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Assessment of Left Ventricular Function by Echocardiography

The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction

Elizabeth Potter, MBBS, Thomas H. Marwick, MBBS, PhD, MPH

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CME/MOC Objective for This Article: After reading this article the reader should be able to: 1) review the test characteristics, limitations, and normal reference ranges of strain for clinical use; 2) recognize the clinical entities in which knowledge of global longitudinal strain can assist in risk prediction; and 3) be able to apply knowledge of global longitudinal strain in clinical decision making.

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ABSTRACT

Left ventricular (LV) ejection fraction (LVEF) is a simple measure of global systolic function that pervades the risk evaluation and management of many cardiovascular diseases. However, this parameter is limited not only by technical challenges, but also by pathophysiological entities where the ratio of stroke volume to LV cavity size is preserved. The assessment of global longitudinal strain (GLS) from speckle-tracking analysis of 2-dimensional echocardiography has become a clinically feasible alternative to LVEF for the measurement of myocardial function. Evidence gathered over the last decade has shown GLS to be more sensitive to left ventricular dysfunction (LVD) than LVEF and to provide additional prognostic information. The technology is validated, reproducible within an acceptable range, and widely available. GLS has been proposed as the test of choice in guidelines for monitoring of asymptomatic cardiotoxicity related to chemotherapy. It also has the potential to improve risk stratification, redefine criteria for disease classification, and determine treatment in asymptomatic LVD resulting from a variety of etiologies. GLS provides utility across the spectrum of heart failure (and LVEF) as well as in the evaluation of valvular heart disease. There is a strong case for incorporation of GLS into clinical decision making. This review appraises the evidence addressing the utility of GLS as a complementary metric to LVEF for incorporation into mainstream clinical practice. (J Am Coll Cardiol Img 2018;11:260–74) © 2018 by the American College of Cardiology Foundation.

The noninvasive assessment of ventricular function remains central to modern cardiology. The volume-based measurement of left ventricular ejection fraction (LVEF) is fundamentally different from direct measurement of myocardial motion by tissue Doppler imaging and myocardial deformation, and the reliability and precision of these measurements are also different. In the era of precision medicine, patient-specific measurements are used to make decisions about therapies in individual patients, as well as guidance across patient populations. Moreover, the current era is also marked by the emergence of heart failure with preserved ejection fraction (HFpEF)—in which ejection fraction (EF) is not useful prognostically—as the predominant form of heart failure (HF) (1). In this contemporary review, LVEF and strain are compared to evaluate the benefits of combining these complementary techniques.

MARKERS OF GLOBAL LV SYSTOLIC FUNCTION

EJECTION FRACTION. Despite differences among techniques, LVEF has remained a cornerstone of therapeutic decisions that are related to myocardial performance. Various LVEF thresholds are pertinent to the initiation of cardioprotective pharmacotherapies and device therapies in HF, as well as the timing of surgery for mitral and aortic regurgitation (AR) (2,3).

However, LVEF can be normal despite left ventricular dysfunction (LVD) in the presence of left ventricular (LV) hypertrophy and small LV cavity size, where a normal EF may hide a small stroke volume. Moreover, 2-dimensional echocardiography, the most common imaging modality by which LVEF is determined, has inherent limitations relating to LV cavity border tracing and geometric assumptions. Although foreshortening has more impact on estimation of LV volumes than EF, this phenomenon needs to be borne in mind with sequential measurements.

LV GLOBAL STRAIN. Strain describes deformation of the myocardium that occurs during the cardiac cycle in the longitudinal, circumferential, and radial planes. These vectors result from the obliquely and oppositely orientated subendocardial and epicardial myofibers that generate an apical counterclockwise twist and a basal clockwise twist driving torsional ventricular contraction (4,5). Strain is a dimensionless index of a change in length between 2 points: Strain (ε) = L − Lo / Lo (where Lo = baseline length,

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

AR = aortic regurgitation

AS = aortic stenosis

CAD = coronary artery disease

CI = confidence interval

CTRCD = cancer therapeutics-related cardiac dysfunction

DM = diabetes mellitus

EF = ejection fraction

GLS = global longitudinal strain

HCM = hypertrophic cardiomyopathy

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

IHD = ischemic heart disease

LA = left atrial

LV = left ventricular

LVD = left ventricular dysfunction

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

L = length after deformation). Measurement of strain rate (the change of strain over time) is accurate when imaging is possible at high temporal resolution.

