JACC: CARDIOVASCULAR IMAGING VOL. 12, NO. 5, 2019

PUBLISHED BY ELSEVIER

iVIEW

EDITOR'S PAGE


Diastolic Function Gets Personal

Frank A. Flachskampf, MD, PhD,[a] Y. Chandrashekhar, MD, DM[b]

Exertional dyspnea is one of the most common symptoms in cardiology, and thus is also a major indication for cardiac imaging. Diastolic ventricular dysfunction is often a prime suspect for a cardiac etiology of exertional dyspnea. Confirmation of diastolic dysfunction offers a plausible diagnosis to both the physician and the patient, abbreviates or sharply focuses further testing, and further management, even if treatment is difficult.

Such a firm diagnosis of diastolic dysfunction, however, is often not easy to obtain. Diastolic dysfunction, lacking an easy to use gold standard, remains a tricky diagnosis despite standardized algorithms to help its discovery. The guidelines themselves have performed variably in different conditions (1,2)—some believe the 2016 criteria aim for specificity at the cost of lower sensitivity, have modest positive predictive value and while it is very good at identifying advanced diastolic dysfunction, it results in a large proportion of patients in the indeterminate categories. There is thus an intense interest in finding alternate methods of diagnosing this condition and understanding its effects on exercise intolerance with novel strategies like using LA strain (3) or RV-PA coupling (4) or even more unconventional techniques that are parameter agnostic, like cluster analysis (5). An easier way of unmasking diastolic dysfunction might, however, be exercise testing (6) since this places an additional strain on the system to relax faster during fast heart rates and increased venous return, that can unravel latent abnormalities in function. This might be able to overcome one limitation of the 2016 criteria—identifying patients with earlier stages of diastolic dysfunction (e.g., those with impaired myocardial relaxation in the presence of normal resting LV filling pressures) since these patients may show increased LVEDP only with exercise (7). It is important to keep in mind that current recommendations aim primarily to diagnose increased filling pressures at rest. Thus, exertional diastolic dysfunction, as implied in the term "exertional dyspnea," may exist even if resting diastolic pressures and their echocardiographic indicators, such as e′, E/e′, left atrial volume, and tricuspid regurgitant velocity, may still be within normal limits at rest. The logical next step, then, may be to evaluate such patients under exercise conditions, obtaining e′, E/e′, and tricuspid regurgitant velocities immediately after peak exercise; this technique has been validated to be able to detect exercise-induced increases in filling pressures (6), although the overall experience is still very limited, especially with regard to prognostic implications and it involves cost as well as increased logistics.

iJACC been very active in bringing out papers that help understand this difficult condition and two articles (8,9) in this issue of the *Journal*, both from the same experienced authors may help further clarify some nuances. In the first paper (8), the authors compared the diagnostic and prognostic implications of diastolic stress echocardiography with a combination of resting echocardiography and a serum biomarker for fibrosis and inflammation, galectin-3, which is also known to be associated with adverse prognosis in heart failure (10).

They examined patients with exertional dyspnea and mild diastolic dysfunction—the very group where traditional indices may perform sub optimally. Since

From the [a]Department of Medical Sciences, Uppsala University, and Clinical Physiology and Cardiology, Akademiska, Uppsala, Sweden; and the [b]Division of Cardiology, University of Minnesota and Veterans Affairs Medical Center, Minneapolis, Minnesota.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2019.04.003

many of these patients cannot exercise well, the authors asked whether a simple combination of an imaging + biologic marker (resting E/e' >11.3 and galectin-3 <1.17 ng/ml) would yield similar diagnostic and prognostic information compared to diastolic stress testing - it indeed did. Using sequential measurements of first E/e' and proceeding to measuring galectin-3 only if E/e' was >11.3, reduced the number of exercise tests by 64% with similar prognostic utility. It is important to emphasize that this study investigated highly selected patients. Nevertheless, such novel combination strategies for imaging are a welcome addition to other ways of combination testing (11,12). Being ultimately clinicians and cardiologists, we must think "outside the box" of pure imaging.

In the second paper (9), the same group tested the effects of spironolactone on exercise imaging imaging markers evaluating active (untwisting rate) and passive (E/e' ratio, a marker of myocardial stiffness) components of diastolic dysfunction. Patients with an exercise-induced E/e' >13 were randomized to spironolactone therapy versus placebo for 6 months, and underwent again exercise test thereafter. Two points were noteworthy—this is one of the few RCTs testing an imaging marker as an entry-criteria for randomization and second, it provides preliminary evidence that imaging markers may help identify drug responders in HFpEF.

