "small and underfilled." This observation has been recently confirmed and quantified in patients with pulmonary hypertension from occlusive pulmonary vascular disease. The most prominent findings from these studies are reductions in left ventricular end-diastolic volume, stroke volume, and ejection fraction (4,5). Some studies also suggest that the mass of the left ventricular free wall may be reduced (6). As a result, it has been proposed that the left ventricle in patients with severe PAH undergoes an adaptive atrophic change that is opposite to the hypertrophy of the right ventricle. This coexistence of a diametrically opposed growth response provides a revealing insight into the mechanisms and pathways that govern myocardial adaptation. The work load imposed on the ventricle must be the primary determinant of the growth response, as systemic variables (i.e., neurohumoral factors) would unlikely trigger a disparate response. This, however, raises the question of why the left ventricle appears to atrophy in severe PAH. One possible explanation is a reduction in left ventricular filling or at the minimum a reduction in the normal variation in left ventricular inflow. Normally, the pulmonary vascular bed can readily accommodate a several-fold increase in blood flow. This allows a normal cardiac output reserve, and the associated fluctuations in volume load provide a growth stimulus. This variation in flow is reduced in patients with PAH, which results in a sheltered and unchallenged left ventricle. Further progression of the underlying pulmonary vasculopathy and right ventricular failure will ultimately reduce left ventricular filling and cardiac output at rest. Other growth stimuli and contributors to cardiac work load, such as preload and heart rate, undoubtedly also influence this process in less predictable ways. However, chronic underutilization provides the most plausible explanation for left ventricular atrophy in PAH, as similar

*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 Division of Cardiology, University of Vermont College of Medicine, Burlington, Vermont. Dr. Meyer has reported that he has no relationships relevant to the contents of this paper to disclose.

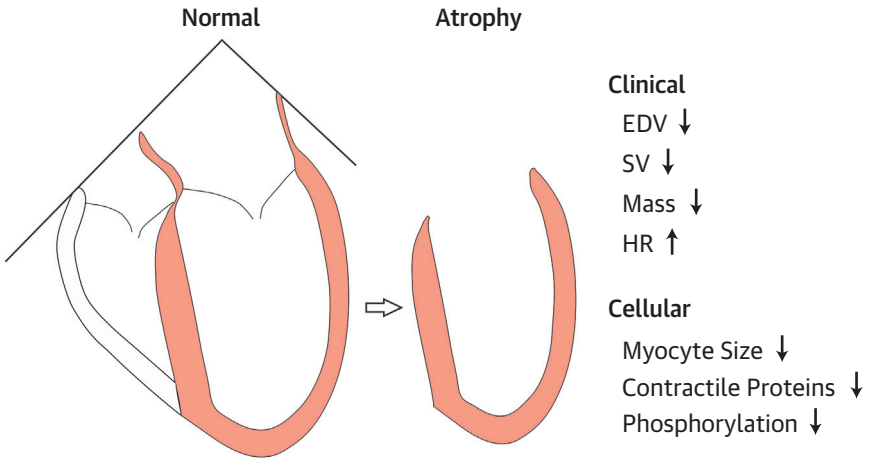

FIGURE 1 **Principal Clinical and Cellular Changes in Left Ventricular Atrophy**

EDV = end-diastolic volume; HR = heart rate; SV = stroke volume.

changes are reported in mitral stenosis and in other settings (7). Extreme physical inactivity induced by bed rest or zero-gravity conditions in healthy subjects has been demonstrated to reduce left ventricular chamber volume and myocardial mass within days to weeks (8,9). These studies demonstrated that the reduction in left ventricular cavity size typically precedes the loss in left ventricular mass (**Fig. 1**). The reported reductions in end-diastolic volume are approximately 10% to 20%, and the reductions in mass are 5% to 15%, depending on the duration of the exposure. A potential maximum in mass reduction of 25% to 35% has been reported in patients with tetraplegia, as this occurs in the context of a complete cessation of all physical activity (10). Left ventricular atrophy also appears to play a role in aging and a sedentary life-style (11).