During systole the left ventricle undergoes longitudinal and circumferential shortening (denoted by a negative value) and radial thickening (denoted by a positive value). Despite initial hopes that this method would improve the quantification of regional function, this application has been disappointing. In contrast, the derivation of global longitudinal strain (GLS) from averaging multiple regions has overcome the effects of regional noise and provided a remarkably robust systolic function marker. Detailed practical and technical guidance relating to strain measurement has been published (6,7). For the purposes of this review, "strain" refers to Lagrangian strain by speckle-tracking echocardiography, which has superseded Doppler-based measurement (natural strain). In the interest of simplicity, GLS values herein are not preceded by a negative sign.

The accuracy of strain has been validated experimentally against in vivo measurement with sonomicrometry and clinically against magnetic resonance tagging techniques (8–11). Precision (or reliability) refers to the measurement reproducibility when the test is repeatedly applied under identical conditions. The presence of minimal variance in a reliable test implies that alteration can be interpreted as a true signal of pathological change. The larger variability of EF over GLS means that the use of GLS carries an advantage in relation to reclassification, both at baseline (**Figure 1A**) and in sequential follow-up (**Figure 1B**). Although association exists between the accuracy of GLS measurement and readers' experience, echocardiographers with no experience in strain imaging have high precision (intraclass correlation coefficient 0.975; 95% confidence interval [CI]: 0.912 to 0.998), similar to that of expert readers (0.996; 95% CI: 0.988 to 1.000, p = 0.0002) (12).

The early phases of the development of strain were marked by significant intervendor variability, and vendor-independent software was used to circumvent this problem (13). Since the publication of the consensus paper from the European Association of Cardiovascular Imaging (EACVI)/American Society of Echocardiography (ASE) Industry Task Force (14), intervendor differences in strain measurements have been markedly reduced to levels similar to (or less than) those of standard parameters, including LVEF (15,16).

REFERENCE RANGES. Although the normal range of LVEF is >53%, the most prognostic value is present when EF is <40%, with very little prognostic information provided in the mild or borderline ranges (**Figure 2**). Normal reference ranges for GLS have been determined by meta-analysis of study control groups and healthy volunteers (17). In 24 studies involving 2,597 subjects, normal values ranged from 15.9% to 22.1% (mean 19.7%; 95% CI: 20.4 to 18.9%). Meta-regression for sources of interstudy variability in strain values found systolic blood pressure to be a significant contributor. Strain declines with age (without a significant drop in LVEF) (18), but sex has a more significant impact on normal strain values. In the general population (without cardiovascular disease or traditional risk factors), the absolute GLS difference between men and women is >1% (19,20).