These findings are undoubtedly welcome news in a field largely lacking successful therapeutic interventions (except, perhaps exercise). Spironolactone therapy has in the past been evaluated in patients with diastolic dysfunction by several groups, including the current authors (13–15). However, despite improvement in diastolic function parameters like E/e′, the effect has been disappointing and clinical results for spironolactone therapy have been largely neutral, prompting the search for subgroups who might benefit, for example, those with an exercise increase in E/e′ (15). Thus, in a logical extension of their previous work, the authors have now found therapeutic benefit in a group characterized by exercise E/e′ increase.

What new insights can we take home for imaging in general? One is that, while refinements continue, all that glitters is not gold. In the hands of very experienced researchers in the field, several "advanced" parameters like untwisting rate, peak longitudinal left atrial strain, or global longitudinal left ventricular strain added little or nothing to identify patients with exercise-inducible diastolic dysfunction or to detect therapeutic benefit with spironolactone therapy. While part of this could be the difficulty in measuring these signals accurately (16), the fact remains that sophisticated testing may not always be the answer. Second, novel imaging strategies, often in combination with non imaging strategies (17), might be needed to make a headway in various forms of early heart failure. Given the explosive growth of knowledge in this field, and the potential for "personalization" of diagnostics, this may be the way forward when imaging alone is not sufficient. Such refinement may then lead to a "personalization" of therapy as exemplified by the identification of a subgroup of patients better responding to therapy than others.

ADDRESS FOR CORRESPONDENCE: Dr. Y. Chandrashekhar, Division of Cardiology, Mail Code: 111c, University of Minnesota/VAMC, 1 Veterans Drive, Minneapolis, Minnesota 55417. E-mail: shekh003@umn.edu.

REFERENCES

1. Andersen OS, Smiseth OA, Dokainish H, et al. Estimating left ventricular filling pressure by echocardiography. J Am Coll Cardiol 2017;69:1937–48.

2. Almeida JG, Fontes-Carvalho R, Sampaio F, et al. Impact of the 2016 ASE/EACVI recommendations on the prevalence of diastolic dysfunction in the general population. Eur Heart J Cardiovasc Imaging 2018;19:380–6.

3. Singh A, Addetia K, Maffessanti F, Mor-Avi V, Lang RM. LA strain for categorization of LV diastolic dysfunction. J Am Coll Cardiol Img 2017;10:735–43.

4. Sugimoto T, Bandera F, Generati G, Alfonzetti E, Bussadori C, Guazzi M. Left atrial function dynamics during Exercise in heart failure. J Am Coll Cardiol Img 2017;10:1253–64.

5. Omar AMS, Narula S, Rahman MAA, et al. Precision phenotyping in heart failure and pattern clustering of ultrasound data for the assessment of diastolic dysfunction. J Am Coll Cardiol Img 2017;10:1291–303.

6. Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol 2006;47:1891–190.

7. Obokata M, Kane GC, Reddy YN, et al. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation 2017;135:825–38.

8. Kosmala W, Przewlocka-Kosmala M, Rojek A, Marwick TH. Comparison of the diastolic stress test with a combined resting echocardiography and biomarker approach to patients with exertional dyspnea: diagnostic and prognostic implications. J Am Coll Cardiol Img 2019;12:771–80.

9. Kosmala W, Przewlocka-Kosmala M, Marwick TH. Association of active and passive components of lv diastolic filling with exercise intolerance in heart failure with preserved ejection fraction: mechanistic insights from spironolactone response. J Am Coll Cardiol Img 2019;12:784–94.

10. de Boer RA, Lok DJ, Jaarsma T, et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. Ann Med 2011;43:60–8.

11. Lubbers M, Coenen A, Kofflard M, et al. Comprehensive cardiac CT with myocardial perfusion imaging versus functional testing in suspected coronary artery disease: the multicenter,

randomized CRESCENT-II trial. J Am Coll Cardiol Img 2018;11:1625–36.

12. Januzzi JL, Suchindran S, Coles A, et al., on behalf of the PROMISE Investigators. High-sensitivity troponin I and coronary computed tomography in symptomatic outpatients with suspected coronary artery disease. J Am Coll Cardiol Img 2018 Mar 14 [E-pub ahead of print].

13. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.

14. Edelmann F, Wachter R, Schmidt AG, et al., for the Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA 2013;309:781–91.

15. Kosmala W, Rojek A, Przewlocka-Kosmala M, Wright L, Mysiak A, Marwick TH. Effect of aldosterone antagonism on exercise tolerance in heart failure with preserved ejection fraction. J Am Coll Cardiol 2016;68:1823–34.

16. Flachskampf FA, Mårtensson M. How should tissue Doppler tracings be measured? Eur Heart J Cardiovasc Imaging 2014;15:828–9.

17. Wang Y, Yang H, Huynh Q, Nolan M, Negishi K, Marwick TH. Diagnosis of nonischemic stage B heart failure in type 2 diabetes mellitus. J Am Coll Cardiol Img 2018;11:1390–400.