JACC: CARDIOVASCULAR IMAGING
VOL. 13, NO. 2, 2020

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Left Ventricular Systolic Function and Outcome in Aortic Stenosis

The Long- and Short-Axis of it*

Gerard P. Aurigemma, MD, Colleen M. Harrington, MD

Left ventricular (LV) remodeling and systolic function in aortic stenosis (AS) fit into a straightforward paradigm. The left ventricle remodels in a concentric hypertrophy pattern, mitigating the increased systolic load (systolic force per unit myocardium, or wall stress) caused by the stenotic aortic valve (1). This adaptation allows ejection fraction (EF) to remain normal despite ventricular systolic pressures that can approach 300 mm Hg. Furthermore, there is an inverse relationship between systolic load and EF (2). In an influential study, Carabello et al. (2) showed that in a series of patients with AS and heart failure (mean age 62), but no coronary disease (CAD), the low EF was usually commensurate with the increased load (afterload mismatch); a smaller subset had reduced EF that was out of proportion to the load (afterload mismatch *and* contractile dysfunction) (**Figure 1A**). When load was reduced by aortic valve replacement (AVR), EF and symptoms improved, with the former even normalizing in some instances.

Today, the AS landscape is different than at the time of the work cited previously; the common AS phenotype is no longer the otherwise healthy 62-year-old with a bicuspid valve, but, the 88-year-old with a calcified trileaflet aortic valve, with decades of hypertension (3), and, not infrequently, CAD and other comorbidities. It can be argued that this AS phenotype is essentially hypertensive/atherosclerotic heart disease in an individual who has survived long enough to develop calcific AS. If this is true, then the amount of concentric remodeling may not be proportional to the systolic load imposed by the valve alone (4,5).

SYSTOLIC FUNCTION AND OUTCOME

The recent work of Ito et al. (6) and the paper that appears in this issue of *iJACC* (7) from the same group shed light on the issue of LV function in contemporary AS. In their initial paper, they retrospectively studied 928 patients with severe AS who had a prior echocardiogram at a time when AS was moderate to evaluate the relationships among LVEF, remodeling, and worsening AS, after the aortic valve area became severely stenotic (≤1.0 cm^2). Interestingly, in those with EF <50%, EF declined further while AS was still moderate. Such a decline was not seen in those with EF ≥60%. The authors concluded that "based on these findings, the normal LVEF level in patients with AS appears to be >60%" (7). (More on this point later.)

