JACC: HEART FAILURE VOL. 6, NO. 4, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Diastole Tracks Cardiometabolic Risk*

Walter J. Paulus, MD, PhD, Elisa Dal Canto, MD

Over the past decennium, left ventricular (LV) diastolic dysfunction (LVDD) has been recognized as a marker of cardiovascular risk and a precursor of heart failure, especially heart failure with preserved ejection fraction (HFpEF). Two opposing views currently prevail on the mechanisms driving LVDD (1). The traditional view rests on an overload paradigm whereby arterial hypertension and high arterial stiffness increase LV wall stress. This provokes a mismatch between myocardial force and load, which triggers pathological LV hypertrophy, fibrosis, and LVDD. The emerging view rests on an inflammatory paradigm whereby comorbidities, especially metabolic comorbidities such as obesity, metabolic syndrome, and diabetes, induce coronary microvascular inflammation and rarefaction, which raise cardiomyocyte stiffness because of limited availability of nitric oxide and induce fibrosis because of myocardial infiltration by activated macrophages. Support for this emerging view is on the rise because of demonstration in HFpEF patients of systemic inflammation and myocardial microvascular rarefaction, respectively, evident from endothelial expression of adhesion molecules and a blunted hyperemic response (2).

SEE PAGE 317

The meticulous study by Nayor et al. (3) in this issue of *JACC: Heart Failure* provides further support for the emerging view by showing epidemiological evidence derived from the Framingham Heart Study. In a large community-based sample of elderly persons (mean age: 64 ± 8 years), longitudinal evolution of LV diastolic function was derived from repetitive echocardiograms with an interval of 5.6 years using single indices of LVDD such as E/A, E′, or E/E′ and a 4-level categorical variable of LVDD (normal, mild, moderate, and severe). Appearance of LVDD was independently related not only to basal blood pressure or change in blood pressure, but also to metabolic measures such as body mass index (BMI), triglycerides, and diabetes status, or change in these metabolic measures. Furthermore, using the categorical classification of LVDD, the authors identified progressing, stable, and regressing LVDD. The first was mostly observed in elderly females and the last in males <60 years of age. Stable or progressive LVDD was related to a composite outcome of incident cardiovascular disease (CVD) or death over a 2.7-year period after the last visit. Finally, a comorbidity score was calculated that accounted for renal insufficiency, chronic obstructive pulmonary disease, musculoskeletal weakness, frailty, and plasma level of C-reactive protein (CRP). The highest comorbidity score was observed in stable and progressive LVDD; a 1-U increase in basal comorbidity score raised the likelihood of moderate or severe LVDD at the repeat visit by 27%. Taken together, the epidemiological evidence provided by Nayor et al. strongly supports the importance of metabolic risk and comorbidities for development of LVDD and CVD.

The study by Nayor et al. (3) confirms the results of a previous study, which similarly addressed longitudinal evolution of LVDD in a community-based cohort (4). This study assessed LVDD through sequential noninvasive determinations of LV end-diastolic elastance and observed at the repeat visit an increase in LV diastolic stiffness, which was in line with the worse diastolic LV function observed by Nayor et al. (3). In this previous study, increased LV diastolic stiffness was observed in the presence of lower blood pressure because many patients were started on

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

From the Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, the Netherlands. Dr. Paulus is supported by grants from Cardiovasculair Onderzoek Nederland (CVON), Dutch Heart Foundation, The Hague, the Netherlands (RECONNECT, EARLY-HFpEF). Dr. Dal Canto has reported that she has no relationships relevant to the contents of this paper to disclose.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2018.01.008

antihypertensive medications after the baseline hospital visit. The lower blood pressure allowed excessive arterial load to be excluded as determinant of the increased LV diastolic stiffness, which could therefore exclusively be ascribed to metabolic risk because of a significant relation between weight gain and change in LV end-diastolic elastance. The study by Nayor et al. (3) comes close to this previous study because it also observed the change in BMI between the 2 visits to be an independent determinant of LVDD.

