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REVIEW

Current and novel echocardiographic assessment of left ventricular systolic function in aortic stenosis—A comprehensive review

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Abstract

Aortic stenosis (AS) is a complex and progressive condition that can significantly reduce the quality of life and increase the incidence of premature mortality. Transthoracic echocardiography (TTE) is the gold standard imaging modality for the assessment of AS severity. While left ventricular ejection fraction (LVEF) derived from TTE is a very well-understood parameter, limitations such as high inter and intra-observer variability, insensitivity to sub-clinical dysfunction, and influence of loading conditions make LVEF a complicated and unreliable parameter. Myocardial deformation imaging has been identified as a promising parameter for identifying subclinical left ventricular dysfunction, however, this parameter is still afterload dependent. Myocardial Work is a promising novel assessment technique that accounts for afterload by combining the use of myocardial deformation imaging and non-invasive blood pressure to provide a more comprehensive assessment of mechanics beyond LVEF. This review evaluates the evidence for various echocardiographic assessment parameters used to quantify left ventricular function including myocardial work in patients with AS.

KEYWORDS
aortic stenosis, ejection fraction, left ventricular function, myocardial strain, myocardial work

1 | INTRODUCTION

Aortic stenosis (AS) is a common form of the degenerative valvular disease characterized by calcification and restriction of the aortic valve leaflets that if left untreated can cause premature cardiovascular morbidity and mortality.[1] The prevalence of this type of valvular heart disease has been shown to be directly related to age affecting around 2%–5% of the population of those over 65 years of age, increasing to nearly 10% of the population for those over the age of 80 years of age.[2,3] Lipid accumulation, gradual fibrosis, and the deposition of focal calcium within the aortic valve leaflet matrix over time have been shown to cause a reduction in leaflet mobility and valve area with concomitant increases in myocardial stress and workload induced by higher left ventricular afterload.[4] AS is a gradual pathological process described as having an asymptomatic latency period where compensatory left ventricular hypertrophy develops to preserve left ventricular systolic function and cardiac output while coping with increases in myocardial wall stress.[5] The risk of AS related mortality has been shown to significantly increase following the development of symptoms such as pre-syncope, syncope, angina, and heart failure.[6]

Transthoracic echocardiography (TTE) is recognized as an effective imaging modality used to accurately quantify aortic valve area, peak, and mean gradients used to determine AS severity.[7] TTE also offers the ability to accurately measure left ventricular systolic and diastolic function in patients with optimal echocardiographic windows.[8] Doppler measurements along with left ventricular ejection fraction (LVEF) derived from TTE are routinely used to risk stratify patients to ascertain if they would benefit from surgical or percutaneous valve intervention. Early recognition of left ventricular dysfunction can risk stratify patients and optimize time of intervention for significant AS.[5,9] It is well established that optimal intervention timing is vital to ensure that patient survival and quality of life is augmented in patients with AS.[10] Current guidelines by the American College of Cardiology and American Heart Association (ACC/AHA) recommend that symptomatic patients with severe AS should be considered for either surgical replacement or transcatheter aortic valve intervention.[7] However, the results from the RECOVERY trial that randomized severe AS participants for conventional or early surgical treatment concluded that the incidence of death was significantly lower in asymptomatic patients referred for early surgical intervention (7% vs. 21%, HR .33; 95% CI .12–.90). The RECOVERY and AVATAR trials suggested that waiting for symptoms to develop as a marker of disease severity is a flawed concept as early intervention improves long-term outcomes.[11,9] The use of myocardial deformation imaging in the AS population has started to show promising results as a strategy to evaluate myocardial function beyond crude volumetric changes provided by left ventricular ejection fraction.[12] Myocardial work (MW) is a novel echocardiographic parameter derived from global longitudinal strain (GLS) which may offer the ability to further evaluate left ventricular mechanics. It may also provide an opportunity to identify patients who could benefit from early intervention. In addition, GLS and MW have the capacity to identify AS patients with subclinical left ventricular dysfunction who are more likely to exhibit poorer outcomes post-intervention. This literature review evaluates current evidence around the pathology and incidence of AS, the current role of LVEF and myocardial deformation imaging in clinical practice along with the promising applications of MW in assessing subclinical dysfunction in AS patients.

2 | LEFT VENTRICULAR RESPONSE TO AORTIC STENOSIS

A gradual increase in afterload associated with a stenotic aortic valve has been shown to elevate myocardial wall stress resulting in an increase in myocardial oxygen consumption.[13] Laplace's law indicates that wall stress is proportional to left ventricular pressure and chamber geometry while inversely proportional to wall thickness. When applying Laplace's law in the context of AS, this explains the predictable morphological changes observed in left ventricular wall mass which offsets elevated wall stress and oxygen demand to maintain adequate left ventricular systolic function and cardiac output.[13,14] Concentric left ventricular hypertrophy (LVH) is a common finding accompanying AS described as a compensatory response reducing the negative influences of wall stress.[15] The response to chronic exaggerated left ventricular pressures induced by AS has been shown to be gender specific with eccentric LVH and larger end-diastolic volumes reported more in men while females often have a higher relative wall thickness, smaller LV cavities and concentric LVH (Figure 1). The underlying mechanism for sex differences in LV remodeling is not very well understood but it is thought that females experience less concentric remodeling with a larger percentage extracellular volume fraction (ECV) reported by MRI T1 mapping at similar hemodynamic loads.[16,17]

