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Quantitative Right Ventricular Function in Pulmonary Arterial Hypertension: A Quest for a More Reliable Metric

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In this issue of the Journal, Motoji and colleagues presented a very interesting communication describing possible association of the apical longitudinal rotation (ALR) and the right ventricular (RV) performance in patients with pulmonary arterial hypertension (PAH).¹ The authors also presented their observation suggesting a possible overestimation of the RV function in PAH, while utilizing the variable widely used in the modern clinic practice—tricuspid annular plane systolic excursion (TAPSE). They postulated that in patients with a marked apical rotation, one should use TAPSE with caution, and should consider other parameters of the RV function (such as the RV free wall strain or the RV fractional area change) for assessment of the RV performance.

Clinical utilization of TAPSE for assessment of the RV function is currently supported by the echocardiography practice guidelines endorsed by the professional Echo societies.² TAPSE is a reliable, simple, and reproducible variable validated against other methodologies, and proven effective both in the research environment and in real-world clinical practice. Notably, calculation of TAPSE is feasible and reproducible using not only echocardiography but other imaging modalities as well, such as cardiac CTA³ or MRI.⁴

In 2006, Forfia and colleagues published a seminal prospective observational study of their prevalent cohort of patients with PAH.⁵ This study was the first to associate an easily obtained echocardiographic metric of RV function, TAPSE, with mortality in this disease. It also laid the groundwork for quantitative RV function to move to the bedside. Quantitative measurement of RV function received more attention in 2011 when van de Veerdonk and colleagues published a subset of their PAH cohort with cardiac MRI-based RV ejection fraction (RVEF). They demonstrated that RVEF <35% despite improved pulmonary

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afterload (pulmonary vascular resistance) on long-term vasoactive therapy resulted in higher mortality.⁶ Thus, although the sine qua non of PAH is increased afterload, the heterogeneous response of the RV may be just as meaningful (or perhaps more). Since then, a potpourri of various noninvasive measurements of RV function have been introduced in the pulmonary vascular world.

At the forefront of the debate, which noninvasive metric of RV function is most meaningful, is finding a variable that is most “load-independent.” Load dependency refers to a measurement closely related to either ventricular contractility or RV systolic elastance (*Ees*). *Ees* is a measure obtained from pressure–volume loop analysis and is constant on a beat-to-beat basis despite acute changes in preload and afterload. *Ees* increases commensurate with afterload by a sustained (several minute) increase in afterload. Therefore, it may more accurately define “intrinsic” RV function and adaptation. RV quantitative echocardiographic measurements have shown differences in load dependency with both RVEF and TAPSE highly load-dependent.⁷

The load dependency of TAPSE was confirmed by Forfia et al.,⁵ but perhaps the most interesting finding in their paper was that 8/32 (25%) patients in the middle and upper TAPSE tertile still died. Further, 6/15 (40%) in the bottom TAPSE tertile were still alive after a median follow-up of 19.3 months. Thus, although the cutoff used, based on stroke volume index, was discriminatory, fine-tuning the factors that lead to under- and overestimation would be beneficial. It is intuitively obvious that underestimation of TAPSE could be from its load dependency. In this regard, a higher afterload may lead to reduced TAPSE despite normal system adaptation (high contractility, *Ees*).

In this issue of the Journal, Motoji and colleagues provide us with additional insights into the mechanisms of TAPSE overestimation of the RV function related to an increased variability in the apical rotation. This phenomenon can be assessed using an advanced Echo application of the speckle tracking–derived longitudinal apical strain. Indeed, the RV contractility is not solely limited to the apex-to-base motion (although many believe this is a predominant pattern on the RV contraction). The pressure-overloaded RV may demonstrate a dominance of other directions of the systolic and diastolic motion. Adding to this complexity is change in the physiology of the interventricular septum in patients with a significant PH. The septum in these conditions becomes a functional part of the RV rather than LV and demonstrates a paradoxical motion, further changing a usual motion pattern of the tricuspid annulus. Accordingly, lateral (free RV wall) to septum direction of the RV contraction may become a predominant pattern in these patients.

In our clinical practice, we noted a significant role of the electromechanical changes in the RV contractility, mainly due to a delayed RV conduction, likely related to two mechanisms: (1) enlarged RV with a significant eccentric and concentric hypertrophy; and (2) increased RV myocardial fibrosis.