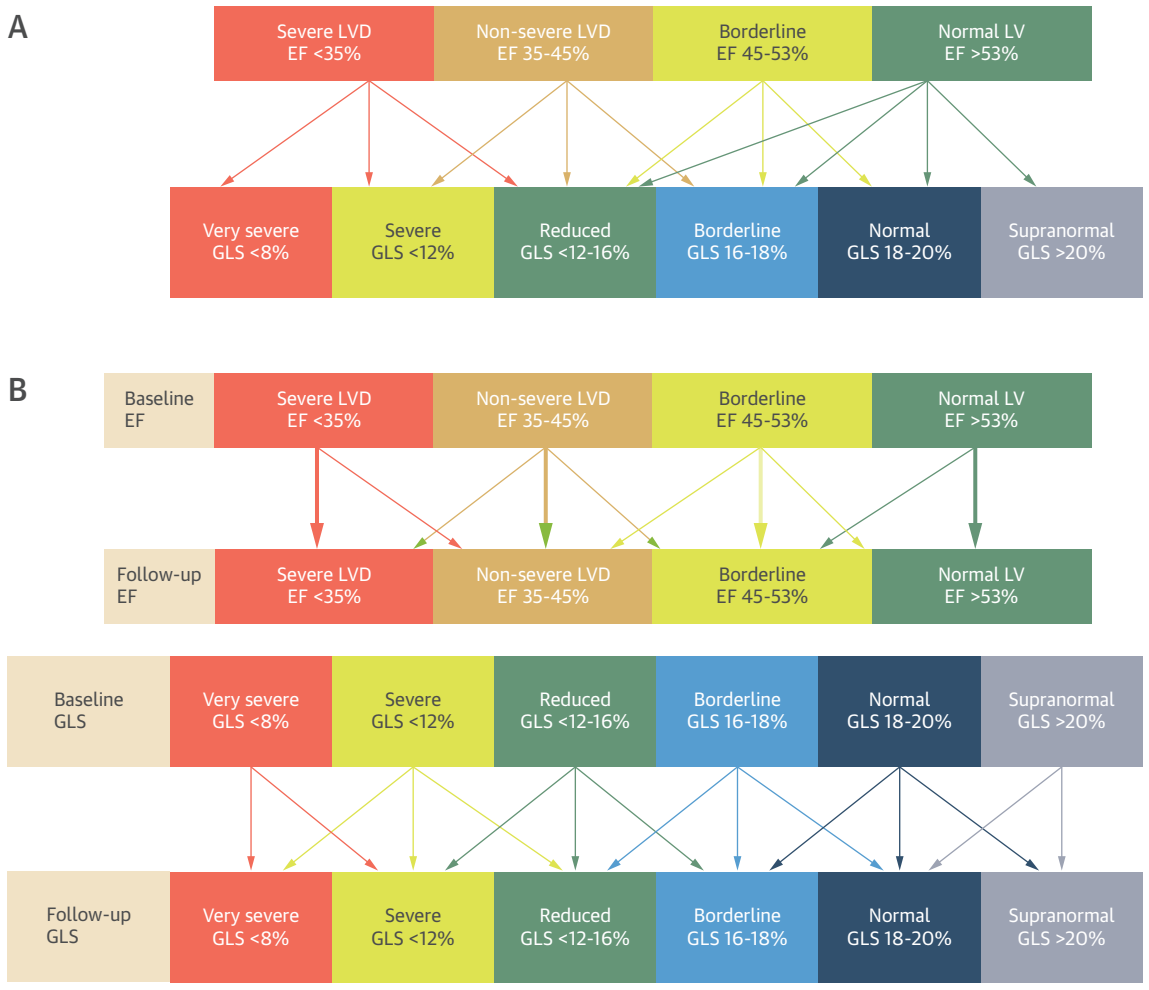
CLINICAL VALUE FROM FUNCTIONAL EVALUATION WITH STRAIN

RISK PREDICTION. Reductions in LVEF portend worse cardiovascular outcomes (21–24). Although there is an inverse relationship between LVEF and all-cause mortality rate, this plateaus at an EF of 40% to 45%, above which EF is unrelated to mortality (**Figure 2**) (24). Despite this finding, patients with HF have a similar 1-year mortality rate irrespective of whether they have preserved EF (HFpEF) or reduced EF (HFrEF) (25). In contrast, GLS is a correlate of mortality, independent of and incremental to LVEF in patients with HFrEF (26–28). In particular, GLS adds significant incremental predictive value for mortality in patients with LVEF >35% (**Figure 3**). A meta-analysis of 5,721 subjects across 16 studies of various cardiac diseases confirmed that GLS is a stronger predictor than LVEF of all-cause mortality and a composite of cardiac death, HF hospitalization, and malignant arrhythmias (28).

Strain imaging has also shown prognostic utility over traditional imaging markers of LV function after acute myocardial infarction (AMI) (29). In 603 patients in the VALIANT (Valsartan in Acute Myocardial Infarction Study) echocardiographic substudy, longitudinal strain rate provided prognostic value for the prediction of all-cause mortality, independent of and incremental to clinical variables and LVEF, and circumferential strain rate identified patients at risk of LV remodeling.

Population-based data also support the prognostic importance of abnormal GLS. The risk of composite

FIGURE 1 Reclassification With GLS

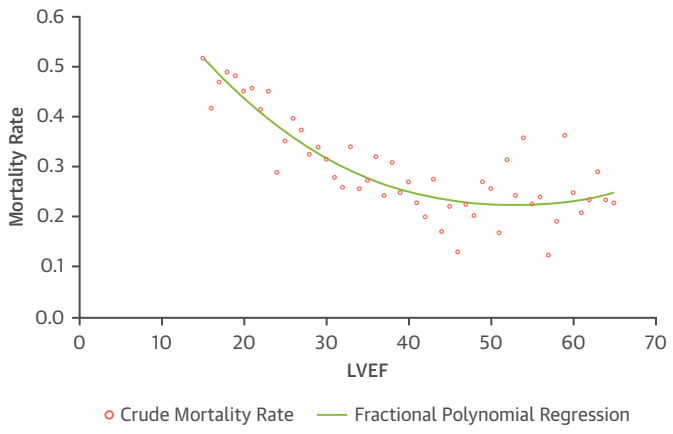


(A) Global longitudinal strain (GLS) may reclassify baseline function at every level of impaired ejection fraction (EF), especially in the normal left ventricle. **(B)** On a longitudinal basis, the test-retest variability of ejection fraction compromises the ability to reclassify function. Global longitudinal strain is more reproducible and more able to reclassify function in sequential follow-up. In both situations, more extensive reclassifications are possible but less common.

AMI, HF, and cardiovascular death appears to be 3 times greater for the highest versus lowest GLS quartiles. GLS improved the predictive ability of the Framingham risk score in a Danish population, whereas natriuretic peptides did not (30). In an older adult population without HF, the prevalence of strain-defined LVD (with a normal EF) was 16.8% compared with 4.2% with an abnormal EF. After adjustment for clinical variables, hemodynamic parameters, and imaging parameters, the respective hazard ratios (HRs) for cardiovascular events were 2.39 (95% CI: 1.2 to 4.77, p = 0.017) and 3.51 (95% CI: 1.25 to 9.88, p = 0.014) (31).

