Journal of the American College of Cardiology Vol. 51, No. 7, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.11.033

EDITORIAL COMMENT

Heart Inefficiency in Pulmonary Hypertension

A Double Jeopardy*

Rafael Beyar, MD, DSc, FACC, FESC

Haifa, Israel

The "dancing" septum, bowing leftward at end-systole, is a well-recognized echocardiographic feature in patients with pulmonary hypertension (PHN) (1,2). It has been shown that delayed onset of relaxation of the right ventricle (RV) relative to the left ventricle (LV) is responsible for that shift (3).

In normal physiology, a fascinating synchronization of right and left ventricular contractions exists. Electrical activation starts near the apex, exiting from the Purkinje fibers and spreading rapidly throughout the myocardium of both ventricles, with the latest activation at the RV outflow tract.

See page 750

Thus, whereas electrical activation is completed with a minor delay for the RV outflow tract, systolic contraction—as measured by the pressure rise—occurs in parallel in both ventricles, leading to the synchronous onset of systole. Normally, there is only a minimal delay in closure of the pulmonary valve with respect to the aortic valve, the well known physiological splitting of the second heart sound, which suggests synchrony at the end of ejection. As shown in the article of Marcus et al. (4) in this issue of the *Journal*, peak shortening as assessed by magnetic resonance imaging (MRI) tagging and strain analysis occurs almost simultaneously at the LV free wall, the septum, and the RV free wall in normal control patients. Right ventricular to LV synchrony in all parameters of contraction and relaxation, under wide ranges of heart rates and systemic loads, is the key to the successful orchestrated function of the heart. In spite of the large inequality in loads, these serially connected low- and high-pressure pumps function in perfect synchronized coordination under normal conditions.

However, the 2 serially connected pumps directly interact within each beat by sharing a common septum (5) and the pericardial space (6,7). Efficiency in delivering hemodynamic energy for both the low- and high-pressure circulations as well as economy in space allocation within the body is probably nature's rationale for such a unique mechanical design.

Pulmonary hypertension is a disease associated with high pulmonary microcirculatory resistance (8). The high resistance leading to increased RV pressure has unique effects on cardiac mechanics during systole. In a previous study using MRI tagging in PHN patients, Dong et al. (9) showed that the septum and the LV free wall that are flattened by high right-sided pressures exhibit reduced shortening that is inversely related to the degree of LV geometrical distortion. Higher distortion with more prominent septal flattening is associated with reduced septal as well as LV free wall shortening. It was suggested that, as a compensatory mechanism, a bellows systolic motion of the septum toward the LV helps to maintain LV systolic ejection fraction, despite the reduced myocardial shortening. This is clearly a mechanism by which the RV high systolic pressure causes a positive effect on LV systolic function.

However, when looking at the dynamics of septal motion at end systole, the picture becomes more complex. It seems that the high resistance between the 2 pumps disrupts the synchrony of contraction between the ventricles. How does the disruption in synchrony lead to multiple hemodynamic consequences that add up to jeopardizing the efficiency of cardiac function in PHN patients? In this issue of the *Journal*, Marcus et al. (4) have elegantly unraveled the time sequence of events that lead to the unique hemodynamic consequences in patients with pulmonary arterial hypertension, by following the dynamic sequence of shortening with MRI tagging. Whereas the onset of shortenings occurs without delay for both PHN and normal control groups, a large delay in the time to peak shortening of the RV free wall with respect to the LV free wall is demonstrated. Therefore, an increase in shortening duration of the RV free wall, which continued to shorten almost 100 ms after the end of LV ejection, is the mechanism by which the synchrony in relaxation is disrupted. This prolonged shortening duration of the RV free wall, continuing at early LV relaxation, causes the post-systolic bowing of the septum into the LV, thus impairing LV filling. The falling pressure in the relaxing LV, while the RV is still contracting, leads to rapid reversal of the trans-septal pressure gradient to negative values at early LV diastole. The RV free wall that helped LV ejection throughout systole, as proposed by Dong et al. (9), is now turned against early LV filling at the onset of diastole. An inefficient late systole of the RV, struggling with its high load, further impairs LV filling by shifting the innocent, already relaxing, septum leftwards. In other words, a rapid LV volume shift by the leftward bowing septum jeopardizes LV filling by preventing the rapid inward mitral flow wave that is expected at that time.

Why this does happen and how is it related to basic heart muscle physiology? The relationship between load and relaxation has been thoroughly investigated by Brutsaert

*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 Rambam Medical Center and Technion-Israel Institute of Technology, Haifa, Israel.

et al. (10) and others (11). Higher afterload imposed on isolated muscles increases the duration of contraction. The complex molecular mechanisms that are associated with acute changes with load are nicely given in a comprehensive model by Landesberg et al. (12). However, the chronic response to hypertrophic stimulus might not be similar to the acute changes. Studies in isolated rat hypertrophied myocytes due to hypertension have shown prolonged action potential, prolonged calcium transient, and prolonged contraction (13,14). Remodeling of the contractile process is playing a major role in the modification of the response of the myocardium to chronic load changes. Both preload and afterload increases can contribute to the prolonged contraction duration.

