Since 2009, there have been ≥170 articles published in the cardiopulmonary literature on right ventricular (RV) echocardiographic strain imaging, including several in *Circulation: Cardiovascular Imaging*. Of particular interest has been the effort to use RV echocardiographic strain imaging to assess RV systolic function in pulmonary hypertension and the relationship of RV strain to disease severity and outcomes. In this issue of *Circulation: Cardiovascular Imaging*, Fine et al., from the Mayo Clinic echo group, report on retrospectively evaluated data on the relationship of RV strain to outcomes in the largest such study to date, encompassing 575 patients with known or suspected pulmonary hypertension without elevated pulmonary venous pressure during a median follow-up period of 16.5 months. The data show a strong association between reductions in mean longitudinal strain and all-cause mortality, and cardiopulmonary mortality and cardiopulmonary events. An exhaustive biostatistical analysis shows the relationship to be quantitative, stronger than that of other echo indices including tricuspid annular plane systolic excursion, independent of clinical covariates and resulting in a significant improvement in predictive value when combined with relevant clinical variables, as reflected in a significant increase in the integrated discrimination improvement index and the c-statistic for the primary end point. Thus, the results promise to improve clinical risk assessment significantly for such patients and may improve clinical decision making.

The apparent benefit is, in large part, a reflection of the relatively weak performance of older 2-dimensional (2D) echocardiographic indices of RV performance including fractional area change and tricuspid annular plane systolic excursion in this setting. RV imaging has been a minefield for echocardiography in adults since its inception. The complexity of ventricular shape, the thinness of the RV free wall, and the limitations in adults of transthoracic and subcostal windows in permitting full visualization of the RV, particularly in the setting of RV dilatation, have conspired to limit echo effectiveness. Thus, indices of RV size and function have failed by and large to make contributions commensurate with the importance of RV dysfunction in a number of settings in adult medicine. The advent of cardiac MRI (CMR) in the 1980s led to rapid development of volumetric 3D methods for left ventricular (LV) size, function, and mass followed shortly by methods for 3D LV strain imaging which continue to be regarded, even today, as the gold standards in the cardiovascular armamentarium. But even so, evaluation of LV volume and mass remained more variable than desirable whereas RV free wall strain assessment remained elusive with CMR until recent years. The advent of tissue Doppler and then speckle tracking echocardiographic strain imaging have led to the explosive development of applications of LV strain imaging since 2000, largely focused on the high sensitivity of LV strain imaging for subclinical abnormalities, with early detection of myocardial dysfunction despite normal ejection fraction and potential prognostic and stress testing applications in the forefront. More recently, the emergence of echo RV free wall strain imaging has opened new possibilities, as reflected in the present study.

However, conspicuously absent from this article is any consideration of the potential value of transthoracic 3D echo imaging of RV structure and function for similar purposes. Unlike LV strain applications, applications of RV strain studies, such as the present one, have addressed issues in more advanced disease which, in the left heart, may be effectively assessed using LV volumes, mass, and ejection fraction. One suspects that similar reliance on 3D RV imaging is likely in the future. For the LV, 3D transthoracic imaging is better developed although still not in routine clinical use outside of more advanced laboratories. Echocardiographic 3D imaging of the RV has, however, been shown to correlate well with CMR data for quite some time and to be feasible in most adults with pulmonary hypertension. Moreover, recent studies have demonstrated progressively wider applicability of newer generations of transthoracic 3D echo software and hardware, even for RV imaging. Furthermore, significant progress has been made in use of knowledge-based reconstruction of 3D RV structure and function from 2D images. Thus, it would seem that the time is ripe for incorporation of RV volumetric analysis into efforts at imaging for prognosis in disorders affecting the RV primarily, such as pulmonary hypertension.

There are other issues that suggest a cautious approach to the findings in the present report. Echo strain imaging and image analysis have been thoroughly proprietary since their inception, with lack of disclosure of some fundamental details of the methods by the various vendors hampering efforts of users to ascertain exactly how image processing and analysis are done. In addition, the technology has been...
evolving rapidly, driven by both advances in the field and market forces. Thus, there have been no assurances that results obtained using hardware and software provided by 1 ultrasound vendor are directly comparable with those obtained with materials provided by other vendors, or even prior and future iterations of such technology from the same vendor. For example, the authors cite reproducibility data for RV strain from the literature obtained at various times with other technology and other analytic approaches, but their relevance is uncertain. Overall, there is a real need for the establishment of technical standards for echocardiographic strain imaging using speckle tracking methods so that we can be confident that strain results obtained on different echo platforms have similar information content.