ASYMPTOMATIC LVD. The most common scenario in which strain is currently used to assess asymptomatic LVD is in cancer therapeutics–related cardiac dysfunction (CTRCD). Increases in cancer survivorship and the use of cardiotoxic biologic therapies and chemotherapies, as well as the burden of HF risk factors in the aging population, are all drivers of increasing risk of cardiotoxicity. The incidence of CTRCD (defined as a decrement of >10 LVEF percentage points to <53%) ranges from 13% to 42% depending on risk profiles, cumulative anthracycline dose, and therapy combinations (32,33). Impairments in GLS precede reductions in LVEF, with a 10% to 15%

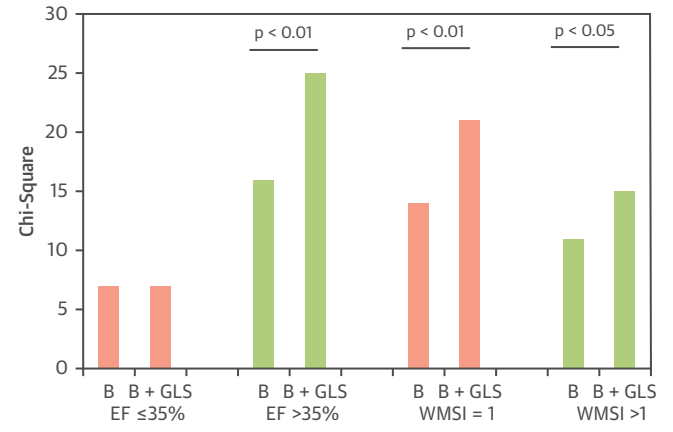
FIGURE 2 Relationship of LVEF With Unadjusted All-Cause Mortality Rate



This figure summarizes mortality versus left ventricular ejection fraction (LVEF) in the Digitalis Investigation Group (DIG) trial. Reprinted with permission from Curtis et al. (24).

relative change in GLS early in treatment predictive of subsequent EF reduction (34). Accordingly, GLS measurement is incorporated into consensus guidelines for abnormal (cardiotoxic) response as a >15% relative reduction in GLS from baseline (32). Whether the use of GLS to guide early cardioprotective therapy results in improved clinical outcomes remains to be established. Nevertheless, it is evident that GLS detects early subclinical LVD in this population, where long-term rates of HF and disease reversibility, particularly with anthracycline-based regimens, are unknown.

