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LV Mechanics in Mitral and Aortic Valve Diseases

Value of Functional Assessment Beyond Ejection Fraction

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ABSTRACT

The assessment of myocardial function in the context of valvular heart disease remains highly challenging. The myocardium deforms simultaneously in 3 dimensions, and global left ventricular (LV) function parameters such as volume and ejection fraction may remain compensated despite the changes in myocardial deformation properties. Current guidelines recommend valve replacement/repair in the presence of symptoms or reduced LV ejection fraction, but the resolution of symptoms or recovery of LV function post-surgery may not be reliably predicted. A wealth of evidence currently suggests that LV dysfunction is frequently subclinical despite normal ejection fraction. It may precede the onset of symptoms and portend a poor outcome due to progressive myocardial remodeling and dysfunction during the post-operative period. The advent of novel tissue-tracking echocardiography techniques has unleashed new opportunities for the clinical identification of early abnormalities in LV function. This review gathers and summarizes current evidence regarding the use of these techniques to assess myocardial deformation in patients with valvular heart disease. (J Am Coll Cardiol Img 2014;7:1151-66) © 2014 by the American College of Cardiology Foundation.

Valvular heart disease (VHD) is a common cause of morbidity and mortality in developing and industrialized countries (1,2). Aortic stenosis (AS) and primary mitral regurgitation (MR) are the 2 most common types of VHD (3,4). The prevalence of these diseases increases sharply with age, due to the increasing burden of degenerative etiologies seen with gradual increase in life expectancy.

The assessment of myocardial function in the context of VHD remains highly challenging. Current guidelines (3,4) recommend valve replacement/repair in cases of severe VHD that cause symptoms or reduced left ventricular ejection fraction (LVEF), but LVEF is often unable to disclose initial LV dysfunction in these patients. Assessment of LV deformation using echocardiography or cardiac magnetic resonance (CMR) allows for the dynamic imaging of the heart and provides a window to study regional and global LV function. Between these 2 techniques, CMR is costly, not easily available, and not feasible for routine clinical application in all patients (5,6). Echocardiographic techniques such as tissue Doppler imaging (TDI) are widely available and allow for the measurement of tissue velocities within the myocardium and the assessment of LV function and filling pressures (7). However, TDI is largely angle-dependent, and it only measures a single component of the regional velocity vector along the scan line (8). Speckle tracking echocardiography (STE) is a relatively newer technique that provides non-Doppler, relatively angle-independent measurement of myocardial deformation and LV systolic and diastolic dynamics (8,9). By estimating spatial gradients in myocardial velocities between features (i.e., the "speckles") oriented in the same plane and at a known distance apart, STE allows for the semi-automated quantification of myocardial deformation (strain and strain rate) in the 3 spatial directions (longitudinal, radial, and circumferential) and a concomitant evaluation of LV mechanics, rotation, and torsion (8,10-12). Such an approach in assessing

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVR = aortic valve replacement

CMR = cardiac magnetic resonance

ESD = end-systolic diameter

GLS = global longitudinal strain

LF = low flow

LG = low gradient

LV = left ventricle

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic diameter

MR = mitral regurgitation

MS = mitral stenosis

RV = right ventricular

STE = speckle tracking echocardiography

TDI = tissue Doppler imaging

VHD = valvular heart disease

the components of LV contraction is important because subclinical LV dysfunction is related to alterations in the structure-function relationship and can manifest in ≥1 direction before the development of abnormalities on conventional measures of LV performance, such as LVEF (13). Although STE is particularly suited for the estimation of systolic function, strain parameters are all partially load-dependent (14). Some studies based on complex mathematical models have shown that peak strain values increase with increasing pre-load as long as contractile function is preserved, whereas peak systolic strain decreases both with increasing ventricular size and afterload (15,16). With respect to strain, strain rate is less dependent on pre-load and afterload, being closest to a representation of regional contractile function (15,16). Nevertheless, strain rate curves are highly dependent on insonation methodology and acquisition frame. Strain rate curves can be noisy (12) and therefore difficult to interpret and apply in routine clinical practice compared to global longitudinal strain (GLS).

This review organizes the evidence regarding the role of deformation imaging and its incremental value beyond conventional measures of LV function in patients with VHD and suggests that the application of these techniques in current clinical practice might provide some useful tools for the evaluation of patients with VHD, particularly in the case of preserved LVEF and mild or no symptoms.

Some recent studies regarding the assessment of rotation and torsion in VHD are also cited, but their data should be evaluated cautiously because the number of patients studied has been limited. The subsequent sections are thus mainly focused on the utility of STE strain for quantitative assessment of myocardial function (longitudinally in particular). Anyway, the definition of absolute values of STE strain magnitude require cautious interpretation in relation to the LV geometrical alterations, loading conditions, presence of dyssynchrony, and segmental interactions that can alter LV strain magnitudes. Moreover, the lack of standardization of speckle-tracking algorithms among vendors make it difficult to compare or establish cutoff values for LV strain (8). The growing interest of professional societies in this field and the call for a standardization of STE analysis software (8) will lead to a lower variability and a wider use of strain in clinical practice.

PRIMARY MITRAL REGURGITATION

Degenerative MR (valve prolapses or flail leaflets) is a common and progressive valve disease that is difficult to manage. Current recommendations (3,4) advocate surgery in symptomatic patients with severe MR or in asymptomatic patients with early signs of LV systolic dysfunction (LVEF <60%; end-systolic diameter [ESD] >40 to 45 mm), atrial fibrillation, or pulmonary artery hypertension. Valve repair is considered reasonably low risk in asymptomatic patients with preserved LVEF, but the optimal timing of this procedure remains controversial (17–19). Indeed, surgery always carries risk, even if it is small (an operative mortality of approximately 1%) (20,21), and the durability of valve repair is not guaranteed. The reported rate of recurrent MR (grade ≥1) accounts for 8.3% per year (22), and the documented late progression to moderate or severe MR is approximately 7.7% (23). Reduced LVEF is a powerful predictor of post-operative LV dysfunction and subsequent cardiac morbidity and mortality (24,25), but a marked drop in LVEF can occur after surgery, even when the pre-operative LVEF is normal (26). The LVEF is often overestimated in the presence of MR, because it simply reflects the entrance and exit of blood in the LV. Therefore, LVEF may remain in the normal or supernormal range for long periods of time, even if alterations in contractility develop. Therefore, the earlier detection of LV contractile dysfunction is of pivotal importance and favors the surgical correction of chronic MR in a timely manner, which theoretically restores normal LV function and life expectancy after surgery (26,27). Unfortunately, this target remains challenging, and the best predictors of post-operative LV function deterioration are subject to debate (28). In a recent retrospective study of 335 patients with severe MR and preserved LVEF, Tribouilloy et al. (17) showed that the combined evaluation of pre-operative LVEF and LVESD had an additive value for the prediction of post-operative LV dysfunction, with the lowest frequency observed in patients with pre-operative LVEF ≥64% and pre-operative LVESD <37 mm. Even if these parameters can be obtained easily using standard transthoracic echocardiography, the sensitivity and specificity of these techniques were quite low (area under the curve of 0.69 and 0.64, respectively), which supports the search for more reliable markers of LV systolic function. Interestingly, the subtle alterations of LV function observed in MR may be associated with the development of pressure half-time (PHT) during exercise (29) and with right ventricular (RV) dysfunction (30), determining a rapid

development of symptoms and a poor prognosis. Moreover, exercise echocardiography can unmask latent subclinical LV dysfunction in patients in whom the LV is compensated at rest. The inability to increase LVEF or reduce the end-systolic volume with stress reflects the presence of an impaired contractile reserve, which influences prognosis and could be an indication for early surgery (29,30). These observations suggest the need to develop more sensitive indices of heart performance in patients with MR and to pay particular attention to those parameters that can indicate an early LV function deterioration.

LONGITUDINAL LV FUNCTION ASSESSMENT USING TDI. Haluska et al. (31) demonstrated that longitudinal LV function, as measured by base-apex velocity gradient with TDI, correlated with contractile reserve at exercise and was a sensitive marker of latent LV dysfunction in 86 patients with asymptomatic MR (31). In a similar population, Agricola et al. (32) showed that a myocardial systolic velocity measured at the lateral mitral annulus (s′) ≤10 cm/s was an independent predictor of ≥10% post-operative LVEF reduction, with a sensitivity and specificity of 90% and 85%, respectively.

