JACC: BASIC TO TRANSLATIONAL SCIENCE
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION.

VOL. 5, NO. 5, 2020

EDITORIAL COMMENT

Interstitial Fibrosis and Diastolic Dysfunction in Aortic Stenosis*

John M. Canty, Jr, MD,[a,b,c,d,e] Brian R. Weil, PhD[a,c,e]

Continuous and progressive left ventricular (LV) pressure overload from hemodynamically significant aortic stenosis or severe sustained hypertension results in a well-characterized progression from compensated to decompensated pathophysiology (1). The classical response to pressure overload is characterized by variable degrees of LV hypertrophy, which normalizes wall stress to maintain systolic function and ejection fraction in the face of markedly elevated LV afterload. Increases in myocardial oxygen consumption arise from the increased LV mass and sustained elevations in systolic pressure. These changes, along with the inability of the coronary microcirculation to proliferate in the hypertrophied ventricle, reduce coronary flow reserve leading to repetitive subendocardial ischemia and angina in the absence of obstructive coronary artery disease (2). Episodes of transient ischemia and increased diastolic myocyte strain from elevations in LV end-diastolic filling pressure lead to myocyte apoptosis as well as myocardial fibrosis, which becomes particularly prominent in the subendocardium. Whereas this compensation can be maintained for some time, sustained pressure overload eventually leads to decompensation characterized by a reduction in systolic function resulting in heart failure with a reduced ejection fraction.

Whereas myocardial fibrosis was originally envisioned to be a relatively late manifestation of pressure overload, recent clinical studies using cardiac magnetic resonance (CMR) imaging have suggested that fibrosis may occur when systolic function is preserved and may provide prognostic significance affecting the timing of aortic valve replacement (1). Both fibrosis and LV hypertrophy alter diastolic properties and can contribute to symptoms of dyspnea in aortic stenosis. In this issue of *JACC: Basic to Translational Science*, Torres et al. (3) provide insight into the temporal evolution of LV diastolic properties in a large animal model of supravalvular aortic stenosis. In contrast to the numerous studies evaluating how aortic banding and hypertensive pressure overload leads to heart failure with a reduced ejection fraction, the experiments were conducted over a time frame before ejection fraction falls with systolic function presumably preserved. Temporal changes in diastolic properties were assessed noninvasively with speckle tracking echocardiography and complimented with invasive diastolic LV pressure-volume relations assessed at 4 or 5 weeks after producing moderately severe aortic stenosis. The in vivo physiological studies were paired with histologic measurements of myocardial collagen content and ex vivo 3-dimensional studies of transmural collagen fiber orientation. The results demonstrate a late shift in indices of collagen microstructure stiffness that reduced global LV chamber stiffness and could be predicted by the analysis of circumferential diastolic stiffness present 1 week after chronic pressure overload. Most of these changes occurred in the

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Veterans Affairs Western New York Health Care System, Buffalo, New York; [b]Department of Medicine, University at Buffalo, Buffalo, New York; [c]Department of Physiology and Biophysics, University at Buffalo, Buffalo, New York; [d]Department of Biomedical Engineering, University at Buffalo, Buffalo, New York; and [e]The Clinical and Translational Science Institute of the University at Buffalo, Buffalo, New York.
Drs. Canty and Weil have received funding from the Department of Veterans Affairs (grant 1IO1BX002659), the American Heart Association (grant 17SDG33660200), the National Center for Advancing Translational Sciences (grant UL1TR001412), and the Albert and Elizabeth Rekate Fund in Cardiovascular Medicine.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2020.03.014

subendocardium. Torres et al. (3) conclude that noninvasive assessment of regional biomechanical function may provide a sensitive approach to monitor the progression of diastolic function when systolic function is preserved.

These are technically demanding studies and the investigators should be congratulated on combining sophisticated and translationally relevant measurements of in vivo LV diastolic function with postmortem characteristics of myocardial fibrosis, collagen quality, and fiber orientation in a chronic swine model. Interestingly, despite significant changes in diastolic properties, the magnitude of the increase in interstitial fibrosis was quite small by picrosirius staining (~6% vs. 4% in normal subjects). Whereas additional analysis supports the investigators' conclusions regarding the importance of collagen quality and fiber orientation, other potential determinants of diastolic properties were not assessed and could contribute to altered diastolic properties. For example, increased titin messenger ribonucleic acid was demonstrated in animals studied with 5 versus 4 weeks of pressure overload, but titin protein content, isoform expression, and phosphorylation status were not assessed. These are determinants of early diastolic properties and may be contributory, particularly because the LV end-diastolic pressure range studied with pressure-volume relations during preload manipulation was low (<12.5 mm Hg, probably reflecting the isoflurane anesthetized state). In addition, the changes in diastolic properties between 4 and 5 weeks after instrumentation are most prominent in the subendocardium and accompanied by transmural variations in collagen with subendocardial collagen content exceeding subepicardial collagen content at 5 weeks. This raises the question as to whether subendocardial ischemia in the hypertrophied heart could be contributing to the observed changes. Finally, alterations in collagen cross-linking may also be playing a role and were not determined but may also contribute to changes in diastolic distensibility.

From a clinical standpoint, the results of this study further inform our understanding of the importance of LV diastolic dysfunction in aortic stenosis. Recent clinical research has focused on the role of diastolic properties in aortic stenosis by evaluating interstitial fibrosis (1). This can be quantified by CMR and may be the result of the aortic stenosis or concomitant comorbidity from heart failure with preserved ejection fraction (HFpEF) or amyloid deposition, which are particularly common in the elderly patient population. Quantifying fibrosis in aortic stenosis can also predict the likelihood of reversible systolic dysfunction and improvement in heart failure prior to valve replacement. The increases in collagen content demonstrated by pathology in the present study would be difficult to quantify with precision using current CMR imaging techniques. Thus, the proposed biomechanical assessment developed by Torres et al. (3) may identify the progression of diastolic myocardial disease before fibrosis develops. Comparative prospective serial studies correlating echocardiographic indices of LV diastolic distensibility, CMR fibrosis, and prognosis or persistent symptoms after aortic valve replacement will be required to address this.