Weight gain and change in BMI are suboptimal measures of metabolic risk. Plasma markers of systemic inflammation, indices of insulin resistance, or determinants of metabolic syndrome are probably more reliable. In this respect the study of Nayor et al. (3) provides novel information. Elevated plasma CRP, a marker of systemic inflammation known to be upregulated in HFpEF, was included in a composite comorbidity score. The highest scores were observed in patients with stable and progressive LVDD, and a 1-unit increase of this score raised the likelihood of LVDD at the repeat visit by 27%. These findings support involvement of comorbidities and systemic inflammation in development of LVDD. The authors also looked at an independent effect of CRP on LVDD, which was absent, however. This negative finding could relate to a confounding effect of increased use after the baseline visit of lipid-lowering agents, which are known to also lower inflammation and CRP. Criteria for metabolic syndrome such as high-density lipoprotein cholesterol and triglycerides were also assessed. High-density lipoprotein cholesterol failed to relate to LVDD, but plasma triglycerides and change in plasma triglycerides did. Finally, the difference in plasma insulin levels between the 2 visits, which reflects development of insulin resistance, also related to LVDD. The positive outcome for changes in plasma triglycerides and insulin and the negative outcome for CRP suggest that insulin resistance could directly harm the coronary microvasculature and lead to LVDD, possibly through postprandial hyperglycemia. Direct harmful effects of hyperglycemia on LV diastolic function are relevant to the EMPA-REG OUTCOME ([Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial, in which empagliflozin lowered both hyperglycemia and heart failure hospitalizations.

A noteworthy finding in the Nayor et al. (3) study was the low proportion of heart failure diagnoses (5 of 27) relative to macrovascular events (both coronary and cerebral: 22 of 27) occurring during the 2.7-year follow-up after the second visit. This high incidence of macrovascular events was compatible with involvement of systemic inflammation affecting both LVDD and plaque stability in the coronary or cerebral arteries. It also favors the use of LVDD as a predictor of overall CVD encompassing both future macrovascular events and heart failure incidence because patients with stable or progressive LVDD were 2.1 times more likely to suffer from CVD during follow-up. Finally, shared inflammatory mechanisms between macrovascular arterial disease and LVDD support future testing in LVDD or HFpEF of an anti-inflammatory strategy with an interleukin-1β antagonist, which was recently established to be effective against macrovascular events in the CANTOS (Cardiovascular Risk Reduction Study [Reduction in Recurrent Major CV Disease Events]) trial.

Use of a 4-level categorical classification of LVDD allowed patients to be classified as presenting with progressing, stable, or regressing LVDD. Intriguing sex- and age-related differences in the propensity of LVDD to progress or regress were observed. Progressing LVDD was more common in women and at older age in contrast to regressing LVDD, which was more frequent in men and at younger age. The reason women were more prone to progress was unrelated to the risk factor profile, which had evolved similarly in men and women in between both visits. More frequent progression of LVDD in elderly women, therefore, suggested mechanisms linking cardiometabolic risk to LVDD to be gender dependent. Evidence obtained in ovariectomized rats (5) supports this suggestion because, in this model, LVDD was accelerated by more intense microvascular inflammation as a result of estrogen deficiency.

In summary, the study by Nayor et al. (3) provides both confirmatory and novel evidence on the relation between LVDD and metabolic risk. LVDD closely tracks metabolic risk, with deterioration mainly observed in elderly women and occasional amelioration in younger men. Furthermore, stable or progressive LVDD predicts a higher incidence of heart failure and coronary or cerebral ischemic events. The latter finding suggests a common inflammatory background in LVDD and macrovascular arterial disease.

ADDRESS FOR CORRESPONDENCE: Prof. Dr. Walter J. Paulus, Institute for Cardiovascular Research (ICaR-VU), VU University Medical Center, O|2 building 10W13, De Boelelaan 1118, 1081 HV Amsterdam, the Netherlands. E-mail: wj.paulus@vumc.nl.

REFERENCES

1. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med 2016;375:1868–77.

2. Paulus WJ, Dal Canto E. Distinct myocardial targets for diabetes therapy in heart failure with preserved or reduced ejection fraction. J Am Coll Cardiol HF 2018;6:1–7.

3. Nayor M, Enserro DM, Xanthakis V, et al. Comorbidities and cardiometabolic disease: relationship with longitudinal changes in diastolic function. J Am Coll Cardiol HF 2018;6:317–25.

4. Borlaug BA, Redfield MM, Melenovsky V, et al. Longitudinal changes in left ventricular stiffness: a community-based study. Circ Heart Fail 2013;6:944–52.

5. Zhao Z, Wang H, Jessup JA, Lindsey SH, Chappell MC, Groban L. Role of estrogen in diastolic dysfunction. Am J Physiol Heart Circ Physiol 2014;306:H628–40.

KEY WORDS diastole, heart failure, metabolic syndrome