SEE PAGE 357

CONCENTRIC REMODELING, MIDWALL SHORTENING, AND OUTCOME

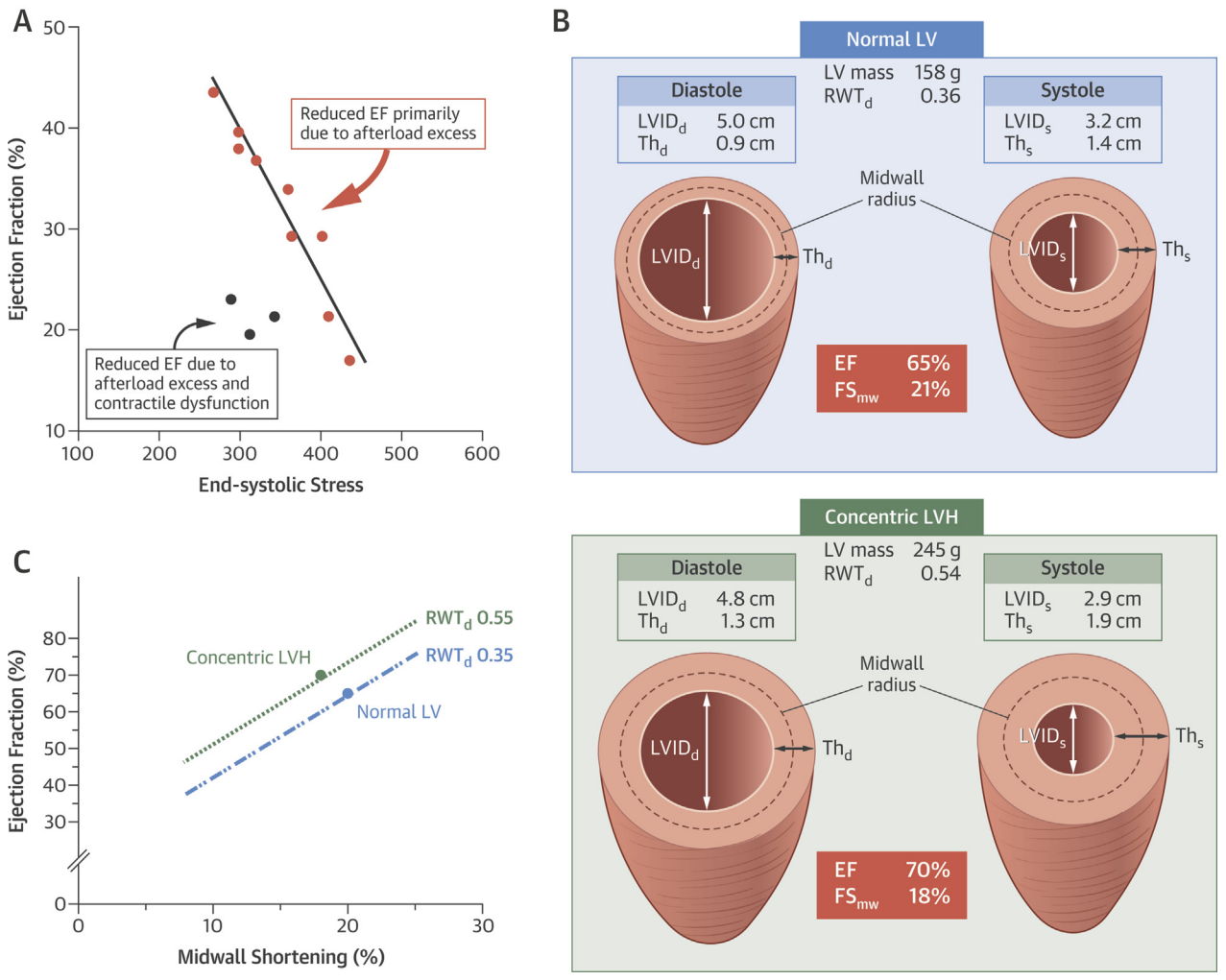
The current, follow-up, paper by Ito et al. (7) uses midwall stress-shortening analysis (FS_{mw})(8) to study systolic function in the same population (**Figures 1B and 1C**). Defining contractility as low FS_{mw} in relation to afterload (circumferential wall stress), they showed that contractile dysfunction was present in both groups 3 years before the diagnosis of severe AS. In those with LVEF <60%, 38% had decreased contractile function on the look-back study (58% when AS became severe), and was associated with worse survival over a median follow-up of 3.4 years. Among those with EF ≥60%, 17% had contractile dysfunction when AS was moderate, and that prevalence rose to 24% when AS was severe. Patients with EF ≥60% and decreased contractile function had larger relative wall thickness, smaller LV dimensions, reduced stroke volume index, and worse survival.

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

From the Division of Cardiovascular Medicine, Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ISSN 1936-878X/$36.00
https://doi.org/10.1016/j.jcmg.2019.03.010