LONGITUDINAL LV FUNCTION ASSESSMENT USING STE. It has recently been suggested that imaging deformation detects subclinical LV dysfunction before the development of abnormalities using conventional measures of LV performance (16,33). GLS is a highly feasible and reproducible parameter with good intraobserver and interobserver agreements, and it is well correlated with LVEF estimated by CMR (34). These characteristics make GLS a suitable candidate for STE application in routine clinical practice. In 71 patients with degenerative MR and normal LVEF, Lancellotti et al. (35) observed that left atrial volume, GLS at rest, and GLS at peak exercise were predictors of post-operative LV dysfunction (LVEF <50%). Using a receiver-operating characteristic curve analysis, an exercise GLS of -18.5% (sensitivity 84.6%, specificity 76.5%) and an exercise-induced change in GLS of 1.9% (sensitivity 92.3%, specificity 73.6%) were identified as the best cutoff values for the prediction of post-operative LV dysfunction (35). In a similar study, Magne et al. (36) showed that an exercise-induced improvement in GLS ≥2% predicted a 2-fold increase in the risk of cardiovascular events, whereas a 4% increase in LVEF did not affect the outcome. This discrepancy reflects the load dependency of LVEF, which is influenced by the concomitant change in MR severity during exercise (36). In 88 subjects with severe MR undergoing mitral valve repair, Mascle et al. (37) showed that patients who developed post-operative LV dysfunction had a lower resting GLS. A resting GLS <-18% was an independent predictor of post-operative LVEF (37). Witkowski et al. (38) confirmed these results and found that a pre-operative GLS >-19.9% was the best predictor of post-operative LV dysfunction. Notably, pre-operative LVEF in all of these studies was not a good predictor of LVEF after surgery, which supports the hypothesis that measuring GLS at baseline and during exercise may provide more accurate information about the presence of contractile reserve and be better able to predict changes in post-operative LV function (38) (**Figure 1**). The interpretation of strain values may require normalization for the size of the

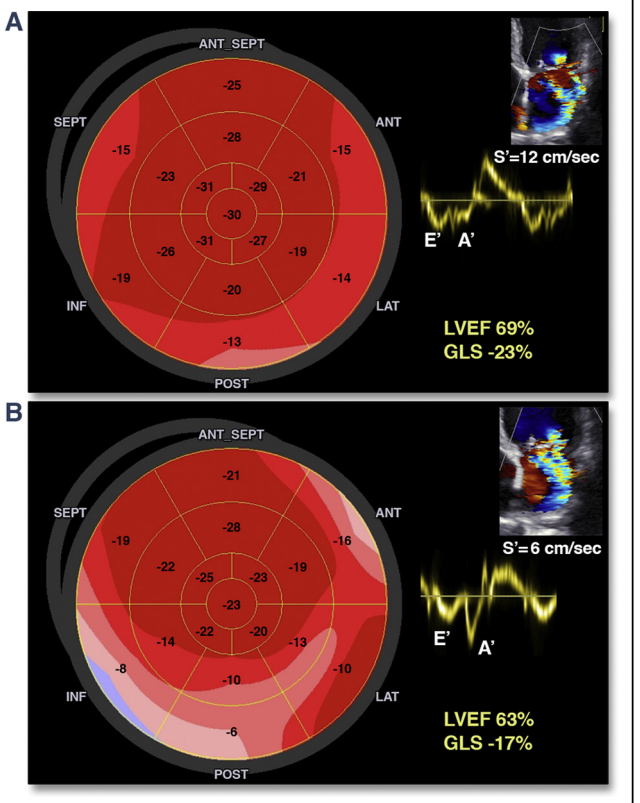

FIGURE 1 GLS in Patients With Severe Primary MR and Preserved LVEF

These bull's-eyes show the difference in global longitudinal strain (GLS) between 2 patients with severe primary mitral regurgitation (MR) and normal left ventricular ejection fraction (LVEF). The reduced GLS observed in patient B can be attributed to more advanced disease with subclinical LV dysfunction. **(A)** Normal GLS of a 60-year-old female patient with a body surface area (BSA) of 1.48 m^2 and an effective regurgitant orifice (ERO) of 0.61 cm^2. **(B)** Reduced GLS of a 75-year-old male patient with BSA of 1.7 m^2 and ERO of 0.50 cm^2. ANT = anterior; INF = inferior; LAT = lateral; POST = posterior; s′ = maximal mitral annulus systolic velocity at tissue Doppler; SEPT = septal.

TABLE 1 Echocardiographic Studies in MR

First Author (Ref. #), Year	n	MR Degree	Symptoms	MV Replacement/ Repair	Stress Echocardiography/ Exercise Testing	LVEF (%)	Main Echocardiographic Method Used	Clinical Outcome	Clinical Outcome Determinants	Sensitivity, Specificity (%)
Haluska et al. (31), 2003	86	Severe	No	No	Yes	≥50	2D, TDI	Lack of LVCR at stress echocardiography	s′ (p = 0.03)	84, 54
Agricola et al. (32), 2004	84	Severe	No	Yes	Yes	67 ± 5	2D, TDI	Post-operative LVEF reduction ≥10%	lateral s′ ≤10 cm/s (p = 0.0001)	90, 85
Marciniak et al. (39), 2007	77	Mild to severe	No	No	No	>60	2D, STE*	–	–	–
Lancellotti et al. (35), 2008	71	Severe	No	Yes (30 pts)	Yes	>60	2D, STE*	Post-operative LVEF <50%	Exercise GLS >-18.5%; exercise ΔGLS <1.9%	84.6, 76.5 92.3, 63.6
Borg et al. (41), 2008	68	Mild to severe	No	No	No	>60	Torsion/twist*	–	–	–
Magne et al. (29), (2010)	78	Moderate to severe	No	No	Yes	>60	2D	Symptoms appearance	Exercise PAH (HR: 3.44, p = 0.002)	–
Zito et al. (40), 2009	50	Mild to severe	No	No	No	>60	2D, STE, torsion/twist*	–	–	–
Tribouilloy et al. (17), 2011	335	Severe	Yes	Yes	No	69 ± 9	2D	Post-operative LVEF <50%	LVEF <64% (p = 0.001); LVESV ≥37 mm (p = 0.001)	69, 64
Moustafa et al. (42), 2011	84	Mild to severe	No	No	No	>60	Torsion/twist†	–	–	–
Donal et al. (27), 2012	88	Severe	Yes	Yes	Yes	67 ± 12	2D, STE*	Post-operative LVEF <50%	GLS/LVESV <-5.7%/mm (p = 0.019)	83, 70
Mascle et al. (37), 2012	88	Severe	Yes	Yes	No	66 ± 7	2D, STE*	Post-operative LVEF <50%	GLS >-18%, p = 0.009	53, 79
Le Tourneau et al. (30), 2013	208	Severe	Yes	Yes	No	63 ± 10	2D	Reduced 10-year overall survival after surgery	LVEF <60% and RVEF <35% (HR: 4.6, p = 0.005)	–
Magne et al. (36), 2014	115	Moderate to severe	No	No	Yes	>60	2D, STE*	CV events (CV death, hospitalization for HF, MV surgery)	$LVCR_{GLS}$ <2% (p = 0.037)	–
Witkowski et al. (38), 2013	223	Moderate to severe	Yes (49 pts)	Yes	No	66 ± 9	2D, STE*	Post-operative LVEF <50%	GLS >-19.9 (OR: 23.16, p < 0.001) LVESD ≥40 mm (OR: 6.71, p = 0.003)	–

*STE performed using EchoPAC (GE Vingmed Ultrasound AS, Horten, Norway). †Torsion/twist determined using Syngo US workstation (Siemens Medical Solutions, Mountain View, California). – = data were not available or that the category is not applicable.

