

EDITORIAL COMMENT

Cor Pulmonale Parvus

Patting the Elephant*



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The right ventricle has historically been poorly understood terra incognita in adult cardiovascular imaging. Neither invasive angiography, first-pass radionuclide imaging, nor 2-dimensional (2D) echocardiography proved sufficiently robust or widely applicable to provide an adequate understanding of right ventricular (RV) pathophysiology in common forms of pulmonary disease. The emergence and development of cardiac magnetic resonance (CMR) imaging and, more recently, cardiac computed tomography angiography have, for the first time, provided robust tools with sufficient volumetric coverage and spatial and temporal resolution to fill this gap. Unfortunately, 3-dimensional echocardiography has played a limited role in these disorders due to the frequent impairment of transthoracic acoustic windows by lung disease.

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In this issue of the *Journal*, a report from MESA (Multi-Ethnic Study of Atherosclerosis) describes relationships between chronic obstructive pulmonary disease (COPD) and emphysema and RV size, mass, and function (1). Data on pulmonary perfusion also were obtained, but are not presented. The authors report that in individuals without overt cardiovascular disease, RV end-diastolic volume, stroke volume, and end-systolic volume are decreased with increasing COPD functional severity, whereas end-diastolic volume and stroke volume are also reduced with increasing severity of emphysema in those with

centrilobular and paraseptal emphysema. In this study, RV mass was unchanged by either COPD or emphysema. The authors term these patterns cor pulmonale parvus.

The observations reported appear to contradict conventional wisdom that advanced COPD is associated with RV hypertrophy, dilation, and, ultimately, pump dysfunction related to progressive pulmonary hypertension. However, this profile has been drawn in the past from studies of more advanced disease using small sample sizes and less robust imaging methods. The authors suggest that selection criteria for the main MESA population, the substudy MESA-RV, the MESA COPD study, and a cancer screening study from which additional patients were drawn, as well as the small number of patients with advanced disease included overall, may account for these discrepancies. They also propose that impaired venous return due to a reduced pressure difference between the abdomen and thorax, with a resultant reduction in central blood volume and decreased preload, may be an important contributor to reduced RV volumes.

An earlier paper on RV from MESA actually reports discrepant results, indicating that “percent emphysema was associated with smaller RV volumes and lower mass” (2). It is not clear to this reader how this conclusion, derived from a larger population, and the conclusion that RV mass is unchanged in the present paper, can both be correct.

Additionally, given the relatively small magnitude of the differences in RV volume reported (15% to 20%), the clinical significance of the present findings remains less than clear. Further, a number of technical considerations render CMR RV quantitation somewhat problematic. As the authors point out, CMR ventricular volume and mass quantitation have tended to include papillary muscles and protruberant trabeculae in chamber volume. For the left ventricle, many studies have shown that this approach produces very reproducible results for left ventricular

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(LV) volumes, ejection fraction, and mass. That makes the method superior to 2D echocardiographic quantitation for use in clinical research (higher reproducibility equals smaller sample sizes) and in application to serial follow-up of individual patients. However, it likely also results in higher absolute volumes and lower myocardial mass than actually exist. It is important to note that validation studies for CMR quantitation in human hearts are all based on comparisons with other imaging results that are actually less reliable than CMR, not with hard physical measurements. In the right ventricle, the situation is more difficult, given the very thin RV wall, the high level of trabeculation, and the oblique orientation of the tricuspid valve plane. In addition, the body of validation studies, such as they are, is much smaller than for the left ventricle.

Although the results of the present study are quite interesting, it is hard to avoid a sense of disappointment at the paucity of pathophysiological insights that emerge and the highly fragmented picture of the right ventricle in lung disease that MESA has provided. Indeed, this report is one of many fragments of the RV story provided by MESA. There are actually 2 overlapping MESA studies that address RV structure and function, MESA-RV and MESA COPD. These studies have produced a total of 23 previous publications on the right ventricle. By and large, each study focused on the relationship of a single variable to RV size, mass, and performance. Factors reported to have significant correlations with RV differences between patients with and without COPD include C-reactive protein; interleukin-6 and fibrinogen; dyspnea; ambient air pollution; use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; von Willebrand factor; brachial artery diameter; selective serotonin reuptake inhibitor use; differences in obesity, race, and sex; matrix metalloproteinase-9 and plasminogen activator inhibitor-1; sex hormones; physical activity; cardiovascular risk factors; and septal myocardial strain. No efforts appear to have been made to characterize the relationships of these factors with each other or characterize the mechanistic basis mediating effects on the right ventricle to provide an integrated perspective on the problem, although each study evaluates quite a number of other potential covariates. Given the small population with COPD in the present study, analysis of all these previously described related factors certainly cannot be done, but it is easy to imagine that the concatenation of them may have influenced these results. Scant reference is made to the bulk of this extensive body of work in the current paper.

Thus, there are many publications, but little pathophysiology. Indeed, this approach seems ubiquitous in clinical cardiovascular research these days. Large sample sizes in multicenter studies combined with improved statistical methods have resulted in much greater ability to demonstrate statistically significant associations between variables. However, association is often taken for causality, and retrospective data often provide the basis for claims of “predictive” value. But association is not causality, and the ability to predict must be demonstrated prospectively. The result in many instances has been a more “knowing” literature that knows less than meets the eye. It is also important to know what you do not know.

Last, the authors overlook a very familiar and plausible phenomenon, observed commonly in the left heart that may well explain the observed results. Concentric LV remodeling, with a normal absolute LV mass but a smaller than normal LV volume, originally described by Ganau et al. (3), is at least as common in systemic hypertension as overt LV hypertrophy. Such remodeling actually normalizes myocardial afterload, often expressed as wall stress, despite increased chamber pressure, thereby representing an important adaptive mechanism in pressure overload states.

The same phenomenon can be found in elderly patients with aortic stenosis and normal LV mass, especially in women. Moreover, as reported in part in MESA itself, this remodeling also occurs with aging in normal men and women in parallel with an age-related increase in average arterial systolic pressure, even in normotensive cohorts (4). Similar age-related changes in the right ventricle also have been described. Determination of RV pressure, dependent on either Doppler velocity of tricuspid regurgitation jets with indirect estimation of right atrial pressure or right heart catheterization, is certainly more problematic than determination of cuff blood pressure and was not performed in the present study. However, the authors have included age as a covariate, so presumably it does not explain the reported findings.

Thus, it is conceivable that the results of Kawut et al. (1) reflect RV concentric remodeling in response to mild increases in pulmonary artery pressure, whether at rest or with physical activity. This seems to me an important pathophysiological possibility that merits both discussion and further exploration. Although the RV in contemporary COPD and emphysema may be parvus, our understanding of it need not be.

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