

EDITORIAL COMMENT

RV Dyssynchrony by Speckle Tracking Strain in Pulmonary Arterial Hypertension

Will This Outcome Variable Take Root?*



Nelson B. Schiller, MD, Siddharth Singh, MBBS, MS

The pressure overload of pulmonary arterial hypertension (PAH) predisposes the right ventricle (RV) to hypertrophy, dilation, and reduced pump function. Alterations in RV functional indexes such as tricuspid annular plane excursion, fractional area change, and tissue Doppler myocardial velocity have been shown to have prognostic significance in PAH (1). With the advent of strain and strain rate imaging, a decrement in RV strain indexes has also been noted in PAH patients.

Data from extensive investigations concerning left ventricular dyssynchrony suggest that defining dyssynchrony descriptors of the RV may be a productive approach to understanding RV dysfunction in PAH. Interventricular and RV intraventricular dyssynchrony have been described in PAH (2-4). The inter-ventricular delay noted due to later peak RV myocardial shortening and the ensuing delayed onset of RV diastolic relaxation lead to reduced left ventricular function by adverse diastolic interaction. Electrophysiological studies have also shown that in PAH, the RV, which completes activation and repolarization later than the left ventricle, exaggerates this delay. Unloading of the left ventricle, typical of PAH, also leads to its atrophic remodeling.

Within the RV itself there is electromechanical dyssynergy in the contraction of the free wall and septum. Both tissue Doppler imaging and speckle tracking algorithms have been used to study intraventricular dyssynchrony in PAH (5,6). RV dyssynchrony in PAH strongly correlates with the extent of

RV functional impairment and adverse RV remodeling (7). It appears that the delayed contraction of basal and mid-RV free wall is the main determinant of intraventricular dyssynchrony in PAH (8). In addition to regional delays in electrical depolarization, the nonuniform distribution of wall stress in the dilated pressure-loaded RV has been postulated as a mechanism responsible for heterogeneity in times to attainment of peak strain for various RV segments.

SEE PAGE 642

In this issue of *iJACC*, Badagliacca et al. (9) take the nascent field of understanding and clinically applying RV dyssynchrony forward by evaluating prognostic impact of intraventricular dyssynchrony on outcomes in patients with PAH. They conducted comprehensive clinical, echocardiographic, and hemodynamic (catheterization) measurements on 80 patients with PAH (mean pulmonary artery pressure, 49 ± 15 mm Hg; 65% World Health Organization (WHO) class III/IV). The patients were followed for 12 months or until clinical worsening occurred, defined as $\geq 15\%$ reduction in 6-min walk test distance, worsening WHO functional class, need for hospitalization, lung transplantation, and/or death. An RV synchronicity index was quantitated by calculating the SD of times to peak longitudinal strain for the 4 basal and mid (septal and free wall) segments (RV-SD4). Given the extent of variation in time to peak for the RV apical segments, these were not included in the calculation of the synchronicity index. To derive the upper threshold for the normal synchronicity index, 40 healthy control subjects were studied, and a threshold of 18 ms was established on the basis of the 2 SD above the mean.

Sixty percent of PAH patients had an abnormal RV synchronicity index. Pulmonary vascular resistance, RV size, and QRS duration emerged as significant predictors of RV dyssynchrony. Patients with RV dyssynchrony had a worse hemodynamic and clinical profile and worse exercise tolerance and echocardiographic

*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 Division of Cardiology, Department of Medicine, University of California San Francisco, San Francisco, California. Dr. Schiller is on the Speakers' Bureau of Lantheus Corp.; is a consultant for HD Medical; and has received equipment research grants from GE Healthcare and Toshiba. Dr. Singh has reported that he has no relationships relevant to the contents of this paper to disclose.

indexes of RV remodeling and systolic dysfunction. After a median follow-up of 297 ± 10 days, 26 patients (33%) presented with clinical worsening. Patients with clinical worsening had a more advanced WHO class, worse clinical and hemodynamic profile, more severe RV functional impairment, and worse RV-SD4 (45 ± 27 ms vs. 19 ± 13 ms) compared with those who remained clinically stable. Of 26 patients who worsened, 24 had an RV synchronicity index >18 ms.

To investigate the prognostic impact of RV dyssynchrony on clinical worsening, the authors added this variable to a multivariable model that included 6-min walk test distance, WHO class, and cardiac index (obtained by catheterization). Interestingly, RV dyssynchrony was not included in the initial stages of multivariable model construction during variable selection. One is left to wonder how it would have fared in the initial multivariate model when 15 variables that were strongly associated with clinical worsening on univariate analysis (Table 5) were deleted. The authors noted that the addition of the RV synchronicity index (as a categorical variable >23 ms on the basis of receiver-operating characteristic curve analysis) increased the c-statistic from 0.74 to 0.81 for the parsimonious model that had 3 variables. They concluded that RV dyssynchrony was an “independent prognostic factor together with WHO functional class IV, 6 MWT and cardiac index.” Although this sounds promising, caution is warranted about this interpretation.

Sole reliance on the c-statistic may be misleading because it only serves as a measure of discrimination (or how well the model separates those in whom the outcome of interest does and does not develop) (10). Calibration (how well predicted probabilities agree with observed outcomes) and reclassification (how well does the model stratify patients into clinically meaningful risk categories) are also of paramount importance in the evaluation of models that predict risk. Evaluating these would have been too lofty a goal to achieve with a small sample like that of Badagliacca et al. (9). However, it may have been feasible to evaluate number of patients at risk of clinical worsening who would be identified by RV dyssynchrony and would otherwise be missed by conventional echocardiography and clinical parameters. This would be of utility to clinicians because it would highlight the incremental value added by the synchronicity index. This consideration becomes more topical because recent work has suggested that RV dyssynchrony using area strain (derived using 3-dimensional echocardiography) may not be associated with survival in PAH patients (11). Development of 3-dimensional echocardiographic algorithms that take into account the complex geometry of the RV will help generate more data to evaluate the prognostic significance of RV deformation

indexes, and evaluate how well they compare with 2-dimensional strain indexes (12).