ECV is a surrogate quantitative measurement of reversible diffuse myocardial fibrosis associated with LV decompensation and a strong predictor of long-term survival and clinical outcomes[19] (Everett *et al*., 2020).[10] A recent study by Tribouilloy *et al.*[20] determined that females with severe AS were more likely to be older ($p < .001$) and more symptomatic ($p = .007$) at presentation when compared to males. Five-year expected survival was also significantly lower in females when compared to age-adjusted males (66% ± 2% [expected-75%] vs. 68% ± 2% [expected-70%], $p < .001$). This ventricular remodeling process has chronic implications in reducing stroke volume while encouraging diastolic and systolic impairment through the accumulation of myocardial fibrosis, eventually progressing to heart failure with adverse clinical outcomes.[14] A recent study performed by Park *et al.*[21] concluded that patients with severe AS with an increase in left ventricular wall thickness were more likely to undergo aortic valve surgery (60% vs 39%, $p < .001$). Park *et al.*[21] also concluded that increased wall thickness was independently associated with an elevated cardiovascular mortality risk (OR: 4.01, CI 1.16–10.68, $p = .028$) when compared to those without LV hypertrophy. As the pathological process of the disease progresses, an increase in myocardial mass is gradually replaced with interstitial fibrosis which can have a negative impact on LV systolic function recovery following aortic valve intervention.[19] Puls *et al.*[22] concluded that myocardial fibrosis in patients with AS was associated with poorer LV function, higher incidence of clinical heart failure and pathological remodelling of the LV prior to intervention. These figures were compounded by significantly higher mortality rates observed in patients with higher myocardial fibrosis (26.5% vs 2%, $p = .0003$) with the results of a multivariate analysis confirming that myocardial fibrosis is an independent predictor of cardiovascular death (HR: 27.4, CI 2.0–369, $p = .001$).

3 | A MEASURE OF SYSTOLIC FUNCTION: LEFT VENTRICULAR EJECTION FRACTION

LVEF is the most convenient and well-understood parameter used in clinical practice which can be measured using various imaging modalities and recognized as an important prognostic marker of the systolic function used to support therapeutic management, cardiac screening, and aid disease prognosis.[23] LVEF is a simple calculation used in TTE, magnetic resonance imaging (MRI) and computed tomography (CT) derived by subtracting the end-systolic volume from end-diastolic volume divided by end-diastolic volume represented as a percentage.[24] By tracing the endocardial left ventricular echocardiographic borders

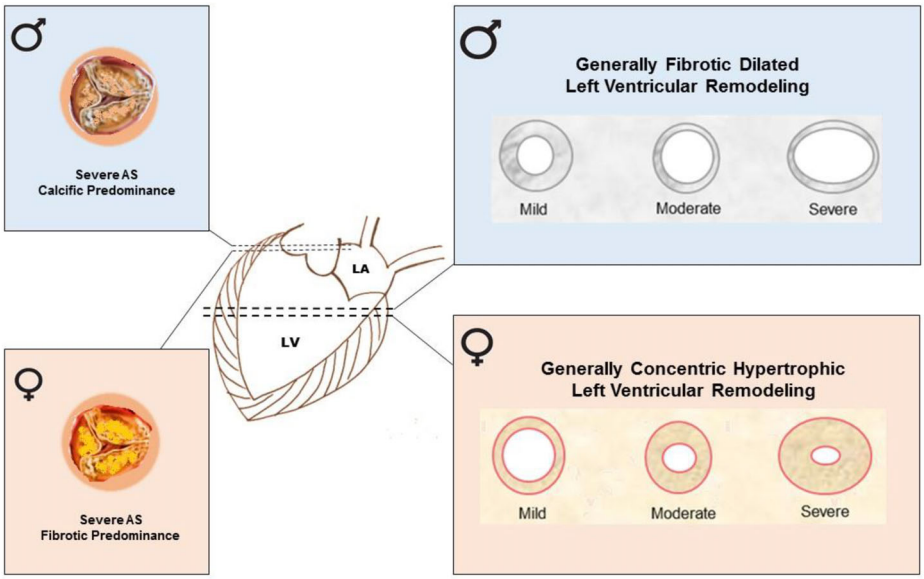

FIGURE 1 Illustrates the differences in aortic stenosis composition and left ventricular remodelling observed between males and females, obtained from Summerhill *et al.*[18]

