JACC: CARDIOVASCULAR IMAGING
VOL. 10, NO. 10, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2017.08.004

EDITORIAL COMMENT

Right Ventricle Dysfunction in Cardiomyopathy

To Measure Is to Know*

Sanjay K. Prasad, MD,[a,b] Amrit S. Lota, BM BCH[a,b]

In recent years, there has been concerted effort to explore the structure and function of the right ventricle in nonischemic dilated cardiomyopathy (DCM), the second most common cause of heart failure and leading indication for cardiac transplantation. Despite a number of clinical studies, there has been a significant lag time in harnessing this information to alter patient management partly due to: 1) a lack of consensus on the threshold for clinically significant right ventricular dysfunction (RVD); and 2) a lack of data regarding its incremental value over and above left ventricular ejection fraction. Another important question is whether RVD represents a predictable consequence of severe left heart disease or rather a distinct entity amenable to established or novel therapy.

SEE PAGE 1225

In this elegant study, Pueschner et al. (1), in this issue of *iJACC*, evaluated the prevalence as well as prognostic value of RVD in 423 patients with nonischemic DCM. Right ventricular ejection fraction (RVEF) and left ventricular ejection fraction were quantified by cardiac magnetic resonance (CMR), the gold standard of assessment of ventricular volumes, particularly important given the complex geometry of the right ventricle. Right heart catheterization was performed contemporaneously with CMR in 24% of the patient cohort. The median follow-up period was 6.2 years for cardiac mortality. The main findings were that: 1) a RVEF of <35% was the optimum threshold for clinically significant RVD; 2) the RVEF was a strong independent predictor of cardiac mortality (hazard ratio: 0.96; 95% confidence interval: 0.94 to 0.98; p = 0.0001); 3) knowledge of RVEF provided incremental clinical value—3.6% of patients were reclassified by the addition of RVEF to the best overall clinical model; and 4) right heart catheterization data indicated that transpulmonary gradient (TPG) was a stronger predictor of RVD than elevated pulmonary capillary wedge pressure (PCWP). This study, therefore, represents an important addition to the literature for a number of reasons.

Although there has been a steady progression from longitudinal echocardiographic indices, radionucleotide studies, and echocardiographic fractional area change, to CMR studies with smaller cohorts, there is little consensus on the definition of RVD. The present study includes the largest number of patients undergoing the accepted gold standard assessment, CMR, which is ideally suited for volumetric assessment of the asymmetrical bellows-shaped right ventricle. The investigators reported good intraobserver and interobserver variability (3.8% and 8.3%, respectively), consistent with previous studies (2). One of the main outputs is the classification of RVD with supportive outcome data. Significant RVD was defined as an RVEF of <35% based on survival curves for 423 patients stratified by RVEF, showing that subgroups with an RVEF of <25% and 25% to 35% had significantly lower probability of survival compared with those with an RVEF of >35%. This work builds on an earlier study by Gulati et al. (3), which defined an RVEF of <45% as an important predictor of adverse outcomes. In the present larger study, the authors refine risk based on further breakdown of the ejection fraction.

RVEF has consistently been shown to be a strong, independent predictor of cardiac mortality on multivariate regression analyses, which is also reflected in

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the [a]National Heart and Lung Institute, Imperial College London, London, United Kingdom; and the [b]Cardiovascular Research Centre, Royal Brompton Hospital, London, United Kingdom. Dr. Prasad has received honoraria for talks from Bayer Schering. Dr. Lota has reported that he has no relationships relevant to the contents of this paper to disclose.

this study (hazard ratio: 0.96; 95% confidence interval: 0.94 to 0.98; p = 0.0001) (3-5). RVD is generally reported in one-third of patients with nonischemic DCM and a common question is whether knowledge of this information provides incremental value to guide decision making in the majority of patients with mild or moderate degrees of RVD. Using a net reclassification index, the investigators showed that 3.6% of patients were correctly reclassified by the addition of RVEF to the best overall clinical model suggesting this assessment has real-world incremental usefulness.