Ventricular interdependence plays a key role in PHN. The mechanical aspects of right and left ventricular interaction have been studied in detail by Dong et al. (15) in animal experiments and by applying a mathematical model (16). It was clearly shown that this interaction is due to the common septum shared by the ventricles, further enhanced by the limited and relatively noncompliant space within the pericardial sac. The mechanical model also showed that RV pressure overload led to diastolic unloading of both the LV free wall and the septum and is a major factor in determining septal curvature.

Returning to our PHN patients with these physiological and mechanical concepts, the increase in pulmonary pressure leads to an increase in RV free wall afterload, which might be partially compensated at the myocardial level by hypertrophy. The myocardial response to increased afterload in acute and chronic conditions (10–14) leads to lengthening of contraction and delay in the time to peak shortening. The increased duration of shortening leads the RV free wall to divert its energy at the last 100 ms of systole to the leftward septal shift. Not only does it impair systolic efficiency of RV ejection by the flaccid bowing septum; it also infringes early diastolic efficiency of LV filling. The rapidly relaxing septum, in synchrony with LV free wall relaxation, "bows" to the rapid reversal of the trans-septal gradient. This double jeopardy is a markedly devastating phenomenon, leading to further progression of the disease. The feedback mechanism of prolonged systole that is employed by the RV wall to overcome its increased load fails and leads to inefficiency in both RV systole and LV diastole.

We may take advantage of our enhanced understanding of the mechanisms involved in cardiac double jeopardy in PHN to find novel ways to treat these patients. Obviously, the underlying mechanism is an increase in pulmonary resistance (8), and the primary target of our therapy is the pulmonary microvasculature. However, can we find additional therapeutic methods to enhance the efficiency of contraction in these patients? When timing and synchrony are at stake, pacing strategies are often sought. Negotiating asynchrony of LV contraction with dual pacing has become an accepted therapeutic modality for heart failure (17). Is it possible that dual pacing can be used to optimize the delayed ejection of the RV? Although such ideas have to be proven in animal models, the challenge would be to reverse or decrease the 100-ms delay by appropriate differential pacing programs. An alternative option is to reduce the imbalance in shortening duration between the chambers with pharmacological methods that will limit the variability and load dependence of relaxation. The challenge in these patients is huge, because the disease is devastating and rapidly progressive once a certain threshold is crossed.

Reprint requests and correspondence: Dr. Rafael Beyar, Rambam Health Care Campus, Women's Division, Technion, 8 Ha'Aliyah St., Haifa 35254, Israel. E-mail: r_beyar@rambam.health.gov.il.

REFERENCES

1. Stojnic BB, Brecker SJ, Xiao HB, et al. Left ventricular filling characteristics in pulmonary hypertension: a new mode of ventricular interaction. Br Heart J 1992;68:16–20.
2. Gan CT, 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.
3. Lopez Candales A, Dohi K, Bazaz R, Edelman K. Relation of right ventricular free wall mechanical delay to right ventricular dysfunction as determined by tissue Doppler imaging. Am J Cardiol 2005;96:602–6.
4. Marcus JT, Gan CT-J, Zwanenburg JJM, et al. 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;51:750–7.
5. Bemis CE, Serur GR, Borkenhagen D, et al. Influence of right ventricular filling pressure on left ventricular pressure and dimension. Circ Res 1974;34:498–504.
6. Glantz SA, Misbach GA, Moores WY, et al. The pericardium substantially affects the left ventricular diastolic pressure volume relationship in the dog. Circ Res 1978;42:433–41.
7. Stokland O, Miller M, Lekven J, Ilebekk A. The significance of the intact pericardium for cardiac performance in the dog. Circ Res 1980;47:27–32.
8. Jain S, Ventura H, de Boisblanc B. Pathophysiology of pulmonary arterial hypertension. Semin Cardiothorac Vasc Anesth 2007;11:104–9.
9. Dong S-J, McGregor JH, Crawley AP, et al. Regional left ventricular systolic function in relation to the cavity geometry in patients with chronic right ventricular pressure overload: a three dimensional tagged magnetic resonance imaging study. Circulation 1995;91:2359–70.
10. Brutsaert DL, Rademakers FE, Sys SU. Triple control of relaxation: implications in cardiac disease. Circulation 1984;69:190–6.
11. Van Heuningen R, Rijnsburger WH, ter Keurs HE. Sarcomere length control in striated muscle. Am J Physiol 1982;242:H411–20.
12. Landesberg A, Markhasin VS, Beyar R, Sideman S. Effect of cellular inhomogeneities on cardiac tissue mechanics based on intracellular control mechanisms. Am J Physiol 1996;270:H1101–14.
13. McCrossan ZA, Billeter R, White E. Transmural changes in size, contractile and electrical properties of SHR left ventricular myocytes during compensated hypertrophy. Cardiovasc Res 2004;63:283–92.
14. Naqvi RU, Tweedie D, MacLeod KT. Evidence for the action potential mediating the changes to contraction observed in cardiac hypertrophy in the rabbit. Int J Cardiol 2000;77:189–206.
15. Dong S-J, Beyar R, Zhou ZN, et al. Determinants of midwall circumferential segment length of the canine ventricular septum at end-diastole. Am J Physiol 1993;265:H2057–65.
16. Beyar R, Dong S-J, Smith ER, Belenkie I, Tyberg JV. Ventricular interaction and septal deformation during global differential loading conditions: a model compared to experimental data. Am J Physiol 1993;265:H2044–56.
17. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA 2007;297:2502–14.