FIGURE 3 Association of Mortality With GLS



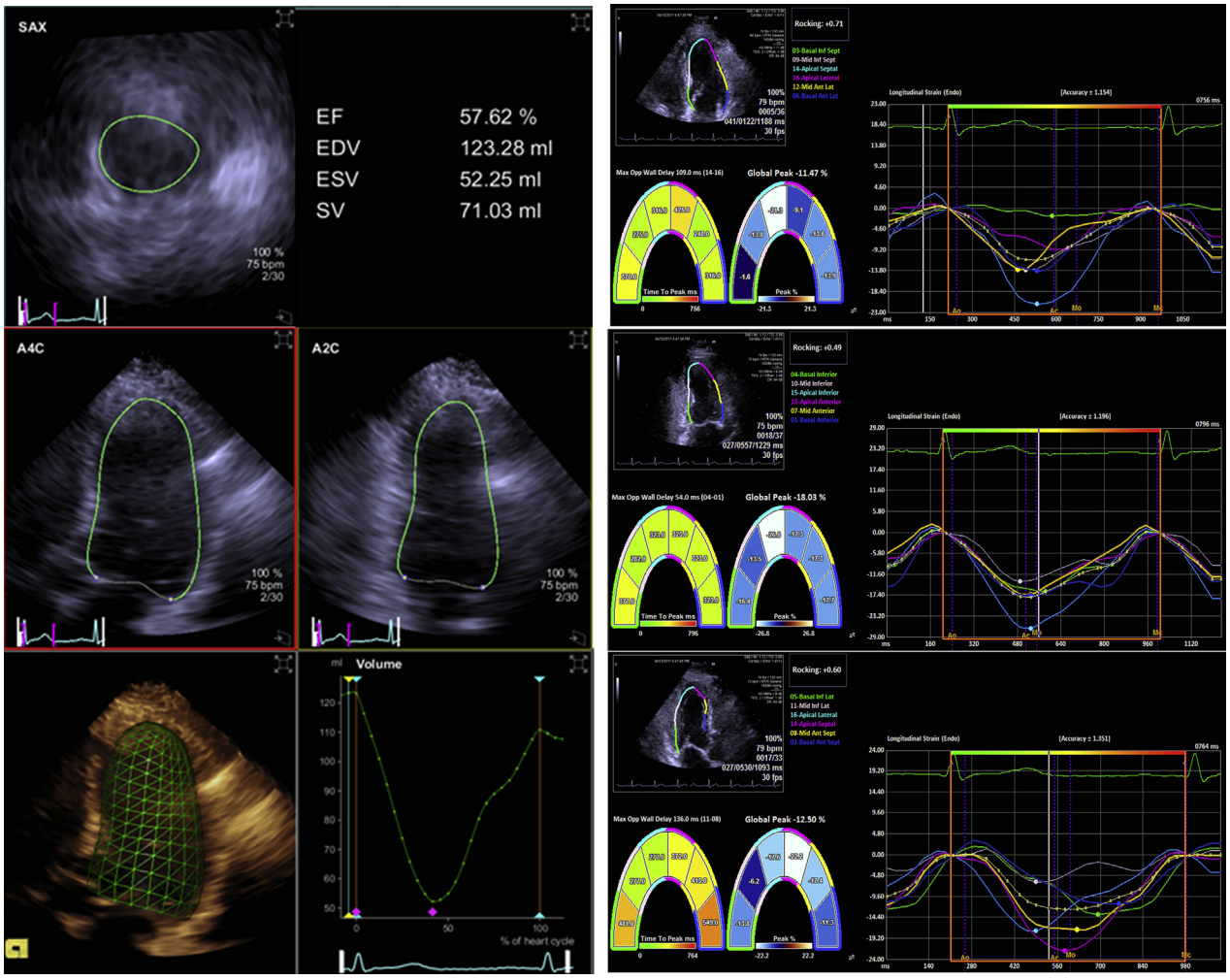
The model chi-square for prediction of mortality when global longitudinal strain (GLS) is added to baseline variables (B), dichotomized by both ejection fraction (EF) ≤35% or >35% and wall motion score index (WMSI) of 1 or >1. Baseline clinical variables are diabetes mellitus, age, and hypertension selected on the basis of independent univariable predictors. Data from Stanton et al. (28).

Although CTRCD is an important current application for deformation imaging, subclinical LVD in cardiometabolic disease may yet prove to be the most important indication for deformation imaging. Reduced strain has been demonstrated in several populations at risk of HF (**Figure 4**), and it may be the only sign of LVD. In hypertensive subjects with normal LVEF, GLS reduction is observed independent of LV hypertrophy and diastolic dysfunction (35), and it confers elevated cardiovascular risk (36). Similarly, LVD has been reported in more than one-half of asymptomatic subjects with diabetes mellitus (DM) (37,38). In the absence of ischemic heart disease (IHD) and hypertension, this entity has been termed diabetic cardiomyopathy (39), and its phenotype is commonly considered one of early diastolic dysfunction. Diastolic dysfunction in this setting has prognostic significance but may be attributable to hypertension and obesity (40,41). Approximately one-third of asymptomatic DM is associated with abnormal GLS with normal diastolic function (and LVEF) (42), and GLS may be a signal that is more specific for diabetic cardiomyopathy than are diastolic changes. GLS improves the sensitivity of echocardiography in detection of early diabetic heart disease. Furthermore, strain-defined LVD is predictive of worse outcomes in DM with normal LVEF (without HF symptoms or IHD) and appears superior in this regard to diastolic dysfunction (assessed by E/e′) (37,43), although some data are conflicting (44). The variation in the relative prognostic roles of GLS and diastolic dysfunction likely relates to the predominant underlying pathophysiology of myocardial disease in DM and hypertension.

Obesity-induced myocardial damage occurs independent of DM, hypertension, and coronary artery disease (CAD), and it shares common pathophysiological mechanisms with diabetic heart disease (45). Overweight is associated with reductions in strain in a "dose-dependent" manner and independent of associated elevations in blood pressure, LV mass, and circulating insulin (46).