Clinical studies demonstrate that patients with HFpEF infrequently progress to systolic dysfunction and usually this is related to underlying coronary artery disease (4). In contrast, prior animal models of sustained pressure overload from aortic banding as well as models of severe hypertension usually demonstrate a progression from preserved to depressed systolic function. This transition is dependent on a number of variables including the severity and duration of pressure overload. Whereas ejection fraction did not decline within the 5-week time frame of the present study, the 5-week time point may be at the threshold of the transition to systolic dysfunction. This is suggested by a reduction in circumferential systolic strain, a marked reduction in LV contractility assessed by LV +dP/dt and an increased N-terminal pro-B-type natriuretic peptide in animals studied at the 5- versus 4-week time point. Whether this would remain stable is unclear, and it seems plausible that a longer duration of pressure overload may have resulted in the predictable transition from a phenotype-dominated diastolic dysfunction to systolic dysfunction. Understanding the longer-term progression of this model along with studies to assess subendocardial perfusion would help address whether the alterations in biomechanical properties are related to diastolic properties, subendocardial ischemia, or reflect an early predictor of systolic dysfunction.

Most animal models of HFpEF developed to date have significant limitations in that they employ variations of severe systolic pressure overload with or without a variety of proinflammatory risk factors (e.g., diabetes, obesity, and hyperlipidemia) associated with endothelial dysfunction. Whereas Torres et al. (3) conclude that aortic stenosis with sustained LV pressure overload and preserved ejection fraction recapitulates multiple phenotypical features of HFpEF, there are differences with the clinical disease state that are also germane to other hypertensive models. First, whereas most patients with HFpEF

have a history of hypertension, it is usually well-controlled and severe sustained pressure overload is quite uncommon. Second, severe LV hypertrophy is uncommon and, depending on enrollment criteria, as many as one-half of patients in clinical trials of HFpEF have a structurally normal echocardiogram without hypertrophy. Finally, increases in interstitial fibrosis in biopsies of patients with HFpEF are typically greater (~10%) than the small increase demonstrated in the present aortic stenosis model (~2%).

How is hypertension related to the development of HFpEF in the absence of sustained systolic pressure elevations? Whereas hypertension is prevalent, antihypertensive therapy and blood pressure control has intensified. Targets for control have fallen from 160 to 120 mm Hg over the last 50 years. Yet, as severe uncontrolled hypertension has declined, the incidence of HFpEF has actually increased to where it now accounts for well over one-half of the patients with congestive heart failure. This disconnect supports the role of proinflammatory states such as diabetes and obesity, which have become more common over this time period. Nevertheless, in preclinical studies, nonhypertensive animal models of obesity and diabetes exhibit minimal impairment of myocardial diastolic properties indicating a key role for a history of hypertension in altering LV distensibility. One possible explanation is that repetitive transient systolic hypertension arising from reduced aortic compliance (particularly common in elderly patients) may be the stimulus that produces HFpEF. In support of this mechanism, brief repetitive pressure overload in swine can lead to a 2-fold increase in interstitial fibrosis and reduced LV compliance (5). This is associated with concentric LV remodeling that develops in the absence of anatomic LV hypertrophy and recapitulates the structural phenotype of many patients with HFpEF.

Whereas all animal models of human disease have strengths and limitations, large animal models continue to play an important role in terms of their translational relevance as well as utility in studying therapeutic interventions prior to clinical application in humans. The work of Torres et al. (3) provides further insight into the complexity of transmural myocardial diastolic properties in compensated aortic stenosis that may ultimately be confirmed to relate to mechanisms of diastolic dysfunction in patients with HFpEF. Understanding whether these are modulated by proinflammatory stimuli may allow the importance of hypertension versus other risk factors to be defined in preclinical studies of HFpEF.

ADDRESS FOR CORRESPONDENCE: Dr. John M. Canty, Jr., Division of Cardiovascular Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Clinical Translational Research Center, Suite 7030, 875 Ellicott Street, Buffalo, New York 14203. E-mail: canty@buffalo.edu.

REFERENCES

1. Bing R, Cavalcante JL, Everett RJ, Clavel MA, Newby DE, Dweck MR. Imaging and impact of myocardial fibrosis in aortic stenosis. J Am Coll Cardiol Img 2019;12:283–96.

2. Duncker DJ, Koller A, Merkus D, Canty JM Jr. Regulation of coronary blood flow in health and ischemic heart disease. Prog Cardiovasc Dis 2015;57:409–22.

3. Torres WM, Barlow SC, Moore A, et al. Changes in myocardial microstructure and mechanics with progressive left ventricular pressure overload. J Am Coll Cardiol Basic Trans Science 2020;5:463–80.

4. Lupon J, Gavidia-Bovadilla G, Ferrer E, et al. Heart failure with preserved ejection fraction infrequently evolves toward a reduced phenotype in long-term survivors. Circ Heart Fail 2019;12:e005652.

5. Weil BR, Techiryan G, Suzuki G, Konecny F, Canty JM Jr. Adaptive reductions in left ventricular diastolic compliance protect the heart from stretch-induced stunning. J Am Coll Cardiol Basic Trans Science 2019;4:527–41.

KEY WORDS aortic stenosis, diastolic dysfunction, heart failure with a preserved ejection fraction, myocardial fibrosis