Circulation: Heart Failure

ON MY MIND

Right Ventricular Afterload Sensitivity Has Been on My Mind

Mohit Pahuja, MD
Daniel Burkhoff, MD, PhD

It is often said that the right ventricle (RV) is more afterload sensitive than the left ventricle (LV). One of the most highly cited references as the source of this concept is a chapter entitled "Cor Pulmonale and Pulmonary Thromboembolism" by McFadden and Braunwald, which appeared in early versions of Dr Braunwald's *Heart Disease: a Textbook of Cardiovascular Medicine*.[1] The now-classic graph comparing changes of RV and LV stroke volume in response to increased afterload pressures in the pulmonary artery and aorta, respectively, is reproduced in Figure (A). They showed that for a 20-mm Hg increase of pulmonary systolic pressure, RV stroke volume decreases by 25%, whereas for a 40-mm Hg increase in arterial pressure, LV stroke volume decreases by only 10%. Aside from the obvious difference in wall thicknesses, which intrinsically renders the normal RV one-fifth to one-seventh as strong as the LV, are other factors fundamental to explain the observed phenomenon? Several mechanisms have been implicated, such as differences between RV and LV geometries, pulmonary pressure-induced shifts of the RV septum, and fundamental differences in the contractile properties of right and left ventricular myocardium. In all instances, some aspect of RV physiology is at the core of the explanation.

The original data from which the often-referenced figure was constructed were derived from 2 separate studies performed by Abel in normal dogs wherein the effects of variations of peripheral and pulmonary vascular resistances were varied using a Blalock clamp. For LV experiments, the clamp was placed on the descending aorta,[2] and for RV experiments, the clamp was placed on the right pulmonary artery.[3] By changing the degree of clamping of the Blalock clamps, pulmonary and systemic vascular resistances could be varied to achieve desired changes in pressures. From a historical perspective, it is noteworthy that neither graph of Figure (A) appeared in the original articles by Abel[2] and Abel and Waldhausen[3]; these graphs appear to have been constructed based on the original raw data presented in the tables and graphs from these 2 articles.

In the modern era, such experiments can be readily repeated in silico with the use of comprehensive cardiovascular models in which circulatory parameters can be controlled and varied over wide ranges. The use of such models can yield additional insights into hemodynamic mechanisms. We replicated the basic study by Abel using such a model that has been used extensively in teaching and research[4] (Figure [B]). The model-based experiment reproduced the real experiment with a very high degree of similarity. Accordingly, one arrives at the same conclusion: for a given increase of arterial pressure, RV stoke volume decreases more in the RV than in the LV.

However, in the course of reproducing the experiments by Abel, one thing became very clear: to achieve the desired changes in RV and LV stroke volumes over the respective ranges of pressure changes, it was required to increase pulmonary vascular resistance by 1400%, which was drastically greater than the