Besides the clinically measurable changes in left ventricular structure and function, not much is known about the mechanisms and pathways that lead to myocardial atrophy. This is due in part to the inherent difficulty in obtaining myocardial tissue from patients and the fact that the majority of animal models do not reproduce the chronicity of the human disease process. Sufficient quantities of human myocardium typically only become available when patients with end-stage conditions undergo cardiac transplantation, which also provides an opportunity to procure donor tissue. Despite some experimental limitations, these studies have been very valuable to our understanding of various myocardial disease processes. In a laudable undertaking, Manders et al. (12) provide us with a first insight into the cellular and molecular alterations associated with left ventricular atrophy in patients. At the morphometric cellular level, they found that left ventricular cardiac myocytes from patients with end-stage PAH are thinner compared with myocytes from donor hearts. The investigators explain this finding by a lower cellular content of the contractile protein myosin, which dominates the protein composition of the cardiac myocyte. In the next set of experiments, the investigators confirmed that the atrophied, smaller cells have indeed a reduced force-generating capacity. They also determined that the relative force generation at submaximal calcium concentrations is greater, which is manifest as a leftward shift in the calcium-force curve. In other words, the interaction of myosin and actin appears to be more sensitive to calcium, which is the main mediator of force generation. Under the assumption that there is no change in calcium cycling, this may represent a partially compensatory mechanism but also could explain the impairment in left ventricular diastolic function that has been reported with this condition (13). The investigators also provide us with a potential explanation as to why cardiac troponin I and cardiac myosin-binding protein C, which both regulate the contractile proteins, are less phosphorylated. These results have clinical relevance because patients with end-stage PAH who receive donor lungs can develop left ventricular failure, which is believed to be due to the re-exposure of the left ventricle to higher workloads (14).

JACC VOL. 64, NO. 1, 2014
JULY 8, 2014:38–40

However, similar to related transplantation-based myocardial tissue studies, there are some inevitable limitations in the experimental approach, mainly a small sample size and the pooling of World Health Organization group 1 patients with variable initiating etiologies.

Nonetheless, this study demonstrates left ventricular atrophy at the cellular and molecular levels in patients. It appears likely that other mechanisms and pathways will be found, and it is certain that many new questions will arise as we better understand this principally reversible physiological adaptation (10,11). An interesting question that came to mind concerns the adaptive response and functional affiliation of septal myocytes in this setting of a conflicting growth stimulus. Left, right, or both?

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Markus Meyer, University of Vermont College of Medicine, Fletcher Allen Health Care, McClure 1, Cardiology, 111 Colchester Avenue, Burlington, Vermont 05401. E-mail: markus.meyer@vtmednet.org.

REFERENCES

1. Hill JA, Olson EN. Cardiac plasticity. N Engl J Med 2008;358:1370–80.

2. Linzbach AJ. Heart failure from the point of view of quantitative anatomy. Am J Cardiol 1960; 5:370–82.

3. Chien KR, Knowlton KU, Zhu H, et al. Regulation of cardiac gene expression during myocardial growth and hypertrophy: molecular studies of an adaptive physiologic response. FASEB J 1991;5: 3037–46.

4. Gan C, Lankhaar JW, Marcus JT, et al. Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension. Am J Physiol Heart Circ Physiol 2006;290:H1528–33.

5. Marcus JT, Vonk Noordegraaf A, Roeleveld RJ, et al. Impaired left ventricular filling due to right ventricular pressure overload in primary pulmonary hypertension: noninvasive monitoring using MRI. Chest 2001;119:1761–5.

6. Hardziyenka M, Campian ME, Reesink HJ, 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.

7. Gash AK, Carabello BA, Cepin D, et al. Left ventricular ejection performance and systolic muscle function in patients with mitral stenosis. Circulation 1983;67:148–54.

8. Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance. Circulation 1997;96:517–25.

9. Perhonen MA, Franco F, Lane LD, et al. Cardiac atrophy after bed rest and spaceflight. J Appl Physiol 2001;91:645–53.

10. Nash MS, Bilsker S, Marcillo AE, et al. Reversal of adaptive left ventricular atrophy following electrically-stimulated exercise training in human tetraplegics. Paraplegia 1991;29:590–9.

11. Fujimoto N, Prasad A, Hastings JL, et al. Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. Circulation 2010;122:1797–805.

12. Manders E, Bogaard H-J, Handoko ML, et al. Contractile dysfunction of left ventricular cardiomyocytes in patients with pulmonary arterial hypertension. J Am Coll Cardiol 2014;64:28–37.

13. Tonelli AR, Plana JC, Heresi GA, et al. Prevalence and prognostic value of left ventricular diastolic dysfunction in idiopathic and heritable pulmonary arterial hypertension. Chest 2012;141:1457–65.

14. Bîrsan T, Kranz A, Mares P, et al. Transient left ventricular failure following bilateral lung transplantation for pulmonary hypertension. J Heart Lung Transplant 1999;18:304–9.

KEY WORDS atrophy, cardiac function, LV, LV dimensions