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The role and clinical implications of diastolic dysfunction in aortic stenosis

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ABSTRACT

Diastolic dysfunction in aortic stenosis results primarily from left ventricular hypertrophy and myocardial fibrosis due to chronically elevated left ventricular systolic pressure. Currently, diastolic dysfunction does not have an explicit clinical role in management of patients with aortic stenosis. Studies have shown that improvement in diastolic dysfunction follows left ventricular remodelling after aortic valve replacement and that it occurs gradually or incompletely. Retrospective studies suggest that advanced grades of diastolic dysfunction at baseline are associated with increased mortality and adverse events even after aortic valve replacement. Recent studies have also associated myocardial fibrosis, a hallmark of diastolic dysfunction, with worse outcomes. In addition, these results were independent of the degree of aortic stenosis or valve replacement. Indirect evidence of the role of diastolic dysfunction in aortic stenosis also comes from paradoxical low-flow, low-gradient aortic stenosis, where disproportionate left ventricular hypertrophy leads to underfilling of the left ventricle, low-flow state and is associated with worse prognosis. Lastly, a limited number of studies suggest that worse diastolic dysfunction at baseline is detrimental in patients who develop aortic regurgitation after transcatheteraortic valve replacement, due to superimposition of volume overload on a stiff left ventricle. Current major limitations in our understanding of the prognostic role of diastolic dysfunction are the lack of universally accepted classification schemes, its dependence on dynamic loading conditions and the lack of larger prospective studies.

INTRODUCTION

Diastolic dysfunction refers to impaired ventricular relaxation and increased ventricular stiffness resulting in increased ventricular filling pressures.[1] Despite the presence of diastolic dysfunction in patients with aortic stenosis (AS),[2] it remains largely unknown whether its evaluation significantly affects the management of these patients and, if so, in what way. A number of retrospective studies have reported a direct correlation between worse diastolic dysfunction and worse outcomes (online supplementary S–CC). Indirect evidence of the impact of worse diastolic dysfunction is seen in patients with paradoxical low-flow, low-gradient AS, where disproportionate left ventricular hypertrophy (LVH) and restrictive physiology lead to decreased left ventricular (LV) filling and low flow. These patients are known to have worse outcomes.[3] Myocardial fibrosis, a hallmark of diastolic dysfunction, has also been associated with worse prognosis even after aortic valve replacement (AVR).[4 5] Additionally, a limited number of studies are suggesting that worse diastolic dysfunction may be detrimental in patients who develop aortic regurgitation (AR) after transcatheter AVR (TAVR).[6 7]

The primary goal of the current review was to investigate the clinical roles of diastolic dysfunction in patients with AS. We reviewed a large spectrum of pertinent studies in the literature, primarily in relation to outcomes and changes of diastolic dysfunction after AVR.

DIASTOLIC DYSFUNCTION BEFORE AND AFTER AVR

Development of diastolic dysfunction

Diastolic function refers to a complex sequence of events that result in filling of the LV with low ventricular end-diastolic pressure. The two major determinants of diastolic function are active ventricular relaxation and passive viscoelastic compliance.[8] Elevated filling pressures as a result of impaired relaxation or decreased compliance are considered the hallmark of diastolic dysfunction.[1 9] In AS, LV systolic pressure increases as a result of the progressive narrowing of the aortic valve orifice. Increased LV systolic pressure leads to compensatory concentric LVH, which maintains normal afterload (wall stress) and normal systolic function according to the Laplace equation.[2] However, concentric LVH also results in impaired LV diastolic function as increased wall thickness impairs early diastolic relaxation and decreases compliance, necessitating amplified filling pressure to achieve a normal end-diastolic volume.[10] In addition to LVH, increased LV systolic pressure leads to progressive extracellular myocardial fibrosis,[11] which contributes to LV stiffness, decreased compliance and subsequently impaired diastolic function. In summary, concentric LVH and myocardial fibrosis are the key pathophysiological mechanisms of diastolic dysfunction in patients with AS and are both a result of increased LV systolic pressure (figure 1). With the progression of AS, filling of the LV is maintained only through increased LV diastolic pressure. This augmented diastolic pressure leads to pulmonary congestion, which manifests clinically as dyspnoea or overt heart failure.

Clinical evaluation of diastolic dysfunction

Direct measurement of LV end-diastolic pressure and the time constant of LV relaxation (τ) via high-fidelity pressure transducers is the most accurate method of diagnosing diastolic dysfunction, but it is limited by the need for cardiac catheterisation.[12] In clinical practice, diastolic dysfunction

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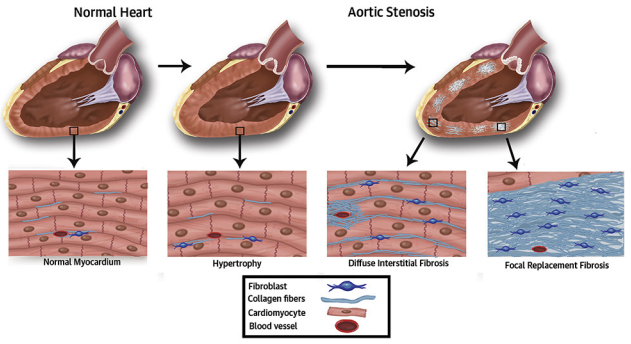