within the apical four and two-chamber views at end-diastole and systole, LVEF can be estimated by 2-dimensional Biplane Simpson method of discs.[25] While LVEF can be measured using a variety of diagnostic modalities, the benefits of TTE which includes being cost-effective, accurate, and safe with the ability to obtain immediate results while performed at the patient's bedside, means TTE is the most common technique used to assess LVEF. Left ventricular dysfunction secondary to cardiac remodeling is a chronic pathological process observed in AS which can negatively modify the geometry, structure, and efficiency of the heart. The 2021 revision of the European Society of Cardiology (ESC) valvular heart disease guidelines advocated that intervention should be considered for severe asymptomatic AS patients with an LVEF < 55% without any other discernible cause.[26] However, this differs from the current guideline recommendations provided by the ACC/AHA that indicate surgical or percutaneous intervention if the LVEF is <50% in asymptomatic AS patients.[7] This increase in the LVEF cut-off noted in the ESC guidelines offers an interesting debate as to whether patients should exhibit subtle changes in LVEF or more pronounced reductions cited in the ACC/AHA guidelines before being recommended for intervention. The rationale for the change in LVEF cut-off observed in the ESC guidelines has been attributed to recent publications identifying that excess mortality in asymptomatic AS patients is significantly higher in those with an LVEF of <55%. A study by Bohbot *et al.*[27] observed a significant reduction in 5-year survival rates in those with an LVEF < 55% (59% ± 4%) compared to participants with an LVEF between 55%–59% (74% ± 2%) and >60% (72% ± 2%) in asymptomatic or minimally symptomatic severe AS ($p < .001$). Findings provided by Dahl *et al.*[28] also concluded that severe AS patients with an LVEF between 50%–59% demonstrated a 58% increase in mortality compared to those with an LVEF > 60% (HR 1.58, $p < .001$), with a similar mortality risk also observed in asymptomatic (HR 1.56, $p < .001$) and participants with perceived symptoms (HR 1.58, $p = .006$). Ito *et al.*[29] further support these findings by identifying that severe AS patients with an LVEF between 50%–59% also demonstrated a heightened risk of mortality when compared to participants with an LVEF > 60% ($p < .001$). These results indicated that even a minor reduction in LVEF can have profound detrimental operative and post-operative outcomes potentially indicating the presence of superimposed cardiac dysfunction.[29,5] These findings have prompted further debate as to whether the recommended ACC/AHA LVEF cut-off point of <50% should be raised optimising the intervention timing to improve outcomes following intervention for AS. The results by Bohbot *et al.*[27] certainly advocate that the optimum threshold for LVEF in asymptomatic AS should be <55%.

While it is important to recognize that TTE is the primary method to indirectly measure LVEF in clinical practice for the diagnosis and therapeutic management of heart failure patients with AS, LVEF contains inherent limitations. LVEF by 2D TTE is heavily dependent upon loading conditions, geometric assumptions and often hampered by suboptimal image quality which can all influence both inter and intra-observer variability when calculating LVEF.[25,30] As LVEF derived by Biplane Simpson attempts to estimate the diastolic and systolic three-dimensional LV volumes using 2D measurements, assumptions about the LV being ellipsoid in shape must be made.[31] Suboptimal image quality due to body habitus, challenging anatomy or lung disease can affect the ability to accurately delineate and trace the LV endocardial border and increases the risk of apical foreshortening.[32] If the ultrasound imaging plane does not cut through the LV apex, the LV geometry becomes distorted where the LV length reduces while the apex becomes hyperdynamic, significantly underestimating any measured LV volumes and invalidating any volume-derived indices including LVEF.[33] The development of three-dimensional TTE has resolved the issues around apical foreshortening and avoids the need for geometric assumptions when assessing LV function via the Biplane Simpson method.[34] However,

there are wider issues around the routine use of 3D TTE which include the lack of accessibility, cost of equipment, lower temporal and spatial resolution and the continual requirement of good endocardial definition to accurately assess LVEF.[32,35] LVEF has been labelled as an insensitive marker of sub-clinical dysfunction associated with certain pathologies including AS, where LVEF may present as normal or even supra-normal in the presence of considerable myocardial fibrosis.[24] LVEF as a marker of function can also be challenging in severe AS patients due to alterations in loading conditions where normal LV function may not necessarily represent normal LV contractility. The inability to distinguish between irreversible LV impairment and transient cardiac fatigue where LVEF may be significantly reduced due to afterload mismatch is another deficiency of LVEF when assessing AS patients.[36] While there is no question that LVEF is a useful surrogate marker for LV dysfunction, well recognized limitations coupled with the inability to detect subclinical dysfunction have allowed researchers to explore other echocardiographic indices such as GLS to augment AS assessment.

4 | QUANTIFICATION OF MYOCARDIAL MOTION: TISSUE DOPPLER AND DEFORMATION IMAGING

Assessment of myocardial tissue motion by Tissue Doppler Imaging (TDI) and myocardial deformation offer the ability to quantify complex myocardial motion beyond the capabilities of LVEF. Longitudinal function derived by amendments in filter settings used to visualize high-intensity, low velocity signals allow the capability to interrogate myocardial motion over time at specific regions using pulse wave Doppler.[37] TDI is a well-established, standardized approach to evaluate cardiac longitudinal function during TTE and validated in numerous cardiac comorbidities including diastolic dysfunction,[38] atrial fibrillation,[39] diabetes,[40] and AS.[41] The benefit of adopting this parameter is the high temporal resolution, ease and reproducibility when evaluating myocardial motion throughout the cardiac cycle which can be broken down into systolic and diastolic components.[42] A recent study evaluating the assessment of mitral annular peak systolic (S') velocities in severe AS patients identified that S' is independently correlated with all-cause mortality (per 1 cm/sec reduction: HR 1.29, 95% CI 1.03–1.60, $p = .025$), with an average S' < 6.5 cm/sec illustrating progressive LV remodelling and higher mortality rates (17.6% vs. 7.5%, $p = .007$) when compared to those with averaged S' values above 6.5 cm/sec.[41] Another investigation evaluating the combined role of TDI and N-terminal Pro-Brain Natriuretic Peptide highlighted the increased incremental prognostic data in asymptomatic moderate to severe AS patients when compared to each parameter independently.[43] While these results identify a use for TDI in AS patients, conflicting findings have also reported that S' and diastolic (E') TDI parameters offer minimal predictive information about symptomatic deterioration in the AS cohort.[44]