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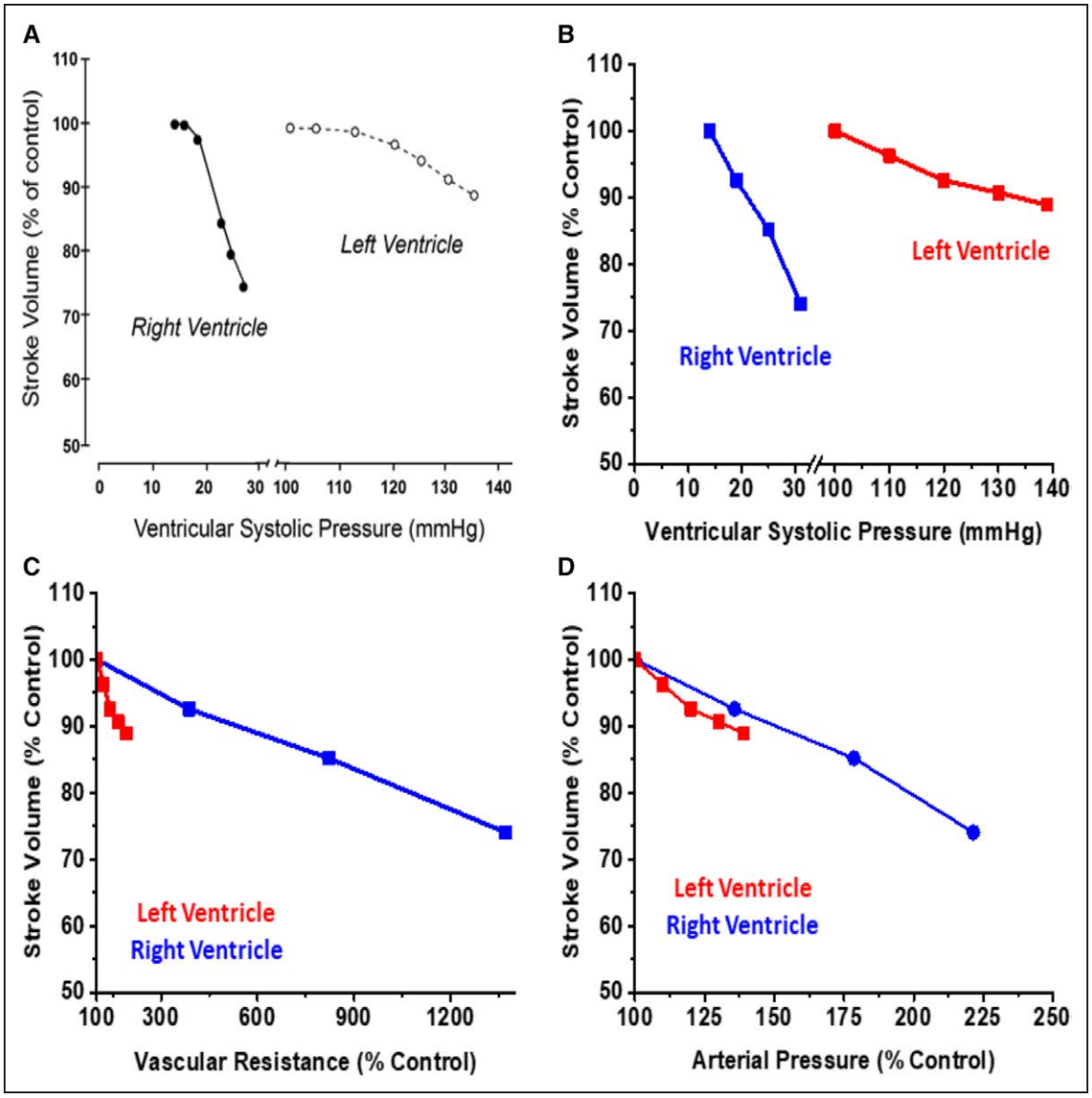

Figure. Showing stroke volume variation in right and left ventricle.
A, original figure from Dr Braunwald's *Heart Disease: A Textbook of Cardiovascular Medicine*[1] showing variation in stroke volume with increasing afterload. **B**, replicated the basic study by Abel using cardiovascular model for both right and left ventricle. **C**, variation of pulmonary and systemic vascular resistance for the desired changes in stroke volume. **D**, variation of percentage of stroke volume over different range of percentage changes in peak pressure for both right and left ventricle.

required 200% increase of systemic vascular resistance (Figure [C]). Thus, a main contributor to the differences between the RV and LV afterload sensitivities did not reside with the ventricles but rather in the nature of the loading systems and the vastly different magnitudes over which they were manipulated.

That pulmonary vascular resistance was modified over a much greater range than systemic vascular resistance mirrors clinical experience. Even in patients with severe arterial hypertension or patients in severe cardiogenic shock treated with high-dose vasoconstrictors, it would be unusual to encounter a patient with an systemic vascular resistance that is even 2× the upper limit of normal. However, increases of pulmonary vascular resistance in patients with chronic heart failure can routinely reach 4 to 6× normal and, not uncommonly, as much as ≥10× normal in acute pulmonary embolism and in chronic pulmonary arterial hypertension.

