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

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.12.023

EDITORIAL COMMENT

Impaired Right Heart and Pulmonary Vascular Function in HFpEF

Time for More Risk Markers?*

David M. Kaye, MBBS, PhD, Thomas H. Marwick, MBBS, PhD, MPH

Heart failure preserved ejection fraction (HFpEF) is a complex disorder in which the clinical picture represents the integrated effects of abnormal cardiovascular function together with comorbidities including diabesity, anemia, lung disease, and chronic kidney disease, typically in an aging population. Beyond left ventricular diastolic dysfunction and elevated left atrial pressure, abnormalities of left ventricular systolic function, right ventricular (RV) performance, pulmonary and systemic vascular function have all been reported in HFpEF. Given the failure of several pharmacological interventions in relatively broadly defined cohorts, there has been an increasing emphasis placed upon on the identification of more specific sub-phenotypes of HFpEF which might respond differentially to specific interventions or which are associated with differing prognoses.

SEE PAGE 1211

A large body of prior data show that pulmonary hypertension and RV dysfunction are common in HFpEF (1). This association is likely explained by the presence of pulmonary venous hypertension together with increased pulmonary arterial resistance. Irrespective of the cause, RV dysfunction is a powerful predictor of outcome in pulmonary hypertension (2), but its interpretation is confounded by the exquisite sensitivity of RV function to RV afterload (3). In this issue of *iJACC*, Guazzi et al. (4) evaluated the ability of the ratio between tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP), to identify specific clinical phenotypes and to determine outcome in HFPEF patients. This measure was used to assess RV to pulmonary arterial (RV-PA) coupling. In a well-characterized cohort, the investigators showed that individuals with the lowest TAPSE:PASP tertile were more likely to have advanced symptoms of heart failure (HF) and to experience a poorer composite outcome. This interesting observation prompts us to contemplate several further questions, including: 1) How does assessment of RV-PA coupling aid the in investigation of HFpEF patients and in understanding pathophysiology? 2) What is the potential clinical utility of the TAPSE:PASP ratio in risk evaluation? and 3) What if any implications are there for targeted therapy?

A recent meta-analysis showed that pulmonary hypertension and RV dysfunction are both associated with incremental risk in HFpEF patients (1). These findings are also consistent with another recent study using a machine learning approach, in which a higher risk population associated with right heart dysfunction was identified (5). These studies highlight the importance of evaluating both pulmonary pressures and RV function in HFpEF. Although the measurement of PA pressures using noninvasive means has some limitations, echocardiographic approaches provide a readily available means for the assessment of this parameter. By contrast, assessment of RV function is far more challenging due to the complex geometry of the RV. Although often assessed subjectively, current guidelines (6) recommend the quantification of RV function with fractional area change (FAC) or TAPSE; however, the accuracy and reproducibility of these measures are limited. Importantly, recent studies performed in an experimental model of pulmonary hypertension showed that TAPSE and RVFAC were only moderately correlated with RV contractility, as measured by the load independent measure, Ees (7). Rather, these 2 measures were more strongly

*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 Heart Failure Research Group, Baker IDI Heart and Diabetes Research Institute, Alfred Hospital, Melbourne, Australia. Prof. Kaye is a co-founder and equity holder of Cardiora; and an advisory board member at Corvia Medical. Dr. Marwick has reported that he has no relationships relevant to the contents of this paper to disclose.

correlated with RV-PA coupling as evaluated by the ratio of Ees to pulmonary arterial elastance (Ea). In the present study, the correlation between TAPSE:PASP and a surrogate RV Ees/Ea measure was relatively limited. TAPSE is susceptible to translational movement, and it is possible that RV strain may be a preferable echocardiographic marker of RV function (8).

The present study shows that subjects with impaired RV-PA coupling experienced higher rates of adverse cardiovascular events including HF hospitalization and death. Interpretation of this observation is complicated by the fact that patients identified in the lowest RV-PA tertile also exhibited several demographic factors associated with increased risk including older age, more advanced symptoms, atrial fibrillation and chronic kidney disease. Low TAPSE:PASP was also associated with evidence of greater degrees of left ventricular hypertrophy, left ventricular diastolic and systolic dysfunction, and more marked RV dilatation and pulmonary hypertension with a mixed pre- and post-capillary physiology. Of note, evidence supporting a clear "dose-response" relationship between the TAPSE:PASP ratio and the clinical features was limited. Together, the findings of more marked myocardial and pulmonary vascular remodeling suggests that the highest risk group may also have had the greatest temporal exposure to both HFpEF and to its driving stimuli. Conceivably, patients with lower TAPSE:PASP ratios may have irreversible RV dysfunction, whereas those with higher TAPSE:PASP ratios may be the most likely to respond to pulmonary vasodilator therapy. In addition to the validation of TAPSE:PASP as an independent prognostic marker in HFpEF, further studies might also explore the utility of this measure and others in predicting specific clinical events. For example, sudden cardiac death and worsening HF are significant contributors to total mortality in HFpEF, whereas HF hospitalization may follow an acute deterioration or a more progressive gradual decline.