Deformation assessment, quantifying changes in myocardial dimensions can be performed using myocardial strain imaging, an effective contemporary echocardiography assessment tool used to quantify global and regional contractile function that overcomes the limitations of LVEF and TDI.[45] Speckle tracking derived strain is a well-validated, reproducible assessment of left ventricular mechanics offering a more sensitive marker of subclinical systolic dysfunction that cannot be detected by LVEF alone.[46] Lagrangian strain is described as the percentage change in myocardial length with respect to its original resting length, with the amount of time this occurs referred to as strain rate.[47] Recognized as a dimensionless index of myocardial deformation, strain can be evaluated within the longitudinal, radial, circumferential, and torsion vector planes as a percentage change in each dimension.[47]

The simple mathematical formula for Lagranian strain is represented below:

$$S_L(t) \equiv \frac{L(t) - L(t_0)}{L(t_0)}$$

S_L = strain, $L(t)$ = length during a specific point in time usually end-systole, $L(t_0)$ = original resting length usually at end-diastole.[48]

As strain is change in fractional length in one specific dimension, myocardial shortening is illustrated as a minus value while lengthening or thickening is represented as a positive figure.[49] This fundamental concept is important as shortening of myocardial fibre length measured by longitudinal and circumferential strain is represented as a negative value with higher negative values indicating better left ventricular shortening in that specific dimension (Abuelkasem *et al*., 2019).[50] Radial strain on the other hand is different as this parameter is evaluating wall thickening in systole shown as a positive value with higher positive values denoting better systolic thickening.[49] While strain was initially developed using tissue Doppler imaging, limitations such as angle dependency, high inter and intra-observer variability and time-consuming data analysis have reduced its use within clinical practice[51] (Voigt *et al.* 2019[52]). Although, recent advances in two-dimensional tracking of gray-scale acoustic ultrasound markers within myocardial tissue throughout the cardiac cycle offers a quick and angle-independent assessment of myocardial contractility.[53] The semi-automated tracking of myocardium allows for accurate and efficient analysis which can be routinely implemented in clinical practice (Voigt *et al.* 2019). Global longitudinal strain (GLS) requires the acquisition of standard apical four, two and long-axis views whereas global circumferential (GCS) and global radial strain (GRS) measurements are obtained using the basal, mid, and apical parasternal views.[54] Optimal image quality and frame rates between 40 and 60 frames per second are both essential to visualize and track the motion of ultrasound myocardial markers to provide an accurate measurement of deformation.[55] In recent years, there have been discrepancies as to what constitutes as normal strain values, which has hampered the use of strain in clinical practice. Ultimately, without specific reference ranges and awareness of inter-vendor variability, clinicians were unsure whether strain data generated for patients was reliable or what the data clinically represented. Defining abnormal strain values has been challenging as like other systolic ejection parameters there is gender, age, and load dependency.[56] The European Association of Cardiovascular