Other potential methodological concerns with this study also merit mention. Electrocardiographic intraventricular conduction delay was listed as an exclusionary criterion, yet QRS widening became a stated endpoint of the study. Electrocardiographic conduction delay and QRS widening are neither defined nor differentiated in the paper, so we are uncertain what they meant or how to factor in these findings. Although QRS duration emerged as a significant predictor of dyssynchrony, the QRS widths between those with RV-SD4 >18 ms and ≤ 18 ms did not differ. It also appears that some of what is being measured as RV dyssynchrony may be confounded by electrical conduction.

Figure 2 also highlights the variation in identification of the moment of peak strain because the peaks are not distinct. The authors who are highly experienced in speckle tracing technique demonstrated good reproducibility. However, echocardiography laboratories associated with centers that specialize in treating PAH have published data that suggest that Doppler pulmonary hemodynamics, in their hands, are inaccurate (13,14). The application of more challenging speckle tracing of the RV might prove equally difficult in these venues as wider clinical application is attempted.

The results of Badagliacca et al. (9) are also promising because they show that improvement in RV dyssynchrony paralleled improvement in RV function, clinical status, and pulmonary vascular resistance. These observations would be particularly interesting if improvement in synchrony presages improvement in RV remodeling and function. Additional studies from larger pooled samples (perhaps echocardiographic data from clinical trials or registries) may be able to further illuminate its prognostic significance. Limited previous animal and human work has also suggested that RV resynchronization with pacing may improve hemodynamics in those with PAH and RV dysfunction due to congenital heart disease and PAH due to chronic thromboembolic disease (3,15). On the basis of the study by Badagliacca et al. (9) and previous work, it is safe to say that RV dyssynchrony partners with adverse RV remodeling and dysfunction seen in PAH. What is its true clinical significance, and whether it should be a distinct therapeutic target await testing in the forge of additional research and clinical use.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Nelson B. Schiller, Division of Cardiology, Department of Medicine, University of California San Francisco, 505 Parnassus Avenue, Moffitt Room 320A, San Francisco, California 94143-0214. E-mail: schiller@medicine.ucsf.edu.

REFERENCES

1. D'Alto M, Scognamiglio G, Dimopoulos K, et al. Right heart and pulmonary vessels structure and function. *Echocardiography* 2015;32 Suppl 1:S3-10.
2. Lopez-Candales A, Dohi K, Rajagopalan N, et al. Right ventricular dyssynchrony in patients with pulmonary hypertension is associated with disease severity and functional class. *Cardiovasc Ultrasound* 2005;3:23.
3. Dubin AM, Janousek J, Rhee E, et al. Resynchronization therapy in pediatric and congenital heart disease patients: an international multi-center study. *J Am Coll Cardiol* 2005;46:2277-83.
4. Marcus JT, Gan CT, Zwanenburg JJ, et al. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *J Am Coll Cardiol* 2008;51:750-7.
5. Lopez-Candales A, Dohi K, Bazaz R, Edelman K. Relation of right ventricular free wall mechanical delay to right ventricular dysfunction as determined by tissue Doppler imaging. *Am J Cardiol* 2005;96:602-6.
6. Rajagopalan N, Dohi K, Simon MA, et al. Right ventricular dyssynchrony in heart failure: a tissue Doppler imaging study. *J Card Fail* 2006;12:263-7.
7. Hill AC, Moxey DM, Rosenthal DN, et al. Electrical and mechanical dyssynchrony in pediatric pulmonary hypertension. *J Heart Lung Transplant* 2012;31:825-30.
8. Kalogeropoulos AP, Georgiopoulou VV, Howell S, et al. Evaluation of right intraventricular dyssynchrony by two-dimensional strain echocardiography in patients with pulmonary arterial hypertension. *J Am Soc Echocardiogr* 2008;21:1028-34.
9. Badagliacca R, Reali M, Poscia R, et al. Right intraventricular dyssynchrony in idiopathic, heritable, and anorexigen-induced pulmonary arterial hypertension: clinical impact and reversibility. *J Am Coll Cardiol Img* 2015;8:642-52.
10. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 2007;115:928-35.
11. Smith BC, Dobson G, Dawson D, Charalampopoulos A, Grapsa J, Nihoyannopoulos P. Three-dimensional speckle tracking of the right ventricle: toward optimal quantification of right ventricular dysfunction in pulmonary hypertension. *J Am Coll Cardiol* 2014;64:41-51.
12. Kong D, Shu X, Dong L, et al. Right ventricular regional systolic function and dyssynchrony in patients with pulmonary hypertension evaluated by three-dimensional echocardiography. *J Am Soc Echocardiogr* 2013;26:649-56.
13. Fisher MR, Criner GJ, Fishman AP, et al. Estimating pulmonary artery pressures by echocardiography in patients with emphysema. *Eur Respir J* 2007;30:914-21.
14. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med* 2009;179:615-21.
15. Hardziyenka M, Surie S, de Groot JR, et al. Right ventricular pacing improves haemodynamics in right ventricular failure from pressure overload: an open observational proof-of-principle study in patients with chronic thromboembolic pulmonary hypertension. *Europace* 2011;13:1753-9.

KEY WORDS clinical worsening, pulmonary arterial hypertension, right ventricular dyssynchrony, right ventricular function