2D = 2-dimensional echocardiography; CV = cardiovascular; GLS = global longitudinal strain; ΔGLS = exercise-induced variation in GLS (percentage); HF = heart failure; HR = hazard ratio; LVCR = left ventricle contractile reserve (defined as LVEF increment with exercise ≥4%); $LVCR_{GLS}$ = exercise-induced improvement in GLS; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; MV = mitral valve; s′ = maximal mitral annulus systolic velocity at tissue Doppler; OR = odds ratio; PAH = pulmonary arterial hypertension; RVEF = right ventricular ejection fraction; STE = speckle tracking echocardiography; TDI = tissue Doppler imaging.

LV cavity and/or loading condition. As evidenced by Marciniak et al. (39) in patients with mild to severe MR, deformation parameters remain unchanged due to a balance of increased stroke volume and progressively increased LV dimension in the initial phase of the disease. Later, such a chronic increase in wall stress will result in myocardial damage and reduced contractility, causing a fall in peak systolic deformation indices. Therefore, correcting LV deformation parameters for changes in geometry could be a sensitive way of detecting very early changes in contractile function. For example, Donal et al. (27) found that exercise GLS normalized for LVESD closely correlated with post-operative LVEF and that a GLS/LVESD cutoff of -5.7% exhibited good sensitivity and specificity in predicting post-operative LV dysfunction.

OTHER COMPONENTS OF LV MECHANICS. The current evidence on the incremental assessment of LV function in circumferential and radial direction in patients with MR is limited. In a small group of patients with moderate to severe MR, Zito et al. (40) observed that circumferential strain has a biphasic pattern, being enhanced in moderate MR and significantly reduced in severe MR with respect to normal subjects. Chronic volume overload states, including MR, may also show changes in LV twist mechanics. In cases of absence of any LV remodeling, increased preload leads to an increase in systolic torsion. However, LV systolic torsional parameters become abnormal with chronic volume overload. Patients with MR may show a delayed onset of untwisting, a slower untwisting during the isovolumic relaxation period, a loss of the clear distinction between early and late untwisting phases, and a reduced untwisting velocity (41). The degree of LV remodeling and the severity of MR are correlated with LV torsional parameters. Moderate MR revealed the highest rotational profile and hyperdynamic or supranormal LV systolic function, and severe MR showed the lowest rotational profile, which suggests incipient LV dysfunction (42). Delayed untwisting could conceivably limit the ability of the LV to generate a suction effect before the onset of filling (41). Moreover, changes in LV torsion may vary transmurally, and such changes are limited to the endocardial region in general. The epicardial rotation may not change significantly despite varying degrees of MR (42). Although preliminary data suggest potential value in LV rotation as a sensitive marker of incipient LV dysfunction, further standardization of strain will be required for routine clinical application (42).

Details of the main cited echocardiographic studies are summarized in **Table 1**.

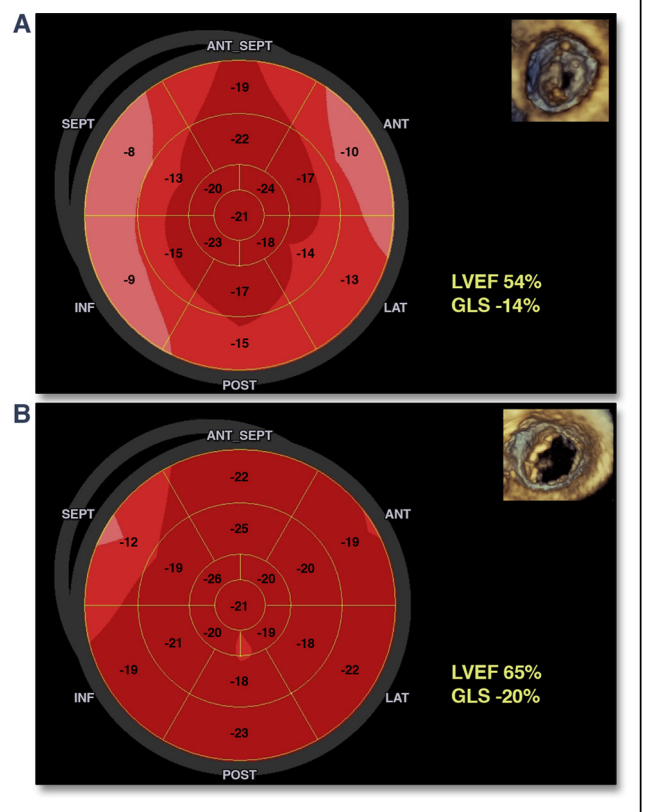

FIGURE 2 GLS in a Patient With Severe MS With Respect to a Normal Subject

These bull's-eyes show the difference in GLS between a patient with severe mitral stenosis (MS) **(A)** and a normal patient **(B)**. Even if in MS the LV function has been often considered "preserved," several studies have shown that a slight reduction in LV performance can be observed. **(A)** Severe MS of a 55-year-old male patient with BSA of 2.15 m^2 and EOA of 1.3 cm^2. **(B)** Normal subject is a 50-year-old patient with BSA of 1.94 m^2 and EOA of 3.5 cm^2. Abbreviations as in **Figure 1**.

MITRAL STENOSIS

LV dysfunction is detected in approximately 25% of mitral stenosis (MS) patients (43). The first studies conducted using LV catheterization showed that MS is associated with a reduction in pre-load, indexed LVEDV, and LVEF (44). The presence of an altered LV function in these patients was confirmed in later pioneer echocardiographic studies (45) and by several later surveys using TDI (46,47). More recently, STE-based studies have confirmed that MS is characterized by a significant reduction in LV function, as demonstrated by the lower value of GLS and global circumferential strain observed in MS patients compared with normal subjects (43,48). Interestingly, Sengupta et al. (48) found that these abnormalities

TABLE 2 Echocardiographic Studies in MS

First Author (Ref. #), Year	n	MS Degree	Symptoms	Balloon Mitral Valvuloplasty	Stress Echocardiography/ Exercise Testing	Main Echocardiographic Method Used	Comparison of LV Performance in MS Patients Versus Normal Patients
McDonald (45), 1976	90	Mild to severe	–	No	No	M-mode	–
Ozdemir et al. (46), 2010	86	Mild to Severe	–	No	No	2D, TDI	LVEF: no difference between groups Mitral annulus (s′) (cm/s) at: IVS: 7.2 ± 1.6 vs. 8.6 ± 1.7, p < 0.001 LW: 8.1 ± 1.7 vs. 10.2 ± 1.6, p < 0.001 IW: 7.4 ± 1.5 vs. 9.5 ± 1.5, p < 0.001 AW: 7.8 ± 1.9 vs. 10.5 ± 1.7, p < 0.001
Ozer et al. (47), 2004	74	Severe	–	No	No	M-mode, 2D, TDI	LVEF: no difference between groups MAPSE (mm): Septal side: 12 ± 3 vs. 14.4 ± 1.5, p = 0.016 Lateral side: 13.2 ± 3 vs. 16.8 ± 2, p = 0.001 Mitral annulus (s′) (cm/s) Septal side: 7.6 ± 1.1 vs. 10.4 ± 3.2, p = 0.03 Lateral side: 7.6 ± 1.1 vs. 10.4 ± 3.2, p = 0.003
Bilen et al. (43), 2011	103	Mild to severe	–	No	No	2D, STE*	LVEF: no difference between groups GLS (%): 16.8 ± 1.54 vs. 19.6 ± 2.0, p < 0.001
Sengupta et al. (48), 2014	66	Severe	–	Yes	No	2D, STE†	Before mitral balloon valvuloplasty: LVEF (%): 56.4 ± 7.0 vs. 59.8 ± 3.5, p = 0.01 GLS (%): -14.6 ± 3.3 vs. -20.1 ± 2.3, p < 0.001 GCS (%): -20.0 ± 5.0 vs. -25.7 ± 3.6, p < 0.001 After mitral balloon valvuloplasty: LVEF (%): 58.2 ± 6.4 vs. 59.8 ± 3.5, NS GLS (%): -17.8 ± 3.5 vs. -20.1 ± 2.3, p < 0.01 GCS (%): -22.5 ± 4.6 vs. -25.7 ± 3.6, p < 0.01

*STE was performed using EchoPAC (GE Vingmed Ultrasound AS). †The 2D cardiac performance analysis was performed using TomTec Imaging (TomTec Imaging Systems GmbH, Munich, Germany). – = data were not available or that the category is not applicable.