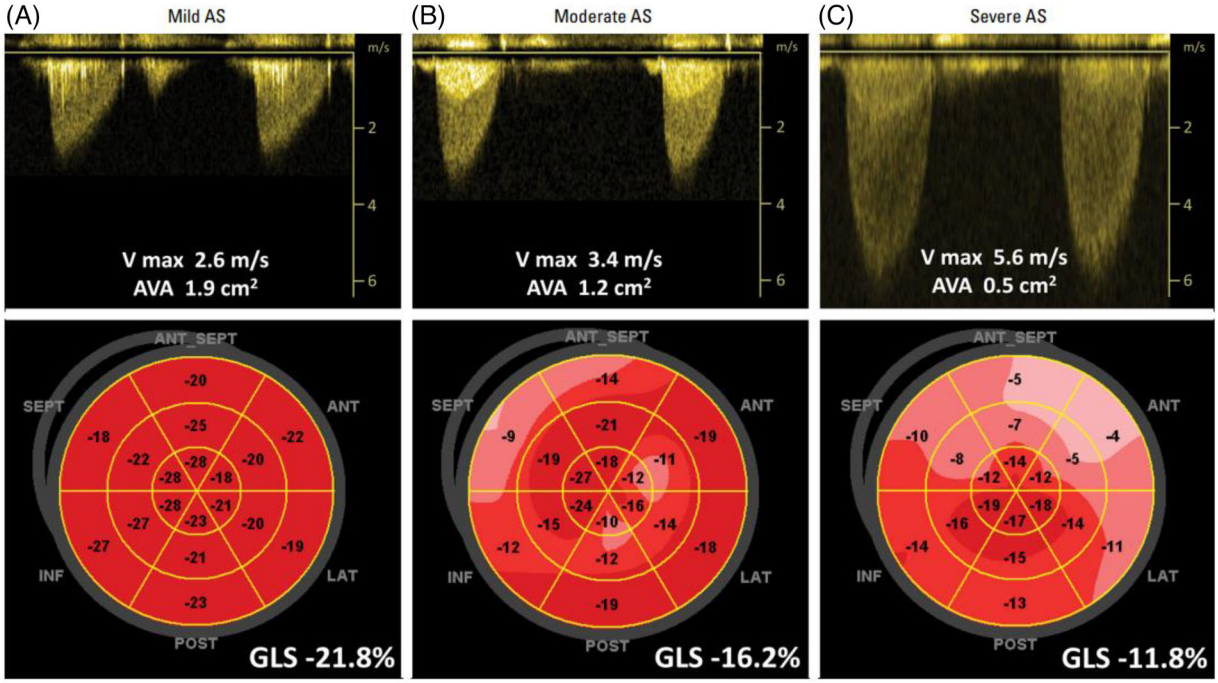

FIGURE 2 Upper panels shows the continuous wave Doppler illustrating the peak velocities and aortic valve areas with the GLS bulls-eye plot shown in the bottom panels for each corresponding patient. The lower panels show the progressive decline in GLS with normal LVEF from −21.8% in a person with mild aortic stenosis, −16.2% in moderate AS, and −11.8% with very severe AS. Adapted from Cvijic and Voigt.[61]

imaging Normal Reference Ranges for Echocardiography (NORRE) study data-set concluded that GLS above −16.7% and −17.8% in males and females respectively should be considered normal.[57] This study also offered reference ranges for GCS (−22.3% and −23.6%) and GRS (20.6% and 21.5%) for males and females respectively along with the findings that age independently reduced GLS, while increasing GCS and GRS. The findings of this study also provided important data suggesting that inter-vendor variability was observed in GCS and GRS measurements, but no significant inter-vendor variability was observed in GLS (−23 ± 2.3 vs. −22.3 ± 2.5, $p = .2$). While this finding is important as GLS is the most frequent strain parameter utilized in clinical practice to determine subclinical dysfunction, the comparison between vendors was retrospectively carried out in a sample of 20 healthy participants and may not be as reproducible in the presence of myocardial disease. Findings provided by Sperry *et al.*[58] support this point identifying that vendor global and regional inter-observer variability was observed in conditions associated with elevated left ventricular wall thickness such as amyloidosis, apical, and septal hypertrophic cardiomyopathy. It is reasonable to assume that along with increases in afterload and wall thickness correlated with AS, variation between vendors continues to be problematic in clinical practice and an important consideration when using GLS for serial screening.

4.1 | Global longitudinal strain in aortic stenosis

There is growing body of evidence that the use of GLS is a more sensitive parameter reflecting the presence of subclinical LV dysfunction that can be used to risk stratify patients with AS.[12,59] GLS is known to progressively worsen with advancing AS disease severity (Figure 2) and is independently correlated with long term mortality.[60] A recent systematic review and meta-analysis conducted by Wang *et al.*[59] offered supporting evidence that impaired GLS in asymptomatic AS patients significantly increased the risk of adverse cardiovascular outcomes independent of LVEF or AS severity and recommended the adoption of GLS into current treatment algorithms.

Similar findings have been identified in a meta-analysis of ten studies containing 1067 asymptomatic significant AS patients, concluding that an impaired GLS with a cut-off of −14.7% in the presence of a normal LVEF is associated with adverse survival.[62] Interestingly, Zhu *et al.*[63] reported that impaired GLS of lower than −15.2% in moderate AS patients was associated with elevated mortality rates at a 5-year follow-up when compared to higher GLS scores greater than −15.2 (48% vs. 19%, $p = .0003$) regardless of LVEF. The increase in mortality did not change following aortic valve replacement (20% vs. 6%, $p = .04$). Similar findings were presented by Povlsen *et al.*[64] who determined that symptomatic severe AS patients undergoing transcatheter aortic valve intervention (TAVI) with impaired GLS was a predictive indicator of all-cause mortality when a cut-off of ← 14% (HR 1.79, CI 95%, 1.02–3.14, $p = .04$). GLS has been acknowledged as a promising, sensitive adjunctive echo imaging modality offering the ability to evaluate myocardial contractility and influence of hypertrophy and fibrosis in patients with significant AS[65] (Slimani *et al.* 2020).[66] However, there are some limitations of these studies as most are retrospective in nature and that GLS is sensitive to loading conditions including acute changes in pre-load and afterload.[67]