Figure 1 LV hypertrophy and myocardial fibrosis are the key pathophysiological mechanisms of diastolic dysfunction in AS. Chronically elevated left ventricular systolic pressure from narrowing of the aortic valve orifice leads to compensatory hypertrophy of the ventricular wall to maintain normal wall stress according to the Laplace equation. However, this eventually results in increased stiffness of the ventricular wall, impaired relaxation and diastolic dysfunction (first two histological representations). In addition, adverse remodelling of the left ventricle promotes fibrosis of its wall that can be diffuse interstitial (third representation) or focal (fourth representation). Myocardial fibrosis further worsens ventricular stiffness and thus impairs diastolic function. AS, aortic stenosis; LV, left ventricle. Adopted with permission from Barone-Rochette *et al*. J Am Coll Cardiol. 2014 15;64(2):144–54.

is mainly evaluated by echocardiography or cardiac magnetic resonance (CMR).[13]

Echocardiographic evaluation of diastolic dysfunction is based on the measurement of two-dimensional and Doppler variables (ie, left atrial volume, transmitral and pulmonary venous flow velocities and time intervals and tissue Doppler of the mitral valve annulus) that reflect impaired LV relaxation and estimate LV end-diastolic pressure. These variables correlate well with measurements derived by cardiac catheterisation.[8 14] However, their interpretation is based on additional echocardiographic measurements such as LV mass, ejection fraction, valvular disease and is related to age, gender and the clinical setting. As a result, diastolic echocardiographic variables are often non-concurrent and can be interpreted differently.[15] The American Society of Echocardiography and the European Association of Cardiovascular Imaging have recently updated their guidelines in an attempt to simplify the evaluation of diastolic dysfunction and recommend a practical, standardised scheme for diagnosis and grading of diastolic dysfunction.[1 16] CMR has emerged as an alternative modality to echocardiography for the evaluation of diastolic dysfunction.[17] Apart from assessing the parameters derived by echocardiography, CMR has the additional benefit of quantifying myocardial fibrosis.

LV remodelling and diastolic dysfunction after AVR

Replacement of the stenotic aortic valve results in immediate relief of LV pressure overload, the upstream pathophysiological stimulus to diastolic dysfunction. However, resolution of LVH and myocardial fibrosis, which are the intermediate mechanisms that sustain diastolic dysfunction, requires a process of LV remodelling that may require years after AVR or be irreversible.[18 19] Improvement in diastolic dysfunction after AVR seems to accompany this slow process.

Most of our knowledge on this topic comes from earlier studies on patients with AS that underwent surgical AVR (SAVR). Online supplementary table 1 summarises studies on LV remodelling after AVR, with a flow chart of pertinent literature search in figure 2. Invasive evaluation of diastolic function using

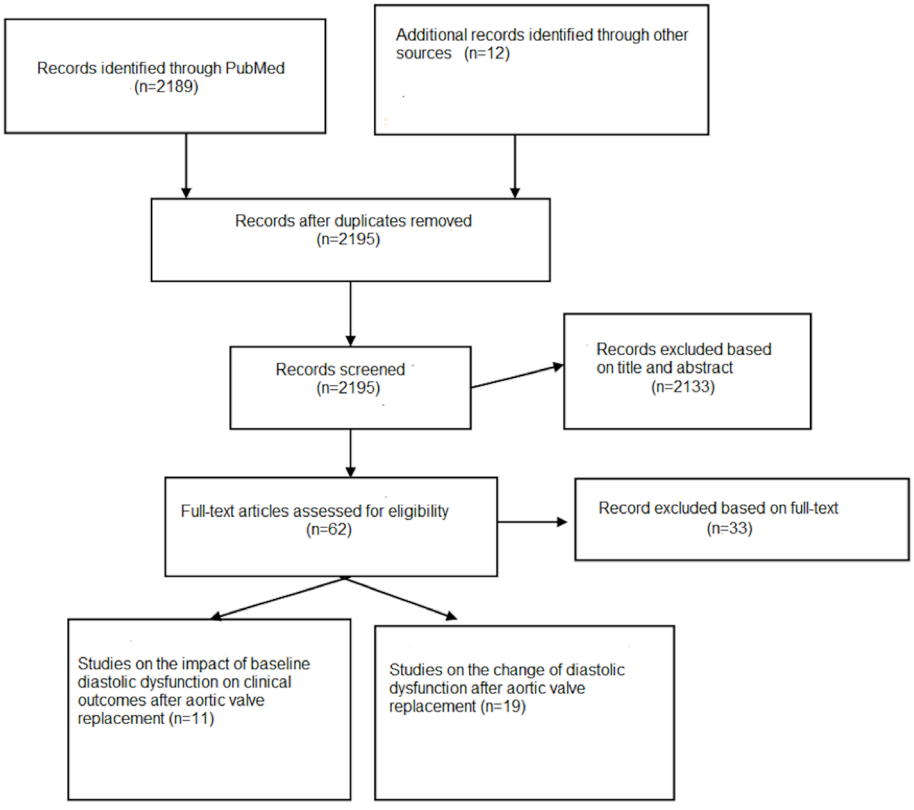

Figure 2 Flow diagram of literature search for studies of diastolic dysfunction in patients with aortic stenosis undergoing aortic valve replacement. One study was eligible in both categories.