AW = anterior wall; GCS = global circumferential strain; IVS = interventricular septum; IW = inferior wall; LW = lateral wall; MAPSE = mitral annular plane systolic excursion; MS = mitral stenosis; NS = not significant; other abbreviations as in Table 1.

are common, with nearly 85% of patients with severe MS having GLS values corresponding to the lowest quartile for the control subjects. LV end-diastolic volume in these patients was the strongest determinant of GLS (48), which suggests that the altered loading conditions determine the impairment in LV contractile performance in MS to a great extent (Figure 2). Several mechanisms have been advocated to explain the recurrence of LV dysfunction in MS patients. Rheumatic heart disease is traditionally considered a pancarditis that affects all layers of the cardiac chamber walls. However, LV myocardial biopsies in MS patients have shown a lack of myocyte damage (49,50) with concomitant ultrastructural alterations involving myofibril and mitochondrial-myofibril ratios, which mirror the alterations observed in chronic unloading states (51). An alternative hypothesis, supported by evidence of postero-basal wall motion abnormalities in MS patients, is that the rigid mitral valve apparatus might induce a tethering effect with a subsequent alteration in LV performance (52). More recently, new techniques for the visualization of intracardiac blood flow (53) have suggested that the lack of optimal vortex formation in MS patients might contribute to the development of LV systolic dysfunction (48) and explain the rapid recovery of cardiac contractility after mitral valvuloplasty (48,54). These studies support the hypothesis of a strong relationship between LV flow and function (55). Although strain data may not be routinely required in the decisional algorithm for treatment of MS, it is worth noting that patients with MS show a decrease in LV systolic function that is largely reversible.

Details from the major echocardiographic studies are summarized in Table 2.

AORTIC STENOSIS

AS is a growing health problem (1). Current recommendations (3,4) state that aortic valve replacement (AVR) is a class I indication in patients with severe AS and symptoms or reduced LVEF. LVEF is normal in most patients with AS even when symptoms develop, and valvular parameters such as aortic valve area and transvalvular gradients do not predict clinical outcome after AVR (56). Pibarot and Dumesnil (57) stated that calcific AS should not be viewed as an isolated disease that is strictly limited to the aortic valve but instead as a systemic disease that often includes an increase in peripheral vascular resistance caused by atherosclerosis and/or aging and a concomitant deep alteration in LV structure and function, even in the presence of a preserved LVEF.

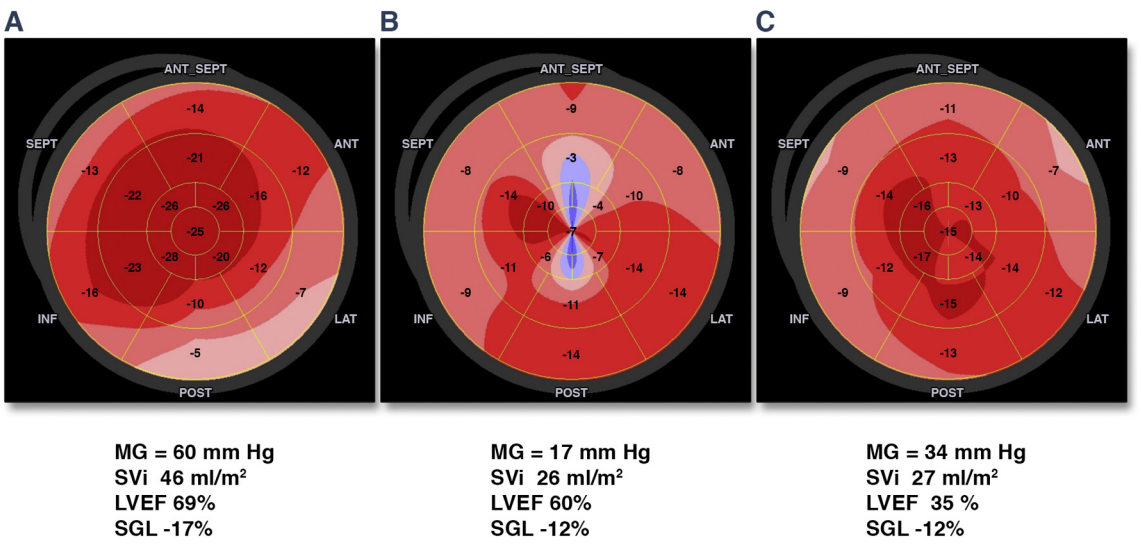

FIGURE 3 GLS in Patients With Severe AS and Various Flow-Gradient Patterns

These bull's-eyes show the difference in GLS among 3 patients with severe aortic stenosis (AS) but different flow-gradient patterns. The magnitude of decrease in GLS was almost similar in both low flow–low gradient patients regardless if LVEF was preserved **(B)** or impaired **(C). (A)** Normal flow–normal gradient AS, normal LVEF, and mildly reduced GLS of an 86-year-old male patient with BSA of 1.89 m^2, EOA of 0.76 cm^2 (0.40 cm^2/m^2), and LV mass of 101 g/m^2. **(B)** Low flow–low gradient AS, normal LVEF, and severely reduced GLS of an 82-year-old female patient with BSA of 1.77 m^2, EOA of 0.75 cm^2 (0.42 cm^2/m^2), and LV mass of 131 g/m^2. **(C)** Low flow–low gradient AS, reduced LVEF, and severely reduced GLS of a 78-year-old male patient with BSA of 1.6 m^2, EOA of 0.53 cm^2 (0.33 cm^2/m^2), and LV mass of 139 g/m^2. MG = mean aortic gradient; SGL = strain global longitudinal; SVi = stroke volume index; other abbreviations as in Figure 1.

FLOW-GRADIENT PATTERNS AND LV LONGITUDINAL FUNCTION IN AS. As indicated in previous paragraphs, LVEF does not estimate the extent of myocardial dysfunction in patients, especially AS patients. Dumesnil et al. (58) observed a dichotomy in the LV contraction of AS patients using a dedicated M-mode tracing analysis, which suggests that a significant decrease in longitudinal contraction was associated with a substantially normal radial contraction and explains the normal LVEF. Lafitte et al. (59) demonstrated that patients with severe AS and preserved LVEF had lower GLS compared with that of matched control subjects (-17.8 ± 3.5% vs. 21.1 ± 1.8%; $p < 0.05$). This difference was more pronounced in the basal LV segments. In this study, a basal longitudinal strain >-13% predicted an abnormal exercise response in AS patients, with a sensitivity and specificity of 77% and 83%, respectively (an area under the curve of 0.81, $p < 0.01$) (59). A lower GLS was also associated with a higher LV mass index and relative wall thickness, which supports a direct connection between concentric remodeling and contractile dysfunction (60). From a physiological point of view, the pressure overload of AS triggers a continuum of changes that start from myocyte hypertrophy and interstitial reactive fibrosis and leads to a self-perpetuating process of cellular atrophy, myocyte death, and replacement fibrosis to cause a progressive deterioration of myocardial function and poor prognosis (61). Replacement fibrosis, quantified by delayed gadolinium enhancement, was not reversible after AVR in 55 patients with symptomatic severe AS undergoing CMR before and after AVR. In this study, myocardial fibrosis was associated with reduced parameters of longitudinal LV systolic function and portended a poor recovery after AVR, as indicated by the lack of improvement in New York Heart Association functional class in patients with severe fibrosis (62). Among recent prognostic studies (63–65), a bicentric study in 163 patients with asymptomatic moderate to severe AS provided evidence that a GLS of ≥-15.9%, a peak transvalvular aortic velocity ≥4.4 m/s, a valvuloarterial impedance >4.9 mm Hg/ml/m^2, and an indexed left atrial area ≥12.2 cm^2/m^2 were the only significant predictors of adverse events, which were defined as the occurrence of symptoms, AVR, or death (63) (**Figure 3**).