Looking at this from a broader perspective, the observations described above serve to emphasize the importance of understanding the differences between the various indexes of afterload. From the perspective of the ventricle, afterload resistance (or impedance) indexes vascular properties and signifies the hydraulic load imposed by the vascular system that the ventricle faces to eject blood. In contrast, afterload pressure does not uniquely characterize vascular properties but is the result of the interaction between ventricle and

vasculature. From the myocardial perspective, however, afterload wall stress (σ) may be a more meaningful index of afterload since this quantifies the forces experienced by the myocytes and sarcomeres during contraction. σ plays a pivotal role in myocardial biology in that it regulates cell growth (concentric hypertrophy); myocytes hypertrophy to maintain σ at as normal a value as possible. Peak wall stress is related to peak chamber pressure, end-systolic volume, radius of curvature (r), and wall thickness (h) via principles based on Laplace law: σ is proportional to P·r/h. Assuming that r and h are relatively constant over the range of stroke volumes encountered in the experiments described above, σ is most strongly dependent on peak chamber pressure. As shown in Figure (D), when changes in stroke volume are plotted as a function of percentage changes of peak pressure, the respective curves for RV and LV behavior are nearly superimposable.

Although these insights may seem trivial, the implications are important. At a minimum, this discussion highlights that when comparing properties of systemic and pulmonary circulations, proportional rather than absolute changes in vascular parameters may provide more meaningful comparisons. The model findings also highlight the importance of understanding different measures of ventricular afterload, as they are not interchangeable, and changes in one does not always result in equivalent or proportional changes in others.

The present discussion is restricted to the physiology of acute changes in pulmonary afterload. In the setting of chronic increases in pulmonary resistance, the RV has a tremendous capacity to hypertrophy and dilate, as reviewed recently.[5] This adaptation serves to reestablish appropriate ventricular-vascular coupling in the short term but in the end can lead to other problems such as (1) tricuspid annular dilatation leading to regurgitation and (2) extreme degrees of myocardial hypertrophy that cause metabolic needs to exceed the blood flow capacity of the right coronary artery and microcirculations.

Questions related to RV afterload sensitivity have resurfaced recently, for example, in the context of emerging percutaneous therapies to treat severe tricuspid regurgitation. Despite relatively limited experience with multiple devices, variable clinical responses have been noted particularly as they relate to the development of acute (severe) RV failure. Can the impact of restoring tricuspid competency (with the associated increase in RV afterload) on RV function be predicted for a given patient? Similarly, complex questions have arisen when it comes to the development of device-based therapies for end-stage pulmonary arterial hypertension. Sound understanding of how to quantify pulmonary hemodynamics and RV contractile properties and how these determine RV-pulmonary vascular coupling will facilitate development of important, testable hypotheses related to therapies dealing with the right side of the circulation. In this regard, the discussions above that have been stimulated by the original studies performed by Abel[2] and Abel and Waldhausen.[3] Although those studies have gone largely unrecognized and in essence forgotten, their interpretation by McFadden and Braunwald[1] has been widely recognized and has proved to be enduring. After >50 years since the original studies, open-minded thinking about those results may lead to new insights and new therapeutic approaches to the challenging problem of RV failure.

ARTICLE INFORMATION

Correspondence

Mohit Pahuja, MD, Division of Cardiology, Department of Internal Medicine, Detroit Medical Center/Wayne State University Medical School of Medicine, 4201 St. Antoine, Suite 5A, Detroit, MI 48201. Email mohitkmc@gmail.com

Affiliations

Division of Cardiology, Department of Internal Medicine, Detroit Medical Center/Wayne State University School of Medicine, MI (M.P.). Cardiovascular Research Foundation and Division of Cardiology, Columbia University, New York, NY (D.B.).

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