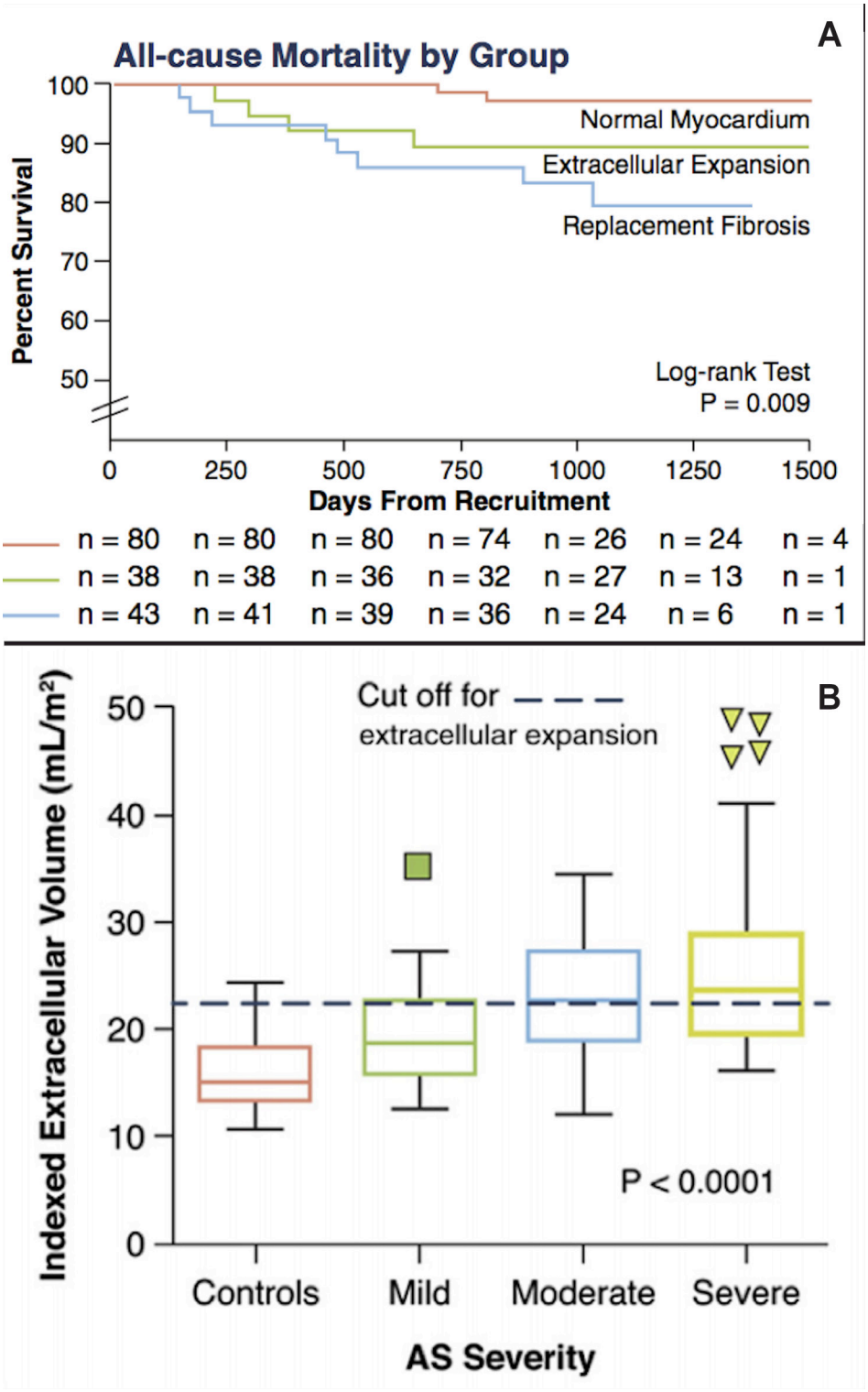

Figure 3 Survival curves of AS patients with different degrees of myocardial fibrosis (top) and presence of indexed extracellular volume in patients with different degrees of AS versus controls (bottom). In this prospective observational study, CMR imaging was used to evaluate myocardial fibrosis in patients with different degrees of AS and in controls (healthy volunteers). Patients were classified as having (1) normal myocardium (n=80), (2) extracellular expansion, an early reversible form of myocardial fibrosis evaluated by extracellular volume expansion above an indexed cut-off (n=38), and (3) replacement fibrosis, detected by presence of mid-wall late gadolinium enhancement (n=43). Patients with myocardial fibrosis and particularly with replacement fibrosis had increased mortality on follow-up regardless of AS severity. Notice that significant extracellular expansion correlates with the severity of AS; however it was present even in less severe AS. Adopted with permission and modified from Chin *et al*.[38] doi: 10.1016/j.jcmg.2016.10.007. Epub ahead of print. Open access under the CC BY licence https://creativecommons.org/licenses/by/4.0/.%20AS, aortic stenosis; CMR, cardiac magnetic resonance.