One research area of interest which is continuing to grow at rapid pace is the link between AS and infiltrative amyloidosis in the elderly population.[68,69] Amyloidosis is recognized as an accumulation of extracellular amyloid fibril deposits within the myocardium and other organs which can affect up to 25% of those over 85 years of age.[70] Amyloid infiltration typically starts at the base of the LV and gradually progresses toward the apex, leading to an increase in biventricular mass, cardiomyocyte separation and stiffness resulting in restrictive cardiomyopathy.[69,71] This pathologically derived increase in myocardial mass causes significant impairment in diastolic and longitudinal function, often with preserved LVEF in a large number of patients.[72] In addition to the typical changes in wall mass and diastolic dysfunction, myocardial strain imaging can be a beneficial adjunctive technique to identify patients with evidence of cardiac amyloidosis.[73] The classical appearance of cardiac amyloidosis without AS is a reduction in strain values at the basal to mid segments consistent with the progressive myocardial infiltration with "apical sparing" which is a specific pattern associated with cardiac amyloidosis.[74] However, a recent study by Robin *et al.*[75] evaluating a sub-type of cardiac amyloid determined that an increase in GLS with apical sparing is common in AS patients even without the presence of amyloidosis. It is suspected that afterload mismatch attributed to AS conceals the typical apical sparing pattern, reducing the clinical usefulness of GLS at identifying cardiac amyloidosis until afterload is removed following intervention.[76] A recent study identified that the coexistence of cardiac amyloid and AS was a common finding observed in 12% of the 407 participants with higher rates of mortality (24.5% vs. 13.9%, $p = .05$) and worsening symptoms in the concomitant group when compared to AS alone.[68] While the pathophysiological mechanism remains unclear as to why some develop cardiac amyloidosis, it has been suggested that elevated myocardial thickening derived by afterload mismatch observed in AS continues to make the diagnosis of concomitant amyloidosis-AS challenging. Findings provided by Scully *et al.*[77] concluded that 13% of their cohort had coexisting amyloidosis but interestingly demonstrated no significant change in mortality rates ($p = .71$) with TAVI significantly improving outcomes of the whole study population ($p < .001$) and those specifically with confirmed amyloidosis ($p = .03$). Having the ability to identify AS patients with coexisting amyloidosis is relevant as it would identify the potential risk of developing symptoms of restrictive cardiomyopathy, however various investigators stress that intervention such as TAVI should not be withheld in the presence of amyloidosis.[68,78]

4.2 | Novel assessment of left ventricular mechanics in aortic stenosis: Myocardial work

MW is a novel echocardiographic parameter used to quantify LV performance derived from non-invasive pressure-strain loops.[79,80] MW combines non-invasive arterial blood pressure along with speckle tracking GLS derived data to estimate the amount of regional and global work performed by the LV during mechanical systole.[79] The addition of sphygmomanometric blood pressure provides the opportunity to overcome limitations of GLS and LVEF being load-dependent

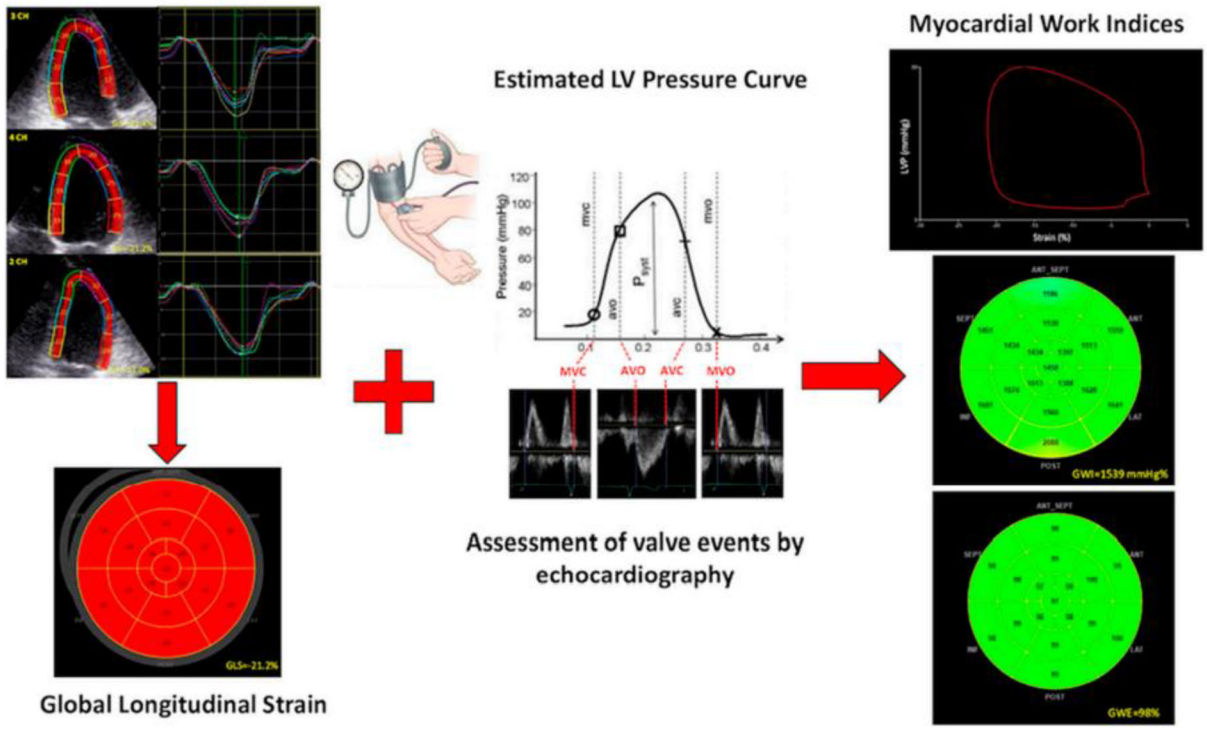

FIGURE 3 Illustrates the generation of myocardial work through the combination of myocardial GLS in panel 1 with the addition to non-invasive blood pressure and Doppler timing events to estimate LV pressure curves used to assess myocardial work represented as a 17 segment bulls-eye plot. Reprinted from Ilard *et al.*[79]