The alterations in LV contractility described in the presence of a preserved LVEF can contribute to explaining the discrepancies between aortic gradient and aortic surface observed in some patients with AS. As evidenced by Hachicha et al. (56), under the

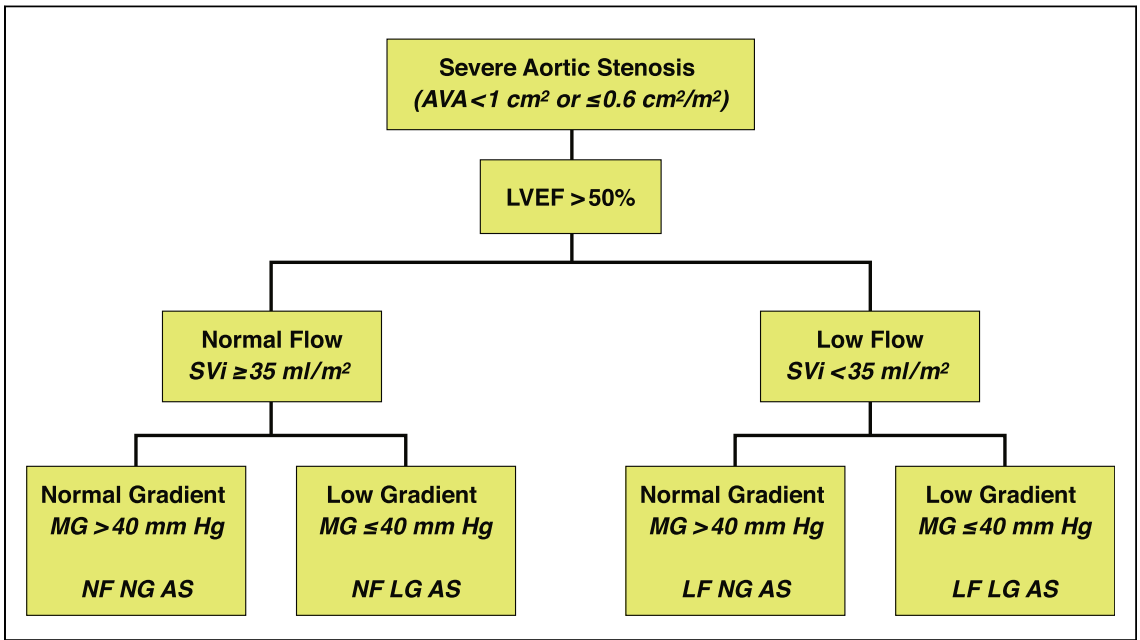

FIGURE 4 Classification of AS According to Different Flow-Gradient Patterns

The diagram illustrates the classification of AS according to different flow-gradient patterns. AVA = aortic valve area; LF = low flow; LG = low gradient; NF = normal flow; NG = normal gradient; other abbreviations as in Figures 1 and 3.

denomination of severe AS, it is possible to identify 4 flow-gradient patterns (Figure 4). According to this classification, the presence of a paradoxical low-flow (LF) pattern—namely, a stroke volume unexpectedly reduced despite preserved LVEF—is consistent with a more advanced stages of the disease, characterized by greater concentric LV remodeling, smaller LV cavity, extensive LV fibrosis, increased afterload, higher risk of developing myocardial dysfunction and symptoms, more elevated brain natriuretic peptide plasma levels, and higher mortality rate (57,66-68). As demonstrated by Adda et al. (68), in 340 patients with AS and preserved LVEF, AS was associated with a reduction in GLS with respect to the referral limit of -20%, but longitudinal LV dysfunction was particularly severe in AS patients with LF. Patients with LF-low gradient (LG) AS showed a significant reduction in basal longitudinal strain compared with patients with a normal flow-high gradient (-11.6 ± 3.4% vs. -13.6 ± 3.2%, $p < 0.05$) and normal flow-LG AS (-11.6 ± 3.4% vs. -14.8 ± 3.0%, $p < 0.001$). These patients also had an increased ventriculoarterial impedance, which confirms the presence of a greater hemodynamic impairment and LV dysfunction (68). In a recent study by Eleid et al. (69), in 1,704 patients with an aortic valve area <1 cm^2 and normal LVEF grouped according to flow status, an LF-LG pattern was the strongest predictor of mortality in multivariable analyses in patients undergoing medical therapy or AVR. In 639 high-risk patients undergoing transcatheter aortic valve replacement, Le Ven et al. (70) observed that LF was an independent predictor of 30-day mortality, cumulative all-cause mortality, and cumulative cardiovascular mortality in multivariable analyses, but that LVEF and mean gradient were not predictors. The higher mortality observed in patients with LF-LG AS is irrespective of treatment and LVEF, which indicates the presence of a syndrome in which the disease is not limited to the calcific aortic valve but also involves increased arterial afterload and abnormal ventricular dynamic properties. All of these data support the hypothesis that the common denominator of severe AS includes subjects with different degrees of LV functional impairment and disease severity. A careful characterization of each patient that involves integrating the flow pattern evaluations and quantifying the peripheral resistances and longitudinal deformation parameters might allow the identification of subjects with greater disease severity who might benefit from more strict follow-up or early surgery. All current evidence points out that GLS is impaired by the increase in afterload. Presence of higher GLS in the face of increased LV afterload should suggest relatively compensated myocardial contractile function, whereas a reduced GLS may correlate with the risk

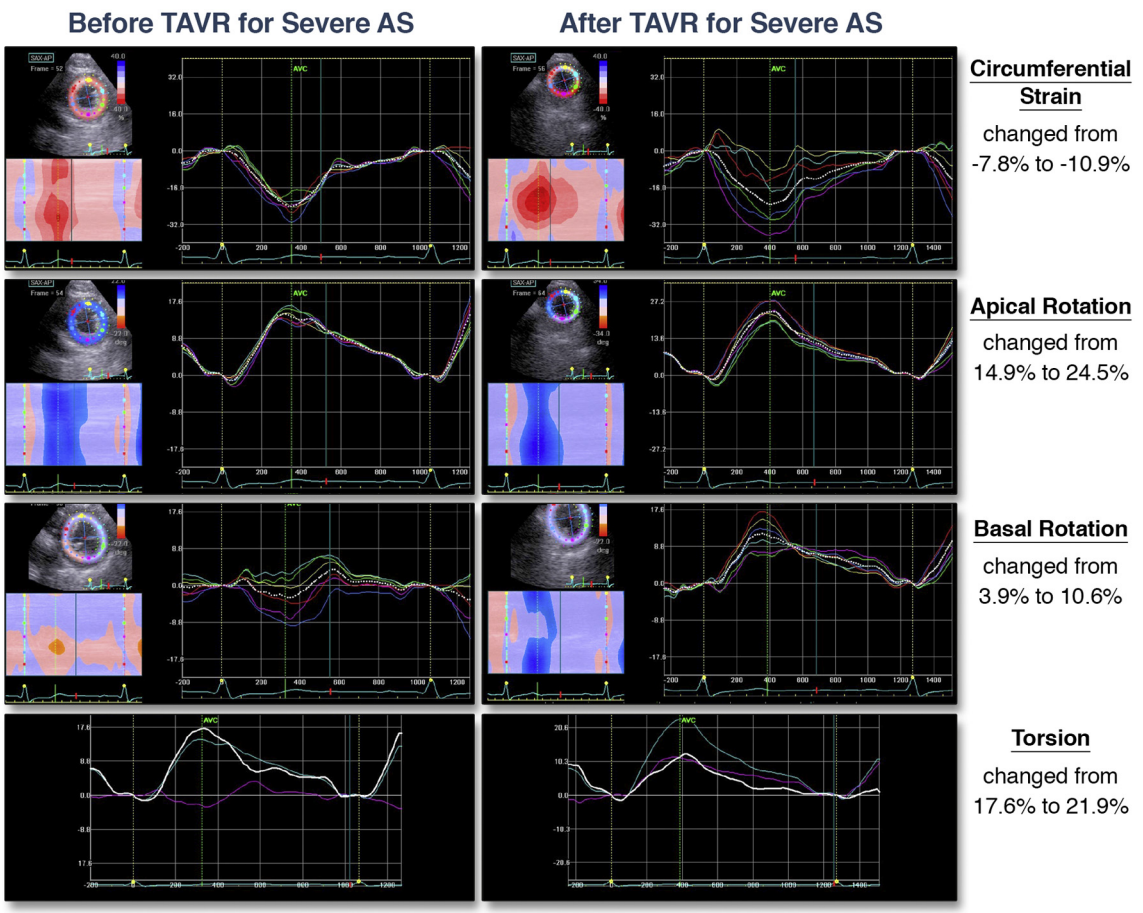

FIGURE 5 Changes in LV Circumferential Strain, Rotation, and Torsion in a Patient With Severe AS

Example of the changes in LV circumferential strain, rotation, and torsion in a patient with severe aortic valve stenosis. The deformation components are obtained before and after successful transarterial implantation of a percutaneous aortic valve. AS = aortic stenosis; LV = left ventricular; TAVR = transcatheter aortic valve replacement.

of symptom development, irreversible myocardial damage, and increased myocardial fibrosis. Moreover, because wall stress is maximal at the basal segments of the LV septum, assessment of LV strain from the basal segments might provide a useful estimate of the magnitude of LV contractile abnormalities in hemodynamically severe AS.