LVD before the onset of cardiac symptoms enables implementation of therapies at a point in the disease course that may slow or halt an otherwise progressive trajectory. The detection and treatment of subclinical global LVD for the prevention of HF are potential models. The HF staging paradigm (stages A to D) describes a continuum from risk factors to refractory HF (2). Stage A HF management targets cardiovascular risk factors. The use of cardiac imaging to identify structural or functional abnormalities provides

FIGURE 4 **Reduced GLS in the Setting of Preserved LVEF**



In this asymptomatic patient, with a 3-dimensional left ventricular ejection fraction (LVEF) of 58% **(left),** the mean global longitudinal strain (GLS) was 14%, showing both spatial and temporal variation in the 4-, 2-, and 3-chamber views. A2C = apical 2-chamber (view); A4C = apical 4-chamber (view); EDV = end-diastolic volume; ESV = end-systolic volume; SAX = short-axis (view); SV = stroke volume.

evidence of stage B HF, but the current functional qualifier of impaired LVEF <40% is insensitive. The evaluation of LV strain, along with diastolic measures, may provide a more sensitive strategy for identifying dysfunction earlier in the natural history of HF. A screening process along these lines is currently not endorsed by appropriate use criteria (47), and in addition to evidence of treatment efficacy, issues of patient selection and economic implications need to be addressed.

ASYMPTOMATIC VALVE DISEASE. Current guidelines have emphasized a classification system analogous to that of HF, including an asymptomatic phase with subclinical LVD.

Aortic stenosis. Aortic valve replacement may be considered for severe aortic stenosis (AS) and impaired LVEF, even in the absence of cardiac symptoms (3). However, LVEF is an insensitive marker of LV systolic function, especially in the setting of LV hypertrophy. Impaired LV longitudinal function correlates with LV fibrosis and is associated with poor symptomatic recovery and even deterioration following surgery for symptomatic severe AS (48). Hence, in asymptomatic severe AS with normal

TABLE 1 Significance of GLS Values in Different Patient Populations

First Author (Ref. #)	Design	N	Population	Outcome	GLS Cutoff (%)	Size of Effect or Test Performance	Analysis Software
Yingchoncharoen et al. (17)	Meta-analysis	2,597	Healthy controls	N/A Determination of reference range	15.9–22.1 (mean 19.7; 95% CI: 20.4–18.9)	N/A	Various
Cheng et al. (20)	Prospective, observational	739	Healthy population cohort (no CVD or traditional risk factors)	N/A Determination of reference range by age group/sex	Mean: M: 20.2 ± 2.7, F: 22.0 ± 3.2 Lower reference limits (age 45–54 yrs) M: 15.2 (95% CI: 25.1–4.1) F: 17.1 (95% CI: 27.5–5.1) Lower reference limits (age 75–84 yrs) M: 14.4 (95% CI: 27.6–0.7) F: 14.4 (95% CI: 27.2–1.8)	N/A	2D Cardiac Performance Analysis v1.1, TomTec Imaging Systems
Zhang et al. (26)	Prospective, observational	416	HFrEF	Composite (all-cause mortality, transplantation and VAD placement)	≤6.5, lowest tertile vs. ≥9.6, highest tertile	HR: 3.9; 95% CI: 2.5–6.1; p < 0.001	TomTec Imaging Systems
Sengelov et al. (27)	Retrospective	1,065	HFrEF	All-cause mortality	Lowest tertile vs. highest tertile (cutoffs not specified) Per 1% GLS decrease	HR: 38; 95% CI: 2.3–5.1; p < 0.001 HR: 1.15; 95% CI: 1.04–1.27; p = 0.008	EchoPAC v12 (GE Healthcare)
Stanton et al. (28)	Retrospective	546	Unselected (established CV disease or risk factors)	All-cause mortality	12.0	Same event-free survival as LVEF <35%	EchoPAC v8 (GE Healthcare)
Biering-Sørensen et al. (30)	Prospective, observational	1,296	General population	HF AMI CVD	<15.8, lowest quartile vs. >20.4, highest quartile	HR: 4.7; 95% CI: 2.0–5.4; p < 0.001 HR: 3.7; 95% CI: 1.4–10.0; p = 0.010 HR: 2.2; 95% CI: 1.1–4.6; p = 0.027	EchoPAC v2008 (GE Healthcare)
Russo et al. (31)	Prospective, observational	708	General population (>50 yrs old)	Composite (AMI, vascular death, stroke)	<14.7	HR: 2.39; 95% CI: 1.20–4.77 (vs. healthy reference sample)	Philips QLAB Advanced Quantification v 8.1
Plana et al. (32)	ASE/EACI guideline	N/A	Cardiotoxic cancer therapy	Cardiotoxicity	>15% *relative* reduction from baseline	N/A	Various
Lee et al. (36)	Prospective, observational	95	Hypertension	CVD, HF, AMI, stroke	<17.6*	Worse event-free survival, p = 0.016	EchoPAC PC 2013 (GE Healthcare)
Holland et al. (37)	Prospective, observational	230	Diabetes mellitus (type 2)	All-cause mortality and hospitalization	<18.9	Worse event-free survival, p = 0.03	EchoPAC v9 (GE Healthcare)
Chen et al.(43)	Prospective, observational	247	Diabetes mellitus (type 2)	Composite (CVD, HF hospitalization, AMI, stroke)	<17.9	Worse event-free survival, p = 0.01	EchoPAC v108.1.5 (GE Healthcare)
Weidemann et al. (48)	Prospective	58	Symptomatic AS	Severe fibrosis, lack of functional improvement post-AVR	<10.0	Mean GLS corresponding to outcome	EchoPAC (GE Healthcare)
Yingchoncharoen et al. (49)	Prospective, observational	79	Asymptomatic AS	CVD and symptom-driven AVR	≤15.0	Worse event-free survival, p = 0.009	Syngo VVI (Siemens)
Olsen (83)	Prospective	33	Moderate or severe asymptomatic AR	Disease progression vs. stability	≤18.0	Sens 88%, spec 60%; AUC 0.72	EchoPAC PC 6.1.1 (GE Healthcare)
Ewe et al. (55)	Prospective	49	Moderate to severe and severe asymptomatic AR	Disease progression vs. stability	≤17.4	Sens 77%, spec 57%; AUC 0.70	EchoPAC 110.0.0 (GE Healthcare)
Mascle et al. (50)	Prospective	88	Severe MR undergoing MVR	Post-op LVD (LVEF <50%)	<18.0	OR: 4.2; 95% CI: 1.4–13; p = 0.009)	EchoPAC PC (GE Healthcare)
Witkowski et al. (52)	Prospective	233	Moderate-severe MR undergoing MVR	LV dysfunction (LVEF <50%) at long-term follow-up	<19.9	Sens 90%, spec 79%; AUC 0.88 (95% CI: 0.83–0.93)	EchoPAC 108.1.5 (GE Healthcare)
Shah et al. (58)	Prospective	447	HFpEF	Composite (cardiovascular death, HF hospitalization, aborted cardiac arrest)	<15.8	HR: 2.14; 95% CI: 1.26–3.66; p = 0.005	NR