TABLE 1 Represents the components of myocardial work, how they are calculated and reference ranges. Reference values expressed as 95% confidence interval or limits of normality ± standard deviation

Myocardial work parameter	Units	Determinants	How it is calculated	Normal Reference values
Global work index (GWI)	mmHg%	Total amount of MW performed during systole including isovolumetric contraction and relaxation phases.	Global area of the PSL from MVC to MVO.	1292–2505
Global constructive work (GCW)	mmHg%	Total work positively contributing to pump function.	Shortening of myocytes in systole + lengthening during isovolumetric relaxation phase.	1582–2881
Global wasted work (GWW)	mmHg%	Total work negatively contributing to pump function.	Systolic lengthening of myocytes + systolic shortening during isovolumetric relaxation against a closed AV.	226 ± 28[a]
Global work efficiency (GWE)	%	Amount of constructive work as a percentage of total work.	GCW ÷ (GCW+GWW)	91 ± 0.8[b]

Note: Table 1 represents the components of myocardial work, how they are calculated and reference ranges. Reference values expressed as 95% confidence interval or limits of normality ± standard deviation.
Abbreviations: PSL, Pressure strain loop; MW, Myocardial work; MVC, Mitral valve closure; MVO, Mitral valve opening; AV, Aortic valve[89] (Manganaro *et al.* 2019[88], Ilandi *et al.* 2021[79]).
[a]Highest expected value.
[b]Lowest expected value.

indices, offering a more accurate and comprehensive evaluation of LV myocardial mechanics expressed in mmHg%.[81,82] Numerous publications have concluded that a clinical benefit exists when adopting MW in a wide range of pathological conditions including chronic hypertension,[83] dilated cardiomyopathy,[84] heart failure,[85] COVID-19,[86] and following myocardial infarction.[87] MW offers an approximation of global and regional constructive and wasted work throughout the cardiac cycle, which is deemed a more sensitive, less load-dependent technique when attempting to quantify ventricular performance when compared to GLS and LVEF (Figure 3).

Table 1 summarizes the components of MW that can be measured and calculated along with normative values from the National Reference Ranges for Echocardiography (NORRE) study evaluating MW in 226 healthy subjects (Manganaro *et al.*, 2019).[88] Those who are free from cardiac disease and considered to have normal LV function, exhibit high GCW with very little GWW as all myocardial segments are simultaneously shortening during systole and lengthening in diastole.[89] In the presence of cardiac disease, more GWW is observed where the myocardium is inappropriately contracting against a closed aortic valve or lengthening during systole.[90] When adopting MW, brachial blood pressure is considered a surrogate measurement and equal to LV systolic pressure without the presence of left ventricular outflow tract obstruction (LVOTO). However, conditions where LV systolic pressure is elevated such as hypertrophic obstructive cardiomyopathy (HOCM) and AS are seen to be the "Achilles heel" of both MW and GLS. Within these specific patients, brachial blood pressure does not accurately reflect true LV peak systolic pressures which can be around 80–100 mmHg higher than peripheral recorded blood pressure measurements in the presence of an LVOT obstruction (Jain *et al.*, 2021).[91]

GLS is also problematic in AS patients as it has been recognized that a gradual increase in afterload without a change in LV contractility can worsen the GLS score leading to the false assumption that myocardial contractility has deteriorated. A recent proof of concept publication by Jain *et al.*[91] concluded that the addition of echocardiographic Doppler derived mean aortic pressure gradient to non-invasive peripheral blood pressure was a highly comparable to invasive LV systolic pressure measurements performed within the catheterization laboratory ($r = .96$). This study observed that GWI significantly reduced in severe AS patients following a TAVI, supporting the notion that myocardial oxygen consumption and LV work is reduced due to the abrupt removal of afterload caused by the valvular obstruction. Interestingly, the findings also identified that GWI post TAVI is abnormal when LVEF continued to be reported as normal (59.8% ± 11.9%) which may suggest subclinical adverse left ventricular remodeling and myocardial fibrosis has occurred (Figure 4).

At present nobody has evaluated whether the percentage change in MW following TAVI or whether assessment of MW prior to TAVI is correlated with short or long-term outcomes such as heart failure related hospital re-admission or mortality. A recent retrospective study by Fortuni *et al.*[92] determined that not only is the assessment of MW feasible in patients with AS, GWI, and GCW were independently correlated with New York Heart Association class heart failure symptoms in severe AS patients. These two proof-of-concept papers highlight the potential benefits of MW in patients with severe AS which may offer further evidence of myocardial remodelling and risk stratify patients to optimize timing of aortic valve intervention. One limitation of the novel MW software application is that it was not designed to be utilized within the AS population. Russell *et al.*[93] originally derived the MW algorithm to better understand LV mechanical