OTHER COMPONENTS OF LV MECHANICS. In a population of 173 patients with asymptomatic AS, circumferential strain and left atrial size were independently associated with increased global LV load (71). The potential incremental value of circumferential strain in patients with AS needs to be confirmed in future studies. LV rotation parameters may be altered in AS patients with preserved LVEF. Typically, LV basal rotation is reduced, and apical rotation is increased, which leads to the overall increase in LV torsion (72). The increased apical rotation contributes to the maintenance of LVEF in the normal range, but it is also associated with a significant prolongation of the apical back-rotation during the LV filling phase, which contributes to progressive diastolic dysfunction, increases in LV filling pressure, elevations in brain natriuretic peptide plasma levels, and symptom development (72,73). However, the concomitant reduction in basal rotation might be related to the augmented wall stress in the basal wall or to the development of myocardial fibrosis, which are more evident in these myocardial segments (74) (**Figure 5**). Quantification of LV rotation or twist deformations seem promising, because these tools allow the diagnosis of incipient LV systolic dysfunction as well as the estimation of diastolic filling capabilities.

TABLE 3 Echocardiography Studies in AS

First Author (Ref. #), Year	n	AS Degree	Symptoms	AVR/ TAVR	Stress Echocardiography/ Exercise Testing	LVEF (%)	Main Echocardiographic Method	Clinical Outcome	Clinical Outcome Determinants	Sensitivity, Specificity (%)
Cramariuc et al. (66), 2009	1,591	Mild to severe	No	No	No	66 ± 7	2D	Stress corrected midwall shortening	ZV_a = 4.48 mm Hg/ml/m^2 ($p < 0.001$)	65, 80
Lafitte et al. (59), 2009	65	Severe	No	Yes, AVR (n = 42)	Yes	64 ± 7	2D, STE*	Abnormal exercise response CV events (CV death, hospitalization for HF)	GLS >-18 ($p < 0.01$) BLS >-13% ($p < 0.01$) GLS >-13% ($p < 0.01$)	68, 75 77, 83
Weidemann et al. (62), 2009	58	Severe	Yes	Yes	No	–	M-mode, 2D, STE*	NYHA class improvement after surgery	MAPSE >7 mm	82, 93
Popescu et al. (73), 2010	101 (61 AS)	Severe	–	No	No	62 ± 3	2D, torsion/twist*	–	–	–
Cramariuc et al. (60), 2010	70	Moderate to severe	Yes (n = 30)	No	No	64 ± 5	2D, STE*	–	–	–
Lancellotti et al. (63), 2010	163	Moderate to severe	No	Yes, AVR (n = 57)	Yes	66 ± 9	2D, STE*	Combination of AVR, hospitalization for HF, CV death	AoV_{max} ≥4.4 m/s (AUC = 0.83) GLS >-15.9% (AUC = 0.70) ZV_a ≥4.9 mm Hg/ml/m^2 (AUC = 0.74) LAAi ≥12.2 cm^2/m^2 (AUC = 0.83)	–
Lancellotti et al. (71), 2010	173	Severe	No	No	No	≥55	2D, STE*	Global LV afterload (calculated as ZV_a)	SAC ($p = 0.001$) GCS ($p = 0.0249$) LAAi ($p = 0.04$)	–
Lancellotti et al. (67), 2012	150	Severe	No	Yes, AVR (n = 70)	No	67 ± 8	2D, STE*	Combination of AVR, hospitalization for HF, CV death	AoV_{max} ($p = 0.013$) LVEDV ($p = 0.003$) LAAi ($p < 0.0001$) LF/HG ($p = 0.04$) LF/LG ($p = 0.001$)	–
Kearney et al. (65), 2012	146	Mild to severe	Yes (n = 41)	Yes, AVR	No	59 ± 11	2D, STE*	Overall death	GLS ($p < 0.001$)	–
Adda et al. (68), 2012	340	Severe	–	–	–	≥50	2D, STE*	–	–	–
Yingchoncharoen et al. (64), 2012	79	Severe	No	Yes, AVR (n = 49)	No	63 ± 8	2D, STE†	Overall death	GLS ($p < 0.01$)	–
Eleid et al. (69), 2013	1,704	Severe	–	Yes, AVR/TAVR (1,057/64)	–	≥50	2D	Overall death	LF/LG no AVR ($p = 0.0003$)	–
Le Ven et al. (70), 2013	639	Severe	Yes	Yes, TAVR	No	54 ± 14	2D	Overall death and CV death	SV_i (per 10 ml/m^2 decrease) ($p < 0.05$) LF/LG ($p = 0.01$)	–

*STE was performed using EchoPAC (GE Vingmed Ultrasound AS). †STE was performed using Syngo Velocity Vector Imaging (Siemens Medical Solutions). – = data were not available or that the category is not applicable.

AoV_{max} = peak aortic velocity; AS = aortic stenosis; AUC = area under the curve; AVR = aortic valve replacement; BLS = basal longitudinal strain; LAAi = indexed left atrial area; LF/HG = low-flow/high-gradient aortic stenosis; LF/LG = low-flow/low-gradient aortic stenosis; LVEDV = left ventricular end-diastolic volume; NYHA = New York Heart Association dyspnea scale; SAC = systemic arterial compliance; SVi = stroke volume index; TAVR = transcatheter aortic valve replacement; ZV_a = valvuloarterial impedance; other abbreviations as in Tables 1 and 2.

Nevertheless, the experience in this field remains limited. Moreover, the repeatability and precision of circumferential strain, rotation, and twist is currently restricted by the limited lateral spatial resolution and the presence of through-plane motion in the short axis. Future studies employing 3-dimensional STE may circumvent some of these limitations and require further consideration (75). Details from the major echocardiographic studies are summarized in **Table 3**.

AORTIC REGURGITATION

Aortic regurgitation (AR) causes a chronic volume overload in the LV, which leads to progressive LV enlargement and LV dysfunction. Current guidelines indicate surgery in symptomatic patients with severe AR or, in the case of asymptomatic patients, when LVESD is >55 mm (25 mm/m^2) or LVEF decreases below 50% (3,4). Despite these indications, the optimal timing of cardiac surgery for chronic AR remains challenging because the development of systolic dysfunction precedes symptom onset in more than one-fourth of patients with this condition (76). These factors arise because the increased LV end-diastolic volume and eccentric hypertrophy act as compensatory mechanisms for long periods of time, which masks the development of afterload mismatch and the progressive exhaustion of myocardial contractile reserve. Therefore, more sensitive parameters of LV function evaluation are needed.