FIGURE 1 **LV Remodeling and Function in Aortic Stenosis**



(A) Inverse relationship between EF and afterload (end-systolic stress) from work of Carabello et al. (2). **(B)** Schematic representation of the concept underlying the advantage of using midwall shortening in patients with concentric LV geometry (high ratio of wall thickness to cavity radius). LV circumferential shortening LVID, Th, RWT, and LV mass are measured in d. The midwall circumference is indicated by the dotted line. Systolic shortening, the percent reduction of the endocardial circumference **(dark inner circle)** and FS_{mw}, the percent reduction of the midwall radius **(dotted line)** are in the normal range. However, when RWT is increased (concentric LVH, **lower panel**), EF increases but FS_m falls because the inner circumference of the wall contributes proportionally more to systolic thickening. **(C)** Relationship between FS_m and EF at different levels of RWT (9); we have graphed the coordinates from the 2 hypothetical patients in **B**. This schematic shows that at any given level of FS_{mw}, the EF will be higher if the RWT is greater. Stated otherwise, if RWT is high, a subnormal FS_{mw} can be associated with a normal EF. d = diastole; EF = ejection fraction; FS_{mw} = midwall stress-shortening analysis; LV = left ventricular; LVH = left ventricular hypertrophy; RWT = relative wall thickness; LVID = left ventricular endocardial dimension; Th = wall thickness.

ANALYSIS

We applaud the use of FS_{mw} to assess systolic function in this paper for 2 reasons: 1) we have known for some time that when EF is ≥60%, there is often an identifiable abnormality in systolic function (9); and 2) there are special advantages of this approach in patients with concentric remodeling of the LV (**Figure 1**). Finally, although there are more elaborate means to analyze contractility, they are not as readily used in population studies.

It is a limitation that we are not given data concerning symptom status or nature of the outcome, beyond survival. Apparently, 55% of the patients in

JACC: CARDIOVASCULAR IMAGING, VOL. 13, NO. 2, 2020
FEBRUARY 2020:370–3

the entire study proceeded to AVR, but the reasons for this are not noted; that the prognosis was better among those who had AVR than those who did not arguably suggests that the Mayo clinicians were good at identifying those who were good surgical candidates. The groups with poor contractile function did worse, with and without AVR, suggesting an important signal in the FS_{mw} data.

A strength of this study, in our opinion, is that the mean age of the population is approximately 80 years of age and has a significant burden of comorbidities; this makes the data relevant to decision making for the contemporary AS population. This was a high-risk group, with only a 51% survival at a median follow-up of 3.4 years, considerably lower than what the same institution reported in 2005 in their natural history study of asymptomatic severe AS patients (mean age 72 years) (10).

One of these comorbidities is coronary heart disease (CAD), which has an independent effect on LV EF, FS_{mw}, and myocardial fibrosis, but which has generally been ignored in prior studies of AS. We would argue that, since in most forms of heart disease, prognosis is strongly related to the EF, it is not a mystery that EF is related to outcome among the current population of AS patients. Although a history of myocardial infarction was included in the multivariable regression by Ito et al. (7), it is possible that they underestimated the impact of CAD on outcome. We would have preferred that they have included the presence of CAD, not just myocardial infarction, to the analysis.

The other important comorbidity is hypertension, which is ubiquitous among AS patients (11), and the effects of hypertension versus those of AS on the myocardium cannot be separated. In fact, roughly one-half of the patients in the Ito et al. (7) series had left ventricular hypertrophy at a time when AS was moderate; another one-third had concentric remodeling. Similar findings have been published by Gerdts et al. (12). We predict that the high prevalence of hypertension will prove to have implications for the amount of hypertrophy regression that might be expect after TAVR, and whether the associated diastolic dysfunction will normalize.

SUMMARY AND QUESTIONS FOR THE FUTURE

Current ultrasound cardiac imaging allows us to understand the regional components—long- and short-axis—shortening and the resultant myocardial thickening. A growing number of studies have now shown that both long-axis shortening and short-axis, (or circumferential) shortening, are reduced among patients with normal EF and concentric geometry (13). What Ito et al. (7) have added, importantly, is outcome data to supplement the pathophysiologic findings. Although there is much excitement about the use of speckle tracking to compute global longitudinal strain (14), a measure of long axis shortening, the calculation of FS_{mw} has the advantage of depending only on parasternal long-axis dimensions, which are available on most echocardiographic studies and therefore lends itself for use in large population studies. Midwall shortening is also conceptually appealing, because more of the LV myocardium is devoted to circumferential, rather than long-axis shortening, and directionally, FS_{mw} and circumferential stress vectors are aligned (8).