Additional problems in the interpretation of RV echocardiographic strain imaging relate to the impact of loading conditions and use of strain parameters in assessment of contractile state. Much of the literature treats both echo and CMR strain results descriptively or even makes reference to the relative load independence of strain or strain rate parameters. However, this is clearly untrue. Systolic strain is largely an ejection phase index and as such is substantially dependent on preload and afterload. Although strain rate may be somewhat less influenced by loading conditions, it is hardly insensitive to those parameters. But the loading parameters required are not the hemodynamic ventricular chamber indices familiar to clinicians, such as end-diastolic pressure and volume and systolic ventricular pressure. Rather, one must address loading at the myocardial level. For the LV, this has traditionally been done using methods for calculation of wall stress dating to the 1960s which make the erroneous assumption that myocardium is an elastic and isotropic material with the same deformability in every direction. However, it is clear that myocardium is neither elastic nor isotropic and that its properties vary from locus to locus in a ventricular wall dependent on fiber direction, local wall thickness, and a variety of other parameters. Unfortunately, efforts to use measurable physical properties of myocardium in finite element analyses tend to be stymied by inability to measure such properties in situ in humans in intact perfused myocardium. It is possible that the emerging technique of CMR myocardial elastography can, in time, address this problem, but that is by no means certain even for LV myocardium at this point in time. But none of this obviates the fact that, absent some index of loading at the myocardial level, interpretation of strain data, comparing patient groups and serially in a single patient, is on shaky ground. At present, preliminary data from our laboratory suggest that the best approach for LV in the short term may be a global expression of the determinants of wall stress, such as the product of ventricular pressure and volume, divided by myocardial mass. However relevance of such an approach to the RV is uncertain given the complexity of RV shape, marked differences in thickness and function of the RV free wall and interventricular septum, and the effects of ventricular interaction. It is also implied in a few places in this article that evaluation of strain is equivalent to evaluation of myocardial contractility. This has been a popular notion, related to the supposed load independence of strain measures and cited in a number of other articles, but is similarly off the mark. If contractility means anything, it is as an expression of the ability of a given piece of myocardium to generate tension and shortening under any loading conditions. There have been approaches proposed that may provide a useful strain-based contractility index, including the ratio of strain to afterload and a strain elastance plot, related to the ventricular elastance approach. Preliminary data from our laboratory suggest that the strain/afterload ratio is promising but that strain elastance approaches will be difficult to implement without autonomic blockade given the sensitivity of the baroreceptor reflex and resultant changes in contractile state. Such autonomic blockade is feasible in normal but almost certainly not in the presence of significant myocardial dysfunction.

Finally, as is true in much of the literature nowadays, this article focuses on prediction of outcomes. However, any meaningful sense, no retrospective analysis of a single series of patients can validate a predictive index. Rather, such analyses show associations of varying strength. I would argue that, to be entitled to the use of the term prediction, a minimum requirement is development of the predictive index in a large training set of data followed by validation prospectively in a second independent and large multicenter sample of subjects, using hard outcomes in both groups. Strangely, although cardiovascular applications of biostatistics have made dramatic progress in rigor in recent years in a number of respects, appropriate use of the term prediction does not seem to be among them.

In summary, the study by Fine et al on use of RV strain imaging to risk stratify patients with pulmonary hypertension in the absence of pulmonary venous hypertension promises to extend the usefulness of 2D echo in this setting at the present time. However, it remains uncertain whether this will lead to the desired result in the long term: a definitive method for prediction of outcomes in pulmonary hypertension. Nor is it clear whether progress in application of 3D RV or 2D knowledge-based volumetric imaging will supersede it or whether advances in image-based evaluation of RV loading conditions will permit meaningful assessment of RV contractility in the future.

Disclosures
None.

References


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