LONGITUDINAL LV FUNCTION ASSESSMENT BY TDI. Some studies have shown that the measure of mitral annular plane systolic excursion using M-mode and s′ by TDI detect early LV impairment in AR. Vinereanu et al. (77) showed that patients with asymptomatic severe AR and reduced functional reserve during exercise have significantly lower mitral annular plane systolic excursion (11 ± 2 mm vs. 14 ± 2 mm, $p < 0.01$) and s′ (8.6 ± 0.6 cm/s vs. 11.9 ± 2.2 cm/s, $p < 0.001$) than did subjects with a preserved LV response. In this small population (n = 21), a resting s′ <9.5 cm/s was the best determinant of poor exercise tolerance with a sensitivity and specificity of 90% and 100%, respectively (77). Patients with an s′ < 9 cm/s also presented higher LV wall stress and end-diastolic pressure (78) and significantly increased LV diameters, volume, and mass at a 12-month follow-up, with a concomitant reduction in longitudinal shortening and LVEF. Interestingly, a cutoff value of 6.25 cm/s in patients with s′ <9 cm/s predicted AVR within the year with a good accuracy (79).

LONGITUDINAL LV FUNCTION ASSESSMENT USING STE. Stefani et al. (80) found that longitudinal strain in the basal lateral wall in young athletes with bicuspid mild AR was at the lower extremes of normality with a marked reduction from the basal to the mid-apical segments (-14.2 ± 2.2% vs. -18.8 ± 4.2%, $p < 0.001$). The first study to comprehensively compare newer echocardiographic modalities for the detection of LV dysfunction in chronic AR was performed by Olsen et al. (81) in 64 patients with moderate to severe AR. In this population, the GLS, peak systolic strain rate, and peak diastolic strain rate were significantly lower in patients who developed heart failure, but no differences in TDI parameters were observed. All speckle-tracking measures were significantly associated with outcomes regardless of the therapeutic approaches, and TDI velocities were associated with outcomes after AVR. In medically treated patients, a GLS of -18% was the best cutoff for the identification of disease progression, and a

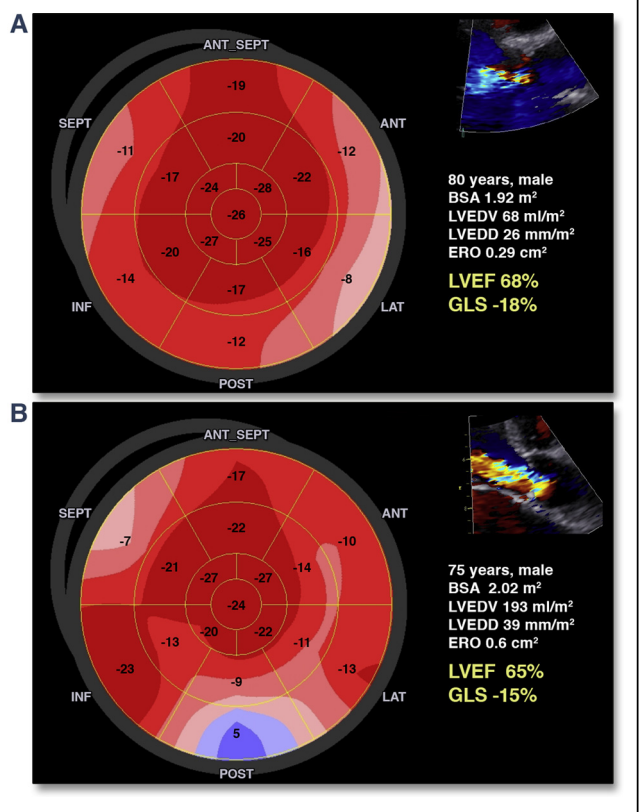

FIGURE 6 GLS in Patients With AR and Preserved LVEF

(A) Moderate aortic regurgitation (AR) of an 80-year-old male patient with BSA of 1.92 m^2 and ERO of 0.29 cm^2. **(B)** Severe AR of a 75-year-old male patient with BSA of 2.02 m^2 and ERO of 0.6 cm^2. LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; other abbreviations as in **Figure 1**.

TABLE 4 Echocardiographic Studies in AR

First Author (Ref. #), Year	n	AR Degree	Symptoms	AVR	Stress Echocardiography/ Exercise Testing	LVEF (%)	Main Echocardiographic Method	Clinical Outcome	Clinical Outcome Determinants	Sensitivity, Specificity (%)
Vinereanu et al. (77), 2001	21	Severe	No	No	Yes	54 ± 4	2D, M-mode, TDI	LVEF decrease during exercise >5%	MAPSE <12 mm s′ (medial annulus) <9.5 cm/s	80, 82 90, 100
Paraskevaidis et al. (78), 2006	84	Mild to severe	No	No	Yes	65 ± 8	2D, TDI	LVEF decrease during exercise >5%	s′ (lateral annulus) <9 cm/s	–
Paraskevaidis et al. (79), 2007	65	Mild to severe	No	Yes (n = 6)	No	>50	2D, TDI	Aortic valve replacement	s′ (lateral annulus) <6.25 cm/s	97, 83
Stefani et al. (80), 2009	60	Mild	No	No	No	>60	2D, STE*	–	–	–
Olsen et al. (81), 2011	64	Moderate to severe	–	Yes (n = 29)	No	55 ± 9	2D, STE†	Disease progression: Symptom onset, $LVESV_i$ increase >15%; LVEF reduction >10% in medically treated patients Development of HF, $LVESV_i$ ≥87 ml/m^2, LVEF <50% in surgically treated patients	Medical therapy: GLS >-18% Surgical treatment: GLS >-14%	88, 60 82, 72
Smedsrud et al. (82), 2011	78	Severe	–	Yes (n = 44)	No	59 ± 5	2D, STE†	Prediction of post-operative LV function	LVEDV, r = 0.65 (p < 0.01) GLS, r = 0.62 (p < 0.01)	–
Mizariene et al. (84), 2011	129	Moderate to severe	–	No	No	–	2D, STE†	Prediction of NT-proBNP >400 pg/ml	GLS >-16% (p < 0.05)	–
Kusunose et al. (83), 2014	159	Moderately severe to severe	No	Yes (n = 50)	Yes	>50	2D, STE‡	AVR	Resting GLS (chi-square = 30.1, p = 0.001) Resting RV strain (chi-square = 49.7, p < 0.001) Exercise TAPSE (chi-square = 64.4, p < 0.001)	–

*STE was performed using X-Strain software (My Lab 30 echo, EsaOte, Italy). †STE was performed using EchoPAC (GE Vingmed Ultrasound AS). ‡STE was performed using Syngo Velocity Vector Imaging (Siemens Medical Solutions). – = data were not available or that the category is not applicable.

AR = aortic regurgitation; NT-proBNP = N-terminal pro B-type natriuretic peptide; $LVESV_i$ = indexed left ventricular end-systolic volume; RV = right ventricle; TAPSE = tricuspid annulus plane systolic excursion; other abbreviations as in Tables 1 to 3.

cutoff of -14% was predictive of poor outcome in patients undergoing AVR (81). These results were reinforced by Smedsrud et al. (82) who demonstrated a reduction in GLS in 47 patients with severe AR compared with healthy control subjects (-17.5 ± -3.1% vs. -22.1 ± 1.8%, $p < 0.01$), even in the presence of a preserved LVEF (**Figure 6**). In a recent study, Kusunose et al. (83) showed that in patients with moderate to severe AR, resting LV strain (chi-square = 30.1, $p = 0.001$), exercise tricuspid annulus plane systolic excursion (chi-square = 64.4, $p < 0.001$), and RV strain at rest (chi-square = 49.7, $p < 0.001$) were all independent predictors of early AVR. In patients with AR, the compensatory increase in stroke volume consequent to the augmented volume load and increased sphericity of the LV is responsible for the prolonged maintenance of global circumferential function and LVEF in AR patients. At this early stage, as already observed in MR patients, the decrease in LV function starts in the subendocardium, where longitudinal myocardial fibers are more abundant, and determines a consequential reduction in longitudinal myocardial function (42), making strain parameters useful to detect LV dysfunction at an earlier stage than LVEF can be detected. The concomitant evidence that alteration in RV function may influence prognosis in AR is in line with the observations made in patients with severe MR (30) and suggests that RV function should be assessed during the clinical evaluation of AR patients.

OTHER COMPONENTS OF LV MECHANICS. Few studies have been performed on LV rotation. However, a decrease in LV torsion has been observed in patients with severe AR with mainly a decrease in LV basal rotation. In contrast, patients with a moderate AR generally have an increase in apical rotation, especially if they do not have hypertension. In regard to circumferential and radial strain, the data are scarce; if there are alterations due to the AR, these alterations are less clear and pronounced than are the observed alterations in the longitudinal direction (84). Details of the major echocardiographic studies are summarized in **Table 4**.