Is an EF of 60% "normal" in AS? We might choose the word "optimal," perhaps, but would avoid the word "normal" because this and other work has proven that there are patients with reduced EF whose contractile function is normal. Normal contractile function implies that the EF will improve following AVR. More important is the question of whether we should we be offering surgery or TAVR to asymptomatic patients with an EF <55% (or even 60%) if global longitudinal strain or FS_{mw} are depressed. We would say "no" to this question, for this reason: these procedures have finite morbidity and mortality, and prosthetic valves do fail, whereas sudden death in asymptomatic AS is still rare (10,15). It is also not clear that valve replacement will reverse the fibrosis, hypertrophy, or diastolic function abnormalities that were caused by pre-existing hypertensive and/or coronary heart disease. Until the answer to that question is known, or AVR can be performed without morbidity or mortality, we will continue to watch AS patients with intermediate EF carefully for the development of symptoms.

ACKNOWLEDGMENT The authors would like to thank Dr. William H. Gaasch for his contributions to the study of LV function in valvular disease and his continuing mentorship.

ADDRESS FOR CORRESPONDENCE: Dr. Gerard P. Aurigemma, University of Massachusetts Medical School, 55 Lake Avenue North, ACC4-240, Worcester, Massachusetts 01655. E-mail: gerard.aurigemma@umassmed.edu.

REFERENCES

1. Ross J Jr. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy. J Am Coll Cardiol 1985;5:811–26.

2. Carabello BA, Green LH, Grossman W, Cohn LH, Koster JK, Collins JJ Jr. Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. Circulation 1980;62:42–8.

3. Antonini-Canterin F, Huang G, Cervesato E, et al. Symptomatic aortic stenosis: does systemic hypertension play an additional role? Hypertension 2003;41:1268–72.

4. Cramariuc D, Rieck AE, Staal EM, et al. Factors influencing left ventricular structure and stress-corrected systolic function in men and women with asymptomatic aortic valve stenosis (a SEAS Substudy). Am J Cardiol 2008;101:510–5.

5. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. J Am Coll Cardiol 2012;60:1854–63.

6. Ito S, Miranda WR, Nkomo VT, et al. Reduced left ventricular ejection fraction in patients with aortic stenosis. J Am Coll Cardiol 2018;71:1313–21.

7. Ito S, Pislaru C, Miranda WR, et al. Left ventricular contractility and wall stress in patients with aortic stenosis with preserved or reduced ejection fraction. J Am Coll Cardiol Img 2020;13:357–69.

8. Shimizu G, Zile MR, Blaustein AS, Gaasch WH. Left ventricular chamber filling and midwall fiber lengthening in patients with left ventricular hypertrophy: overestimation of fiber velocities by conventional midwall measurements. Circulation 1985;71:266–72.

9. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995;26:195–202.

10. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005;111:3290–5.

11. Lindman BR, Otto CM, Douglas PS, et al. Blood pressure and arterial load after transcatheter aortic valve replacement for aortic stenosis. Circ Cardiovasc Imaging 2017;10(7).

12. Gerdts E, Rossebo AB, Pedersen TR, et al. Relation of left ventricular mass to prognosis in initially asymptomatic mild to moderate aortic valve stenosis. Circ Cardiovasc Imaging 2015;8:e003644.

13. Cioffi G, Mazzone C, Barbati G, et al. Combined circumferential and longitudinal left ventricular systolic dysfunction in patients with asymptomatic aortic stenosis. Echocardiography 2015;32:1064–72.

14. Marwick TH. Ejection fraction pros and cons: JACC state-of-the-art review. J Am Coll Cardiol 2018;72:2360–79.

15. Lancellotti P, Magne J, Dulgheru R, et al. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. JAMA Cardiol 2018;3:1060–8.

KEY WORDS aortic stenosis, echocardiography, midwall shortening