Continued on the next page

TABLE 1 Continued

First Author (Ref. #)	Design	N	Population	Outcome	GLS Cutoff (%)	Size of Effect or Test Performance	Analysis Software
Liu et al. (69)	Prospective	400	HCM	Composite (new onset VF/VT, HF, cardiac transplantation, all-cause death	<10 vs. >16	HR: 4.0; 95% CI: 1.5–10.5; p = 0.006	EchoPAC 112 (GE Healthcare)
Ng et al. (60)	Prospective	424	ICD (primary prevention)	All-cause mortality Appropriate ICD discharge	<9.9† <9.9†	Worse event-free survival, p = 0.046 Worse event-free survival, p = 0.088	EchoPAC v7.0.0 (GE Healthcare)
Biering-Sørensen et al. (74)	Prospective	296	Chest pain (low-intermediate risk)	CAD (≥70% stenosis)	18.4	NPV 89%, PPV 50%; sens 74%, spec 58%	EchoPAC (GE Healthcare)
Choi et al. (75)	Prospective	96	Suspected CAD (normal regional motion, LVEF >50%)	CAD, high risk (LMCA stenosis, 3-vessel disease)	<17.9	NPV 85%, PPV 71%; sens 78.9%, spec 79.3%	EchoPAC BT 06.6.1.0 (GE Healthcare)
Liou et al. (77)	Meta-analysis	1,385	CAD (suspected, stable, ACS)	CAD (≥50% stenosis)	"Abnormal" per individual study definition (mean 16.5; 95% CI: 15.8-17.3)	Sens 74%, spec 72%; AUC 0.81	EchoPAC, various versions
Dhalslett et al. (78)	Prospective	64	Suspected NSTEACS	CAD (>50% stenosis)	21.0	NPV 92%, PPV 74%; sens 93%, spec 78%	EchoPAC v112 (GE Healthcare)
Antoni et al. (80)	Prospective, observational	659	Post-AMI	All-cause mortality	<15.1	HR: 4.5 (95% CI: 2.1-9.7)	EchoPAC v7.0.0 (GE Healthcare)

*Epicardial longitudinal strain. †Peri-infarct strain.

AMI = acute myocardial infarction; AR = aortic regurgitation; AS = aortic stenosis; ASE = American Society of Echocardiography; AUC = area under the curve; AVR = aortic value replacement; CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular death; EACI = European Association of Cardiovascular Imaging; F = female; GLS = global longitudinal strain; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; ICD = implantable cardioverter defibrillator; LMCA = left main coronary artery; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; M = male; MR = mitral regurgitation; MVR = mitral value replacement; N/A = not applicable; NPV = negative predictive value; NR = not reported; NSTEACS = non-ST-segment elevation acute coronary syndrome; OR = odds ratio; post-op = post-operative; PPV = positive predictive value; sens = sensitivity; spec = specificity; VAD = ventricular assist device; VF = ventricular fibrillation; VT = ventricular tachycardia.