CONCLUSIONS AND FUTURE DIRECTIONS

VHD occurs less frequently than coronary artery disease, heart failure, or hypertension, but it represents a major health problem in Western countries, with an increasing prevalence in an aging population. As indicated by the results of the Euro Heart Survey, further efforts should be undertaken to reach an optimal adherence to guidelines in VHD in symptomatic and asymptomatic patients. Interestingly, a tendency toward early intervention in asymptomatic or mildly symptomatic patients was found in this survey, which reveals the need for studies aimed at identifying the effective benefits of an early surgery strategy.

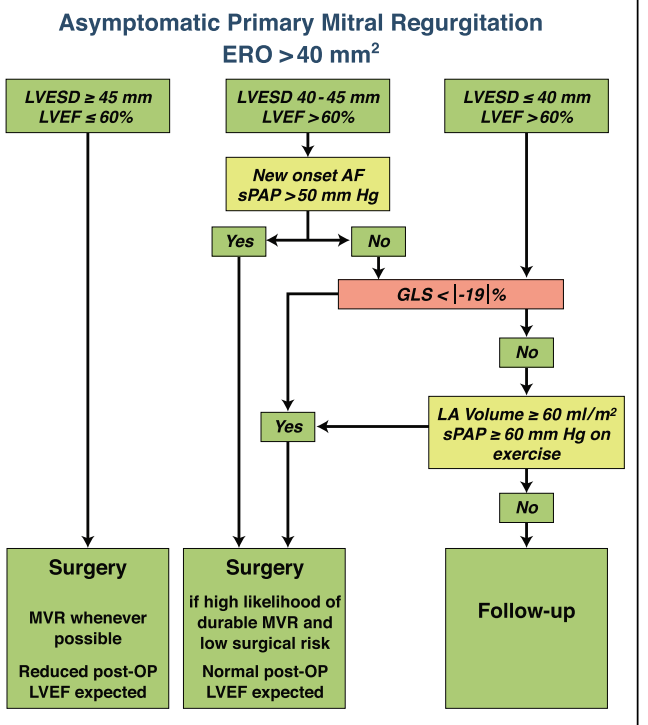

FIGURE 7 Potential Role of GLS in Management of Patients With Primary MR

Algorithm depicting the potential role of GLS in the clinical management of patients with primary mitral regurgitation (MR). AF = atrial fibrillation; LA = left atrium; LVESD = left ventricular end-systolic diameter; MVR = mitral valve replacement/repair; post-OP = post-operative; sPAP = systolic pulmonary artery pressure; other abbreviations as in **Figure 1**.

This challenging perspective is of paramount significance if we consider that subclinical LV dysfunction—intrinsic myocardial dysfunction despite normal LVEF—in VHD patients may be present before the onset of symptoms, which portends a dismal prognosis.

All of these observations highlight the major need to use more robust parameters to assess LV function, particularly in the case of preserved LVEF. Although some limitations were indicated previously, 2-dimensional STE longitudinal strain is highly reproducible and accurate and has proven to be clinically valuable and reliable, therefore representing an interesting alternative to the measurement of LVEF. Conversely, circumferential and radial strains, and rotation and torsion, are less reproducible and not yet ready for clinical applications.

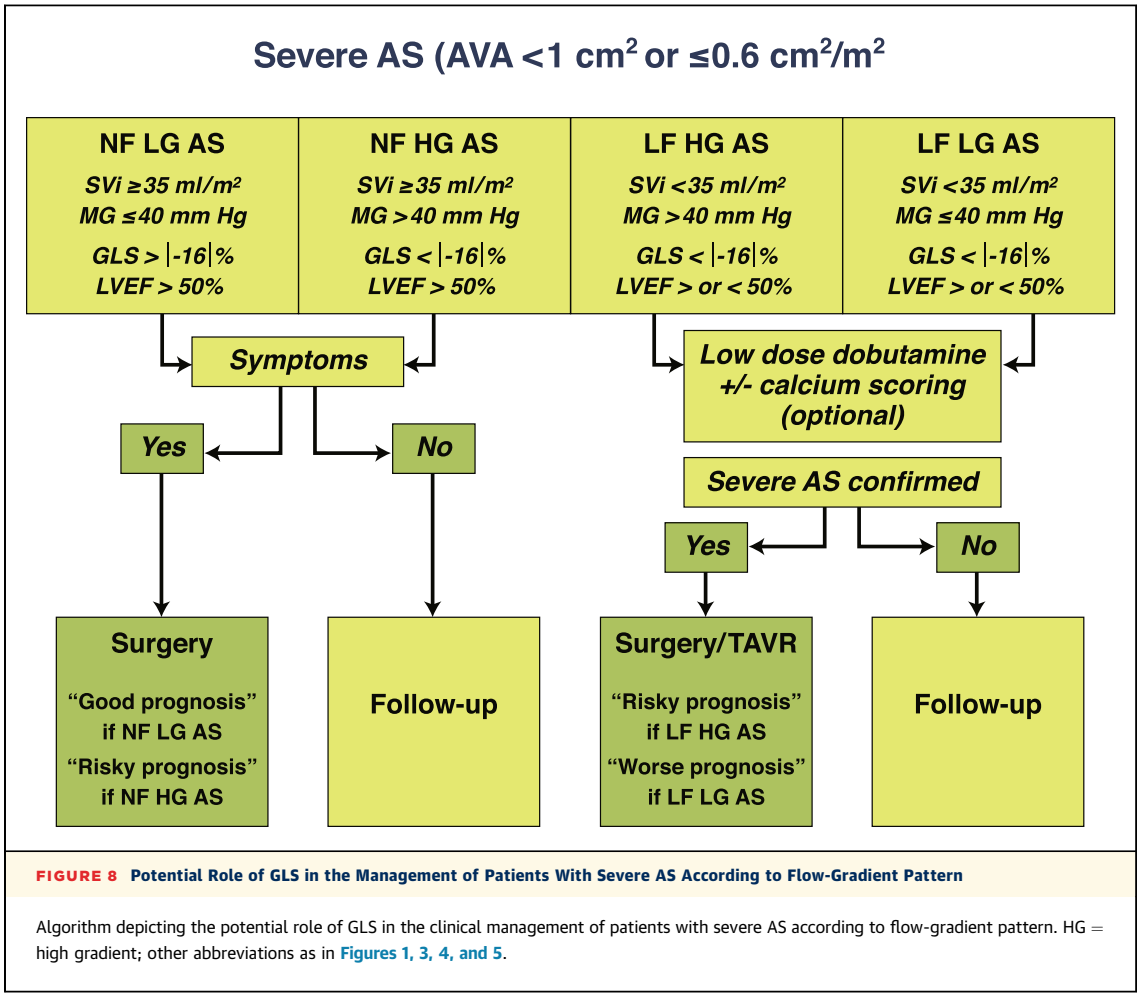

FIGURE 8 Potential Role of GLS in the Management of Patients With Severe AS According to Flow-Gradient Pattern

Algorithm depicting the potential role of GLS in the clinical management of patients with severe AS according to flow-gradient pattern. HG = high gradient; other abbreviations as in Figures 1, 3, 4, and 5.

The present review has gathered all the available evidence that supports the incremental value of GLS in the diagnostic workup of VHD, especially in the setting of primary MR (Figure 7) and AS (Figure 8). To deeply anchor the role of deformation imaging in the clinical algorithm evaluation of VHD, development of further large prospective trials and registries are needed. For example, registries such as the HAVEC (HeArt ValvE Clinic International Database) registry, set up by Lancellotti et al. (personal communication, 2014) in the European Union and the United States, will allow substantial contributions to the field. Meanwhile, continued efforts on the standardization of 2-dimensional STE analysis for mitigating vendors' differences and widespread education of the cardiology and surgical fraternity regarding the incremental value of strain imaging beyond EF will enable routine acceptance of 2-dimensional STE for the clinical assessment of patients with VHD.

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