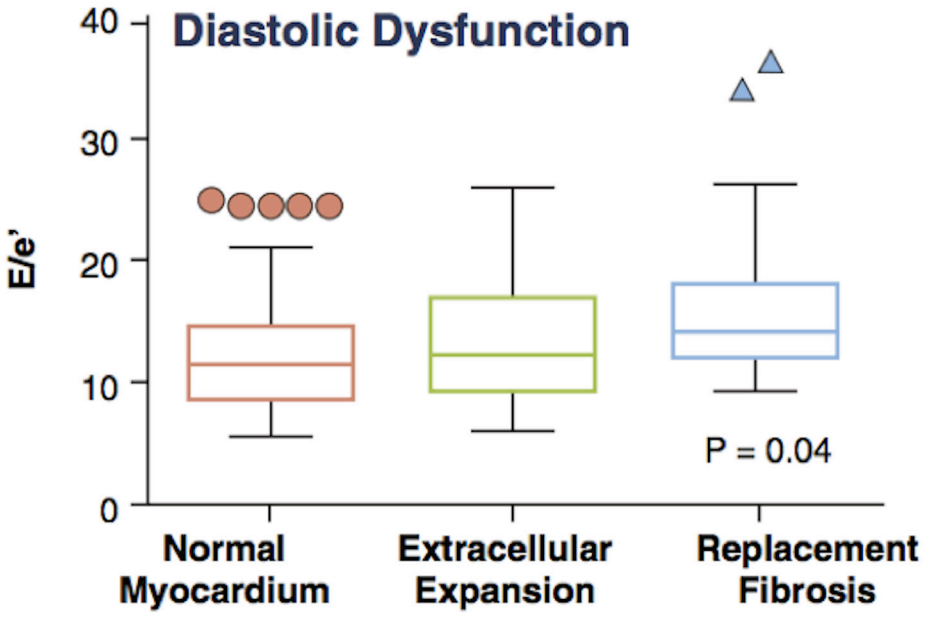

Figure 4 E/e' ratio increases in AS patients with more myocardial fibrosis regardless of AS severity. In this prospective observational study, CMR imaging was used to evaluate myocardial fibrosis in patients with different degrees of AS and in controls (healthy volunteers). Patients were classified as having (1) normal myocardium (n=80), (2) extracellular expansion, an early reversible form of myocardial fibrosis evaluated by extracellular volume expansion above an indexed cut-off (n=38) and (3) replacement fibrosis, evaluated by presence of mid-wall late gadolinium enhancement (n=43). Echocardiography was used to measure E/e' ratio as a marker of diastolic dysfunction. E/e' ratio was significantly different among the groups with more advanced myocardial fibrosis correlating with higher E/e' and thus worse diastolic dysfunction. Adopted with permission and modified from Chin *et al*.[38] doi: 10.1016/j.jcmg.2016.10.007. Epub ahead of print. Open access under the CC BY licence https://creativecommons.org/licenses/by/4.0/.%20AS, aortic stenosis; CMR, cardiac magnetic resonance.

high-fidelity pressure measurements with concurrent endomyocardial biopsies has shown that diastolic dysfunction normalises late (81 months) but not early (22 months) after AVR with concurrent changes in myocardial fibrosis. In fact, myocardial stiffness (ie, diastolic dysfunction) worsened early after AVR in parallel to increased myocardial fibrosis, a finding that has been attributed to a relative increase of myocardial fibrosis as cardiac myocyte hypertrophy decreases earlier after AVR.[10] Despite significant heterogeneity in the evaluation of diastolic dysfunction, non-invasive studies of diastolic function have shown similar gradual improvement in diastolic dysfunction late after AVR parallel to LV remodelling. Residual and even worsened diastolic dysfunction has been noted even up to 10 years after AVR (online supplementary A–S).

The identification of factors contributing to incomplete or delayed LV remodelling after AVR has been an issue of debate.[20] Known cardiac factors that act unfavourably for diastolic function improvement include patient–prosthesis mismatch, uncontrolled hypertension[21] and extensive myocardial fibrosis or profound baseline LVH[18] such as in the case of low-flow, low-gradient AS. Patient–prosthesis mismatch, defined as effective orifice area after replacement of the valve that is too small in relation to body size, is a marker of incomplete relief of pressure overload after AVR.[22] As a result, it has been associated with slower rates of LV mass regression, LV remodelling and worse outcomes.[23 24]

Diastolic dysfunction after TAVR

Although long-term follow-up data after TAVR is not available, LV remodelling seems to be comparable with that after SAVR, with the notable exception of slower regression of LV mass and decreased frequency of patient–prosthesis mismatch.[25] Studies on diastolic dysfunction after TAVR have been limited in number. Early after TAVR and parallel to favourable LV remodelling, improvement in diastolic dysfunction has been shown in several studies as summarised in online supplementary table 1, L–S).

However, there is no prior surgical literature on inoperable patients with AS. Additionally, we have to note that TAVR patients have a few distinct characteristics compared with SAVR patients that predispose them to poor LV response to AVR and likely persistent diastolic dysfunction. They are more elderly, have more comorbidities, worse baseline functional status, more advanced myocardial fibrosis and possibly worse LVH.[5] As a result, they may have worse diastolic dysfunction at baseline with possibly less complete improvement compared with patients with SAVR. Furthermore, AR is more common after TAVR and is known to negatively affect outcomes.

IMPACT OF DIASTOLIC DYSFUNCTION ON OUTCOMES AFTER AVR

The fact that diastolic dysfunction resolves slowly or incompletely in parallel to LV remodelling after AVR leads to the question whether worse diastolic function at baseline results in unfavourable clinical outcomes. Potential mechanisms for that are heart failure and arrhythmias from a persistently failing LV. In fact, persistent LVH and dilated left atrium have been associated with increased mortality after AVR.[18] In addition, paradoxical low-flow, low-gradient AS and myocardial fibrosis, which provide indirect evidence to diastolic dysfunction, have separately been associated with increased mortality.