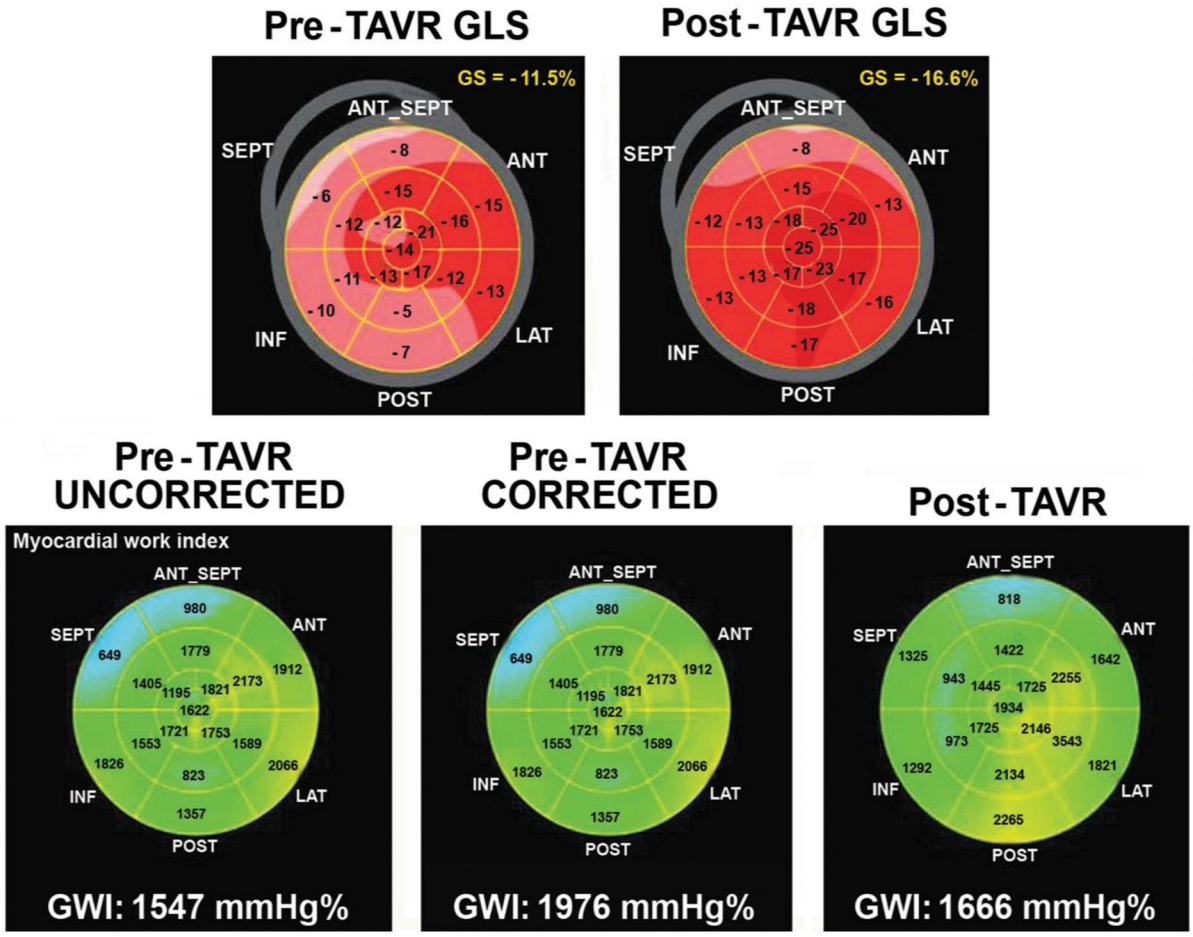

FIGURE 4 Illustrating the changes seen within GLS and GWI in a patient prior and following a transcatheter aortic valve replacement. Note that GLS and GWI improves from −11.5% to −16.6% and 1547–1666 mmHg%, respectively while GWI when corrected for elevated mean aortic pressure reduces from 1976 to 1666 mmHg%. Reprinted from Jain *et al.* 2021.

dysynchrony and improve the incidence of cardiac resynchronization therapy responders. As the LV pressure-strain loop templates used in MW are based upon patients with left ventricular dysfunction, ischaemia, and bundle branch blocks associated with cardiac resynchronisation therapy, caution should be taken when attempting to extrapolate the findings of these papers in severe AS. Further long-term investigations are warranted to identify if these findings can be replicated in prospective studies and determine if these positive preliminary findings can be used to in addition to symptoms, LVEF and GLS to further optimize aortic valve intervention timing and predict long-term outcomes.

5 | CONCLUSION

AS is a complex and progressive disease that can significantly impact upon quality of life and early incidence of mortality. While still utilized in clinical practice today, limitations around the sole use of LVEF as an accurate assessment of LV function in severe AS are starting to become apparent. The benefits of GLS in identifying subclinical dysfunction and myocardial fibrosis are encouraging which could easily be introduced into standard practice to facilitate management of patients with severe AS. MW is a novel parameter that may provide a more sensitive assessment of LV mechanics which is less afterload dependent compared to parameters such as GLS and EF used in clinical practice. Future studies should prospectively evaluate MW in severe AS patients to establish if this parameter can better predict short and long-term outcomes and ascertain if it could be effectively used to further optimize intervention timing in AS management.

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CONFLICT OF INTEREST

There are no conflicts of interest from all authors of the manuscript.

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