This paradox may further increase the RV dyssynchrony and change a normal apex-to-base contractile motion of the RV, influencing, in turn, a diagnostic value of the TAPSE. No doubt that regardless of the clinical scenario, any abnormal pattern of the RV contraction will

significantly influence the RV hemodynamic performance. To assess this complex RV contractility change, we must utilize all the available clinically methodologies. In this regard, utilization of the RV fractional area change (in addition to TAPSE) could elicit changes in the lateral (RV free wall to septum) contractility and further enhance diagnostic potential of the 2D echocardiographic study. Further yield in the diagnostic potential of the Echo applications in management of the PAH is associated with the use of the RV free wall longitudinal strain based on the speckle tracking methodology. RV strain may identify patients with early functional abnormalities and predict outcome in patients with PAH.⁸ However, the major limitation for the clinical utilization of the RV strain is an absence of the validated and dedicated RV strain software applications.

Another very promising echocardiographic application is a utilization of the 3D methodology for evaluation of the RV anatomy and function. The RV volumes and function values derived from the 3D datasets closely correlate with these derived from the cardiac MRI.⁹ Compared to MRI, 3D Echo applications are significantly cheaper and are available for bedside assessment even in the unstable patients who cannot undergo MRI. The 3D applications eliminate a major problem of the RV volumetric assessment, as there is no need in the simplification of the RV geometry assumptions. Assessment of the 3D-based RV strain and dyssynchrony may prove useful in future research in the RV pathology in general, and especially in patients with PAH.

In early 2013 at the World Symposium on Pulmonary Hypertension in Nice, France, the PAH clinical trial design was discussed.¹⁰ A significant topic of discussion relates to surrogate markers of PAH. There was a consensus that clinically meaningful surrogate markers are needed. This implies a marker of disease severity that lies on the causal pathway from disease to outcome and, thus, is not just related (by correlation for example) but modified by progression or therapy. However, there remains a paradox. Surrogate markers must be verified against a gold standard, which has yet to come to the forefront other than mortality. The implication is a study carried out based on a long follow-up period or retrospective analysis. Further, disease-specific markers should show more than agreement with the gold standard at a specified time but also a concomitant variation with the standard by repeated measurement.

Although we have made tremendous headway in determination of hemodynamic and imaging measures related to PAH prognosis, treatment response, and functional status, we have yet to study these measures serially from diagnosis to long-term follow-up and/or death. These large improvements have also increased the bar, as we no longer accept nonspecific measures such as cardiac index as a sufficient parameter to change or add therapy. Just as important as defining a “gold standard” is individualizing diagnosis and identification of the unique pulmonary vascular phenotypes. Motoji et al.¹ have taken an important step in further defining a subgroup of patients that may possibly deteriorate despite high TAPSE. This paper once again demonstrates a significant demand in further research to more reliably assess the RV performance and identify unique subgroups of the pulmonary hypertension patients that we would follow or treat differently as compared to our current PH clinical management paradigm.

One of the great experts in the RV hemodynamics research, James A. Goldstein, noted in one of his editorials¹¹ that the right and left ventricles differ in their architecture, mechanical performance, metabolism, and coronary blood flow, and thus, it should not be surprising that they differ markedly in their hemodynamic responses—even to ischemia. Following this important statement, we should not extrapolate our LV diagnostic imaging approach and historical experience to the RV; even a visual assessment of the LV function by the expert (the “eyeball” method), proven effective for decades in the clinical echocardiography, does not work well for the RV. We should not base our RV functional assessment (and management) just on a single variable such as TAPSE or even the RVEF. Utilization of all the available RV volumetric and functional echocardiographic parameters based on a local expertise, hardware, and postprocessing software may enhance diagnostic power of the imaging, as well as improve a clinical management of the patients and provide an individualized treatment option for the patients with PAH.

As the PAH population is highly heterogeneous, we expect that there will be a different “fingerprint” of the novel RV assessment methodologies in each clinical subset of the patients with PAH, closely related to their phenotype and genotype. In the next several years, ongoing global national and international PAH databases will provide us with a fascinating analysis of these phenotypic, genomic, and metabolic changes and will strongly enhance our clinical armamentarium in managing this serious disorder. While waiting for the results of this exciting new research, we have to keep in mind that using multiple echocardiographic variables for the RV functional assessment should become a standard clinical practice.

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