Several small retrospective studies have demonstrated increased mortality and morbidity from the perioperative period through long-term follow-up for patients with evidence of advanced baseline diastolic dysfunction undergoing AVR, thus supporting

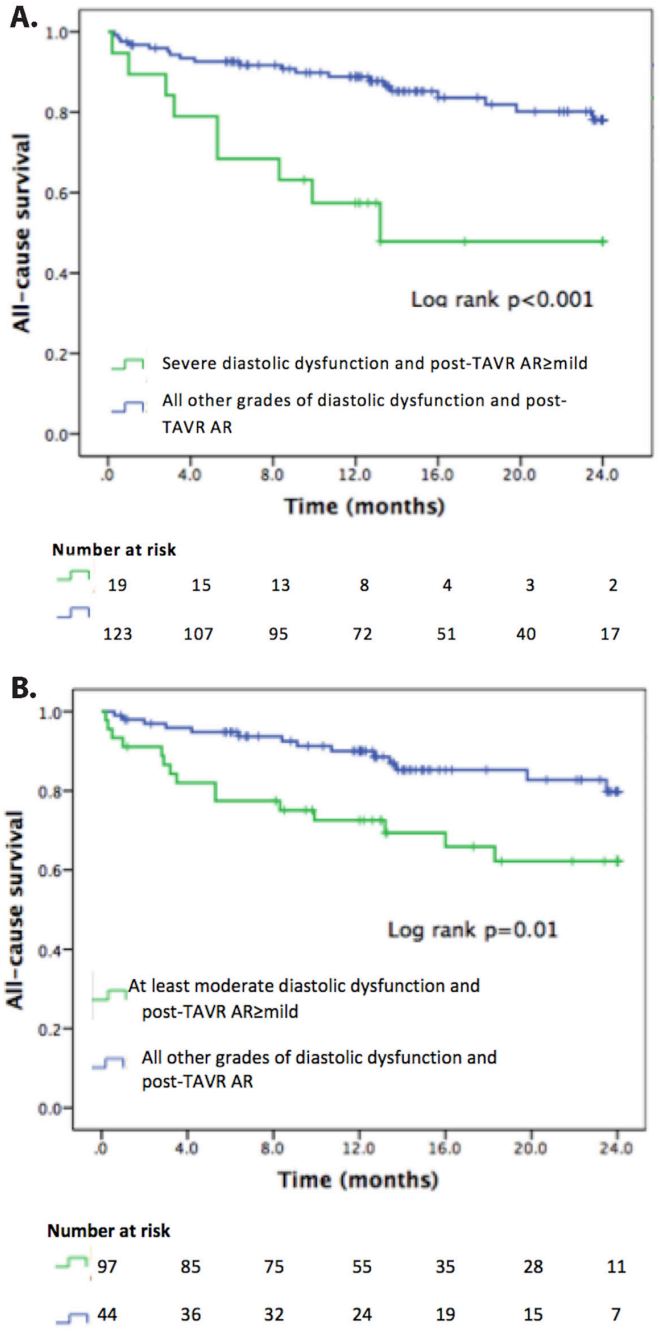

Figure 5 Survival curves after TAVR in patients with different degrees of baseline diastolic dysfunction and post-TAVR AR. In this retrospective observational study patients were classified in different groups according to the severity of baseline diastolic dysfunction prior to TAVR and the severity of post-TAVR AR. Patients with severe diastolic dysfunction at baseline and at least mild post-TAVR AR (n=19) had significantly increased mortality (p<0.001) compared with all other patients (n=123) (up). Patients with moderate diastolic dysfunction at baseline who developed at least mild post-TAVR AR (n=97) also had significantly increased mortality compared with all other patients (n=44); however, the statistical significance was lower (p=0.01) (down). Adopted with permission and modified from Kampaktsis *et al*. Catheter Cardiovasc Interv. 2017. 15;89(3):445–451. AR, aortic regurgitation; TAVR, transcatheter aortic valve replacement.

the above-mentioned hypothesis (online supplementary table 2, S–CC). The majority of these studies so far have been on patients undergoing SAVR (online supplementary T–BB). In the perioperative setting, worse baseline diastolic dysfunction has been associated with difficulty weaning off cardiopulmonary bypass for AVR or other cardiac surgery, resulting in increased rates of complications during hospitalisation. Giertsson *et al* graded baseline diastolic dysfunction in 399 patients and reported an association of moderate-to-severe diastolic dysfunction with increased long-term (12 years) mortality after AVR. In another study with 1200 patients with different AS severity, moderate-to-severe diastolic dysfunction was associated with increased rates of AVR or mid-term (2 years) mortality. The non-invasive estimation of LV filling pressure E/e′ is a widely accepted predictor of worse outcomes in several cardiac diseases including inoperable AS[26 27] and has been associated with increased in-hospital, early-mid mortality or cardiovascular events. E/A and E wave deceleration time have also been associated with early and long-term mortality after AVR. Another diastolic dysfunction variable that has been associated with increased short-term and long-term mortality after AVR is LV fast filling fraction (per cent of total filling volume in first half of diastole defined by LV ventriculography).

In the TAVR setting, there are limited data regarding the prognostic value of diastolic dysfunction. A study on 350 patients reported no difference in mortality among patients with different degrees of diastolic dysfunction (online supplementary S). Interestingly though, significantly increased mortality was noted in the subgroup of patients with severe diastolic dysfunction that did not improve at 1-year post-TAVR compared with patients with severe diastolic dysfunction that improved. A smaller study by our group on 190 patients showed a trend towards higher mortality in patients with severe diastolic dysfunction versus less than severe diastolic dysfunction at baseline.[7]

A major limitation of the above-mentioned studies besides their limited number is heterogeneity in the definition and classification of diastolic dysfunction. In addition, the impact of earlier versus later/incomplete improvement in diastolic dysfunction on outcomes has been inadequately studied.