Exercise limitation is a fundamental feature of HFpEF and impaired left ventricular diastolic reserve and elevated left atrial pressure have been proposed to be a key contributing mechanism (9). Recent open label studies of inter-atrial shunt devices designed to reduce left atrial pressure, particularly during physical activity, have been associated with symptomatic and hemodynamic benefit (10). One potential theoretical concern of such an approach is the potential for RV overload and failure, although this has not been observed. Given the limitations of current approaches to accurately assess RV contractility and RV-PA coupling, evaluation of TAPSE:PASP may provide a more sensitive means by which to monitor for changes in RV function. Evaluation of RV-PA coupling may also yield new insights into other contributory mechanisms for exercise intolerance in HFpEF. Several investigators have now shown the presence of a steeper pulmonary pressure-flow relationship which only becomes evident during exertion and which may unmask an impairment in RV contractile reserve (11).

The recognition that impaired RV-PA coupling may directly contribute to the pathophysiology of HFpEF has stimulated interest in testing the role of pulmonary vasodilators including sildenafil and the soluble guanylate cyclase inhibitor. Acute intravenous sildenafil administration was associated with a modest but significant reduction in resting pulmonary artery pressure, with an increase in exercise capacity in the absence of altered left ventricular systolic or diastolic function (12). This finding could be explained by a favorable effect of the RV pressure-flow relationship. However, these findings did not translate into benefit in a larger scale study. Riociguat treatment was associated with increased cardiac output; however, this was secondary to a reduction in systemic afterload, rather than a change in pulmonary vascular resistance (13). Using an alternative strategy, the effect of intravenous milrinone on resting and exercise hemodynamics was recently reported in HFpEF patients (14). This study showed a reduction in pulmonary arterial pressures with an increase in cardiac output at rest and during exercise, with little change in systemic blood pressure, raising the possibility of beneficial effect of the drug on myocardial contractility and pulmonary arterial elastance.

Collectively, the current study and other recent complementary investigations reinforce the importance of comprehensively evaluating the right heart and pulmonary circulation in HFpEF patients. Given the demographic of these patients and the fact that HFpEF is now a population-level disease, a noninvasive approach seems desirable. The ability of echo-Doppler to assess both RV function and PA pressure makes this an attractive modality. We should also not neglect the notion that these patients become symptomatic with exercise, so the stress-response of these parameters is relevant. Thus, further studies are needed to identify the most sensitive and reproducible measure(s) that provide clinically useful information regarding incremental risk, and which may be used to predict and evaluate response to therapy.

ADDRESS FOR CORRESPONDENCE: Prof. David M. Kaye, Heart Failure Research Group, Baker IDI Heart and Diabetes Institute, Alfred Hospital, 75 Commercial Road, Melbourne 3004, Australia. E-mail: david.kaye@bakeridi.edu.au.

JACC: CARDIOVASCULAR IMAGING, VOL. 10, NO. 10, 2017
OCTOBER 2017:1222–4

REFERENCES

1. Gorter TM, Hoendermis ES, van Veldhuisen DJ, et al. Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Heart Fail 2016;18:1472–87.

2. Wright LM, Dwyer N, Celermajer D, Kritharides L, Marwick TH. Follow-up of pulmonary hypertension with echocardiography. J Am Coll Cardiol Img 2016;9:733–46.

3. Pinsky MR. The right ventricle: interaction with the pulmonary circulation. Critical Care (London, England) 2016;20:266.

4. Guazzi M, Dixon D, Labate V, et al. RV contractile function and its coupling to pulmonary circulation in heart failure with preserved ejection fraction: stratification of clinical phenotypes and outcomes. J Am Coll Cardiol Img 2017;10:1211–21.

5. Shah SJ, Katz DH, Selvaraj S, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. Circulation 2015;131:269–79.

6. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults. J Am Soc Echocardiogr 2010;23:685–713; quiz 786–8.

7. Guihaire J, Haddad F, Boulate D, et al. Non-invasive indices of right ventricular function are markers of ventricular-arterial coupling rather than ventricular contractility: insights from a porcine model of chronic pressure overload. Eur Heart J Cardiovasc Imaging 2013;14:1140–9.

8. Park JH, Kusunose K, Kwon DH, et al. Relationship between right ventricular longitudinal strain, invasive hemodynamics, and functional assessment in pulmonary arterial hypertension. Korean Circ J 2015;45:398–407.

9. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. J Am Coll Cardiol 2010;56:855–63.

10. Kaye DM, Hasenfuss G, Neuzil P, et al. One-year outcomes after transcatheter insertion of an interatrial shunt device for the management of heart failure with preserved ejection fraction. Circ Heart Fail 2016;9.

11. Lewis GD, Bossone E, Naeije R, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. Circulation 2013;128:1470–9.

12. Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: results of a 1-year, prospective, randomized, placebo-controlled study. Circ Heart Fail 2011;4:8–17.

13. Bonderman D, Pretsch I, Steringer-Mascherbauer R, et al. Acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): a randomized, double-blind, placebo-controlled, single-dose study. Chest 2014;146:1274–85.

14. Kaye DM, Nanayakkara S, Vizi D, Byrne M, Mariani JA. Effects of milrinone on rest and exercise hemodynamics in heart failure with preserved ejection fraction. J Am Coll Cardiol 2016;67:2554–6.

KEY WORDS heart failure preserved ejection fraction, pulmonary hypertension, right ventricle