Another important and novel aspect of this paper are the insights into the mechanistic basis for RVD provided by contemporaneous hemodynamic data on the determinants of RVD. The pathophysiology of pulmonary hypertension in heart failure is complex and heterogeneous with many gaps in our understanding (6,7). Post-capillary pulmonary hypertension is defined as elevated left atrial pressure (PCWP >15 mm Hg), and TPG refers to the pressure difference across the pulmonary circulation (mean pulmonary artery pressure [mPAP] − PCWP) with a value of >12 mm Hg indicating a disproportionate increase in mPAP due to neurohormonal activation, pulmonary vasoconstriction, and vascular remodeling. Hemodynamic assessment forms the cornerstone of evaluation in cardiac transplant candidates, where elevated pulmonary vascular resistance (derived from TPG/cardiac output) refractory to medical therapy ('fixed' pulmonary hypertension) represents a contraindication to cardiac transplantation (8). Approximately one-quarter of all patients underwent a clinically indicated right heart catheterization, perhaps introducing an element of referral bias but nevertheless reflecting real-world clinical practice. The investigators report that, although mPAP was predictive of RVD as one might expect, PCWP alone was not predictive, despite its primary elevation in left heart disease. However, other parameters, specifically, right atrial pressure (preload) and TPG (the pulmonary vasculature component of afterload), were predictive of RVD. The strength of this association was such that TPG remained 1 of the 3 strongest independent predictors of RVD alongside LVEF and systolic blood pressure.

The clinical implications of the hemodynamic findings are highly relevant. First, the importance of early detection of decline in RVEF as a strong indicator of rising TPG and, therefore, diminishing window for therapeutic intervention. Second, serial assessment of RVEF by CMR may be a valuable tool to monitor response to escalation in therapy. Third, the potential role of vasoactive compounds beyond the confines of idiopathic pulmonary hypertension. In small studies, patients with DCM treated with sildenafil have shown improvement in exercise capacity, natriuretic peptide levels, and quality of life with significant reductions in mPAP, TPG, and PVR, but only modest reduction in PCWP (9). Taken together, these findings support the idea that vasoactive therapy targeted against the pulmonary vasculature may benefit patients with heart failure with secondary (and still reactive) pulmonary hypertension, and that perhaps such therapy may be considered before the onset of RVD. Further studies are much needed to explore how the use of such vasoactive compounds may be translated to improve outcomes for patients with heart failure.

Overall, this study demonstrates the importance of quantitative assessment of right ventricular size and function, the cutoff value for significant RVD, hemodynamic predictors of RVD, and its prognostic value as an independent and incremental marker of adverse prognosis in one-third of patients. Put simply in the words of Lord Kelvin, "if you cannot measure it, you cannot improve it." The clinical challenge is now how to embrace this information to improve outcomes and personalize therapy.

ADDRESS FOR CORRESPONDENCE: Dr. Sanjay K. Prasad, Cardiovascular Research Centre, Royal Brompton Hospital, Sydney Street, London SW3 6NP, United Kingdom. E-mail: s.prasad@rbht.nhs.uk.

REFERENCES

1. Pueschner A, Chattranukulchai P, Heitner JF, et al. The prevalence, correlates, and impact on cardiac mortality of right ventricular dysfunction in nonischemic cardiomyopathy. J Am Coll Cardiol Img 2017;10:1225-36.

2. Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J 2006;27:2879–88.

3. Gulati A, Ismail TF, Jabbour A, et al. The prevalence and prognostic significance of right ventricular systolic dysfunction in nonischemic dilated cardiomyopathy. Circulation 2013;128:1623–33.

4. Merlo M, Gobbo M, Stolfo D, et al. The prognostic impact of the evolution of RV function in idiopathic DCM. J Am Coll Cardiol Img 2016;9:1034–42.

5. Kjaergaard J, Akkan D, Iversen KK, Kober L, Torp-Pedersen C, Hassager C. Right ventricular dysfunction as an independent predictor of short- and long-term mortality in patients with heart failure. Eur J Heart Fail 2007;9:610–6.

6. Guazzi M, Naeije R. Pulmonary hypertension in heart failure: pathophysiology, pathobiology, and

emerging clinical perspectives. J Am Coll Cardiol 2017;69:1718–34.

7. Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiery JL. Left ventricular heart failure and pulmonary hypertension. Eur Heart J 2016;37:942–54.

8. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant 2016;35:1–23.

9. Dumitrescu D, Seck C, Möhle L, Erdmann E, Rosenkranz S. Therapeutic potential of sildenafil in patients with heart failure and reactive pulmonary hypertension. Int J Cardiol 2012;154:205–6.

KEY WORDS heart failure, nonischemic cardiomyopathy, right ventricular dysfunction