Low-flow, low-gradient AS and diastolic dysfunction

Paradoxical low-flow, low-gradient represents an extreme but not infrequent side of diastolic dysfunction in AS and is accompanied by clear clinical implications and worse prognosis. Although a high mean aortic valve gradient, typically >40 mm Hg signifies the presence of severe AS, in low-flow states severe AS can result in a lower aortic valve gradient. Low-flow severe AS occurs in classical and paradoxical low-flow, low-gradient forms.[3] These two types of low-flow, low-gradient AS, representing maladaptive LV responses to pressure overload, are associated with increased myocardial fibrosis and, importantly, correlate with worse outcomes compared with normal-flow, high-gradient AS.[28 29] In regards to the underlying pathophysiological mechanism of the low-flow state, classical low-flow, low-gradient AS results primarily from LV dilatation and depressed systolic function. Paradoxical low-flow, low-gradient AS is thought to result primarily from profound LV remodelling leading to diastolic dysfunction, restrictive physiology and impaired filling of the LV. However, no studies have evaluated diastolic function in patients with paradoxical low-flow, low-gradient AS.

Distinguishing paradoxical low-flow, low-gradient from moderate AS in a symptomatic patient is crucial and challenging. A comprehensive clinical and echocardiographic approach has

been proposed by experts on the field.[30] However, the importance of diastolic function evaluation in this clinical setting has not been well studied.

Myocardial fibrosis and diastolic dysfunction in AS

Myocardial fibrosis is a main pathophysiological feature of advanced diastolic dysfunction[31] and in fact of all advanced cardiomyopathies.[32] Non-invasively, CMR via post-contrast T1 mapping of extracellular volume and late gadolinium enhancement are methods of choice to detect either localised or diffuse myocardial fibrosis. Recent studies suggest that the degree of myocardial fibrosis as defined by CMR correlates well with the degree of diastolic dysfunction as measured both invasively[33] and non-invasively.[4] More interestingly, there is growing evidence that myocardial fibrosis is an independent predictor of mortality in patients with AS after AVR, even when detected in the asymptomatic phase of the disease.[5 34–36] There is still no clear pathophysiological link between myocardial fibrosis and increased mortality; however, worse diastolic dysfunction and associated heart failure, as well as arrhythmogenesis are likely culprits.[37] In a recent study, Chin *et al* used CMR to classify patients in three groups of myocardial fibrosis severity regardless of AS severity (figure 3). In their study, diastolic dysfunction grade correlated with myocardial fibrosis grade, and myocardial fibrosis grade was associated with increased mortality regardless of AS severity[38] (figures 3 and 4). These findings suggest that diastolic dysfunction and myocardial fibrosis severity potentially have additional prognostic significance independent of AS severity alone. An interesting question, therefore, is whether the prognostic value of myocardial fibrosis is independent of diastolic dysfunction grade, or whether diastolic dysfunction and myocardial fibrosis both contribute to more accurate prognostication. Nevertheless, it remains unclear whether myocardial fibrosis can contribute to clinical management of patients with AS given the lack of widely accepted clinical algorithms for its use and the large cost of CMR.

DIASTOLIC DYSFUNCTION AND TIMING OF AVR FOR SEVERE AS

Current guideline-based practice for treatment of AS is largely based on its severity (per aortic valve area and gradient) and the onset of symptoms, with AVR classically recommended for severe symptomatic AS. These recommendations are derived from older studies that examined the outcomes of symptomatic patients who did not undergo AVR and suffered a mortality rate of 25% per year.[39 40] In contrast to symptomatic AS, there is no prospective randomised trial comparing AVR versus no AVR in severe asymptomatic AS, and there is ongoing debate in regards to the management of these patients.[41] Most such patients have a good short-term prognosis with a risk of sudden death of <1% per year, whereas AVR carries a small but non-trivial risk even in experienced centres.[42] Current guidelines therefore recommend AVR in high-risk asymptomatic patients with depressed LV ejection fraction or rapid progression of AS, with exercise stress tests used to unmask symptoms.[43] A retrospective study with propensity score matching comparing severe asymptomatic AS patients who underwent early AVR versus conservative treatment showed improved survival in the first group.[44] Unfortunately, there were no available data on diastolic dysfunction or myocardial fibrosis in these patients.

Available evidence suggesting prognostic roles for severe diastolic dysfunction, low-flow, low-gradient AS and myocardial fibrosis raises the question of whether their use can help better characterise: (1) high-risk groups of asymptomatic patients that would benefit from AVR; (2) very high-risk groups of symptomatic patients where AVR should be performed urgently; and (3) extremely high-risk groups where AVR may not be of benefit such as subgroups of patients with TAVR.

ROLE OF DIASTOLIC DYSFUNCTION IN POST-TAVR AR

Despite the fact that the incidence of post-TAVR AR has decreased with improved new generation bioprosthetic valves, better patient selection and improved imaging,[45] it remains a significant predictor of increased mortality, even when mild in older studies.[46 47] The exact pathophysiological mechanism of post-TAVR AR-associated death is not known. It is thought to reflect adverse haemodynamics imposed by superimposing volume overload due to new AR post-TAVR on an LV with established diastolic dysfunction from chronic pressure overload.[48 49] As the degree of diastolic dysfunction varies in severe AS,[11] similar adverse haemodynamics could occur in patients who develop smaller degrees of post-TAVR AR but have worse baseline diastolic dysfunction. According to a limited number of studies, worse baseline diastolic dysfunction is associated with increased mortality and worse post-TAVR diastolic dysfunction in patients with even mild post-TAVR AR (figure 5).[6 7 50] If that is true, patients with baseline diastolic dysfunction who develop post-TAVR AR may benefit from additional, otherwise high-risk interventions, such as post-deployment re-expansion of the bioprosthetic valve to eliminate AR. In addition, selection of bioprosthetic valves with lower rates of post-TAVR AR may provide beneficial primary prevention for patients with significant baseline diastolic dysfunction.

CONCLUSIONS AND FUTURE DIRECTIONS

In patients with AS, studies have shown gradual or incomplete improvement in diastolic dysfunction after AVR. More interestingly, a number of studies suggest that worse diastolic dysfunction at baseline is associated with increased mortality and adverse events even after AVR. Myocardial fibrosis, a hallmark of diastolic dysfunction, is also associated with worse outcomes. In addition, the association of paradoxical low-flow, low-gradient AS with increased mortality also provides indirect evidence for the prognostic role of diastolic dysfunction, since this condition is associated with profound LVH that leads to underfilling of the LV. Furthermore, there is evidence from a very limited number of studies that worse diastolic dysfunction is associated with worse outcomes in patients who develop post-TAVR AR.

Major limitations in our understanding of the role of diastolic dysfunction are the lack of universally accepted classification schemes, its dependence on loading conditions and the lack of larger studies. Additionally, due to increased heterogeneity across studies and limited large-scale studies, a systematic review that could form the basis for clinical guideline type recommendations cannot be currently performed. Larger studies are needed to verify whether the evaluation of diastolic dysfunction has a true prognostic role in patients with AS and to identify whether this is independent of myocardial fibrosis and paradoxical low-flow, low-gradient AS.

Contributors PNK: study design, systematic search, data extraction, analysis and interpretation of data and overall content responsibility. DGK: systematic search and data extraction. S-CW: analysis and interpretation of data, critical revision and study design. MV: critical revision. NJS: critical revision. RBD: study design, critical revision and overall content responsibility.

Competing interests None declared.

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REFERENCES

1 Nagueh SF, Smiseth OA, Appleton CP, *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277–314.
2 Carabello BA, Paulus WJ. Aortic stenosis. *Lancet* 2009;373:956–66.
3 Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. *J Am Coll Cardiol* 2012;60:1845–53.
4 My S, Lin LY, Tseng YH, *et al*. CMR-verified diffuse myocardial fibrosis is associated with diastolic dysfunction in HFpEF. *JACC Cardiovascular Imaging* 2014.
5 Barone-Rochette G, Piérard S, De Meester de Ravenstein C, *et al*. Prognostic significance of LGE by CMR in aortic stenosis patients undergoing valve replacement. *J Am Coll Cardiol* 2014;64:144–54.
6 Halkin A, Steinvil A, Aviram G, *et al*. Aortic regurgitation following transcatheter aortic valve replacement: impact of preprocedural left ventricular diastolic filling patterns on late clinical outcomes. *Catheter Cardiovasc Interv* 2016;87:1156–63.
7 Kampaktsis PN, Bang CN, Chiu Wong S, *et al*. Prognostic Importance of diastolic dysfunction in relation to Post Procedural aortic insufficiency in patients undergoing transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2017;89:445–51.
8 Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: doppler echocardiography is the clinician's Rosetta Stone. *J Am Coll Cardiol* 1997;30:8–18.
9 Paulus WJ, Tschöpe C, Sanderson JE, *et al*. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539–50.
10 Hess OM, Ritter M, Schneider J, *et al*. Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. *Circulation* 1984;69:855–65.
11 Krayenbuehl HP, Hess OM, Monrad ES, *et al*. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. *Circulation* 1989;79:744–55.
12 Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. *Am J Physiol Heart Circ Physiol* 2005;289:H501–H512.
13 Oh JK, Park SJ, Nagueh SF. Established and novel clinical applications of diastolic function assessment by echocardiography. *Circ Cardiovasc Imaging* 2011;4:444–55.
14 Kasner M, Westermann D, Steendijk P, *et al*. Utility of Doppler echocardiography and tissue doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative doppler-conductance catheterization study. *Circulation* 2007;116:637–47.
15 Chapman CB, Ewer SM, Kelly AF, *et al*. Classification of left ventricular diastolic function using American Society of Echocardiography guidelines: agreement among echocardiographers. *Echocardiography* 2013;30:1022–31.
16 Nagueh SF, Appleton CP, Gillebert TC, *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;10:165–93.
17 Westenberg JJ. CMR for Assessment of diastolic function. *Curr Cardiovasc Imaging Rep* 2011;4:149–58.
18 Beach JM, Mihaljevic T, Rajeswaran J, *et al*. Ventricular hypertrophy and left atrial dilatation persist and are associated with reduced survival after valve replacement for aortic stenosis. *J Thorac Cardiovasc Surg* 2014;147:362–9.
19 Yarbrough WM, Mukherjee R, Ikonomidis JS, *et al*. Myocardial remodeling with aortic stenosis and after aortic valve replacement: mechanisms and future prognostic implications. *J Thorac Cardiovasc Surg* 2012;143:656–64.
20 Villa E, Troise G, Cirillo M, *et al*. Factors affecting left ventricular remodeling after valve replacement for aortic stenosis. an overview. *Cardiovasc Ultrasound* 2006;4:25.
21 Gavina C, Falcão-Pires I, Rodrigues J, *et al*. Load independent impairment of reverse remodeling after valve replacement in hypertensive aortic stenosis patients. *Int J Cardiol* 2014;170:324–30.
22 Pibarot P. Prosthesis-patient mismatch: definition, clinical impact, and prevention. *Heart Br Card Soc* 2006;92:1022–9.
23 Tasca G, Mhagna Z, Perotti S, *et al*. Impact of prosthesis-patient mismatch on cardiac events and midterm mortality after aortic valve replacement in patients with pure aortic stenosis. *Circulation* 2006;113:570–6.
24 Rao V, Jamieson WRE, Ivanov J, *et al*. Prosthesis-patient mismatch affects survival after aortic valve replacement. *Circulation* 2000;102:III-5–0.
25 Kim SJ, Samad Z, Bloomfield GS, *et al*. A critical review of hemodynamic changes and left ventricular remodeling after surgical aortic valve replacement and percutaneous aortic valve replacement. *Am Heart J* 2014;168:150–9.
26 Nagueh SF, Middleton KJ, Kopelen HA, *et al*. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30:1527–33.
27 Biner S, Rafique AM, Goykhman P, *et al*. Prognostic value of E/E' ratio in patients with unoperated severe aortic stenosis. *JACC Cardiovasc Imaging* 2010;3:899–907.
28 Herrmann S, Störk S, Niemann M, *et al*. Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. *J Am Coll Cardiol* 2011;58:402–12.
29 Dayan V, Vignolo G, Magne J, *et al*. Outcome and impact of aortic valve replacement in patients with preserved LVEF and low-gradient aortic stenosis. *J Am Coll Cardiol* 2015;66:2594–603.
30 Dumesnil JG, Pibarot P, Carabello B. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment. *Eur Heart J* 2010;31:281–9.
31 Mohammed SF, Hussain S, Mirzoyev SA, *et al*. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation* 2015;131:550–9.
32 Heling A, Zimmermann R, Kostin S, *et al*. Increased expression of cytoskeletal, linkage, and extracellular proteins in failing human myocardium. *Circ Res* 2000;86:846–53.
33 Ellims AH, Shaw JA, Stub D, *et al*. Diffuse myocardial fibrosis evaluated by post-contrast t1 mapping correlates with left ventricular stiffness. *J Am Coll Cardiol* 2014;63:1112–8.
34 Dweck MR, Joshi S, Murigu T, *et al*. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Am Coll Cardiol* 2011;58:1271–9.
35 Azevedo CF, Nigri M, Higuchi ML, *et al*. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. *J Am Coll Cardiol* 2010;56:278–87.
36 Milano AD, Faggian G, Dodonov M, *et al*. Prognostic value of myocardial fibrosis in patients with severe aortic valve stenosis. *J Thorac Cardiovasc Surg* 2012;144:830–7.
37 Disertori M, Rigoni M, Pace N, *et al*. Myocardial fibrosis assessment by LGE is a powerful predictor of ventricular tachyarrhythmias in ischemic and nonischemic LV dysfunction: a meta-analysis. *JACC Cardiovasc Imaging* 2016;9:1046–55.
38 Chin CW, Everett RJ, Kwiecinski J, *et al*. Myocardial fibrosis and cardiac decompensation in aortic Stenosis. *JACC Cardiovasc Imaging* 2016.
39 Ross J, Braunwald E. Aortic stenosis. *Circulation* 1968;38(1 Suppl):61–7.
40 Schwarz F, Baumann P, Manthey J, *et al*. The effect of aortic valve replacement on survival. *Circulation* 1982;66:1105–10.
41 Généreux P, Stone GW, O'Gara PT, *et al*. Natural history, diagnostic approaches, and therapeutic strategies for patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol* 2016;67:2263–88.
42 Carabello BA. Should severe aortic stenosis be operated on before symptom onset? aortic valve replacement should be operated on before symptom onset. *Circulation* 2012;126:112–7.
43 Nishimura RA, Otto CM, Bonow RO, *et al*. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2438–88.
44 Taniguchi T, Morimoto T, Shiomi H, *et al*. Initial Surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol* 2015;66:2827–38.
45 Hamm CW, Arsalan M, Mack MJ. The future of transcatheter aortic valve implantation. *Eur Heart J* 2015.
46 Athappan G, Patvardhan E, Tuzcu EM, *et al*. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. *J Am Coll Cardiol* 2013;61:1585–95.
47 Kodali SK, Williams MR, Smith CR, *et al*. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;366:1686–95.
48 Gotzmann M, Lindstaedt M, Mügge A. From pressure overload to volume overload: aortic regurgitation after transcatheter aortic valve implantation. *Am Heart J* 2012;163:903–11.
49 Jerez-Valero M, Urena M, Webb JG, *et al*. Clinical impact of aortic regurgitation after transcatheter aortic valve replacement: insights into the degree and acuteness of presentation. *JACC Cardiovasc Interv* 2014;7:1022–32.
50 Caballero L, Saura D, García-Lara J, *et al*. Influence of aortic regurgitation after TAVI on left ventricular filling pattern. *Eur J Clin Invest* 2015;45:18–26.

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