EF (>50%), reduced strain (GLS <15%) has an association with mortality and symptom-driven valve replacement, independent of and incremental to standard severity indices (49). Strain imaging in this setting has the potential to provide pathophysiological insights and improve risk prediction, perhaps enabling selection of patients who would gain survival benefit from earlier intervention than guidelines currently recommend.

Mitral regurgitation. As with AS, guideline-directed surgical management for asymptomatic severe mitral regurgitation (MR) incorporates LVEF, with the aim of intervention before LVD develops. However, EF is poorly representative of LV contractile function in MR, and this is reflected by a "supranormal" LVEF cutoff (≤60%) (3). In severe primary MR, pre-operative GLS impairment (<18%) is a strong independent predictor of post-operative LVD (LVEF <50%) irrespective of pre-operative EF (50–52).

Aortic regurgitation. The risk of failing to recognize LVD is less in AR than in MR because the LV does not eject into the low-pressure left atrium. Consequently, a policy of watchful waiting remains the norm in severe asymptomatic AR with preserved EF without LV dilatation. Nonetheless, post-surgical recovery depends on the duration of impaired LV function (53). Hence the identification of impaired systolic function by reduced GLS before LVEF decline may support more vigilant surveillance or earlier valve replacement. Furthermore, interpreting subtle symptoms in patients can be challenging, and adjunct objective echocardiographic markers may assist in decision-making. Symptomatic patients with moderate to severe and severe AR with preserved LVEF demonstrate significantly lower GLS than do asymptomatic individuals and control subjects, even after controlling for loading conditions by normalizing GLS to LV end-diastolic volume (54). Asymptomatic patients with AR who develop a surgical indication exhibit significantly lower GLS versus those that do not (15.7 ± 2.0% vs. 17.6 ± 2.7%, p = 0.009), despite the lack of difference in conventional echocardiographic parameters including LVEF and clinical variables apart from age (55). GLS is independently associated with need for aortic valve surgery after adjustment for clinical variables and LV volumes; a GLS of ≥19.3% can rule out need for aortic valve surgery with a negative predictive value of 100%. An optimized cutoff (**Table 1**) of ≤17.4%

has been defined for risk of progression during conservative management.

SYMPTOMATIC LVD WITH PRESERVED EF. Although HFpEF has been considered in clinical trials as a single entity, it seems more probable that this disease represents a variety of disease phenotypes, which may be distinguished on the basis of clinical and echocardiographic features. Impaired longitudinal systolic function has been demonstrated in HFpEF and asymptomatic diastolic dysfunction by tissue Doppler and strain imaging (56,57). Abnormal strain is found in around 50% to 60% of cases of HFpEF (58), probably more with an ischemic etiology (57). Although isolated GLS reduction was rare (6%) in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, reduced strain (to ≤15.8%) was associated with higher risk of cardiovascular death and HF hospitalization, and it added incremental ability to clinical and standard echocardiographic variables for the prediction of cardiovascular death (58).

The importance of assessment of diastolic function is increasing with the rising prevalence of HFpEF, but despite integration of several indices, significant proportions of cases are found to be indeterminate. Measurement of left atrial (LA) strain follows the same principles as for GLS and has good interobserver agreement ($r = 0.94$) (59). LA strain correlates with invasively measured LV filling pressures, and it may facilitate the detection and grading of diastolic dysfunction. LA reservoir strain decreases sequentially and significantly with rising diastolic dysfunction grades, and cutoff values were able to discriminate grades with excellent accuracy (59). LA strain holds promise in diastolic evaluation, but further validation of cutoff values in larger and more diverse patient groups is warranted.

SYMPTOMATIC LVD WITH REDUCED EF. LVEF determines eligibility for primary prevention implantable defibrillator devices after AMI and cardiac resynchronization in HFrEF, but many patients have ventricular arrhythmias despite preserved EF. Although EF has clear prognostic value in HFrEF, GLS still carries incremental prognostic value. In established ischemic cardiomyopathy, peri-infarct strain is the only independent predictor of ventricular tachycardia and fibrillation (HR: 1.22; 95% CI: 1.09 to 1.36) (60), and specific scar sites identified by regional strain may be more proarrhythmogenic than others (61). Mechanical dispersion, evidenced by variation in the time to maximal deformation in segmental strain curves (**Figure 5**), reflects heterogeneous electrical conduction and thus an arrhythmogenic substrate in cardiomyopathies, channelopathies, and IHD (62). A dispersion cutoff of ≥47 ms has 88% sensitivity and 62% specificity for ventricular tachycardia and sudden cardiac death.

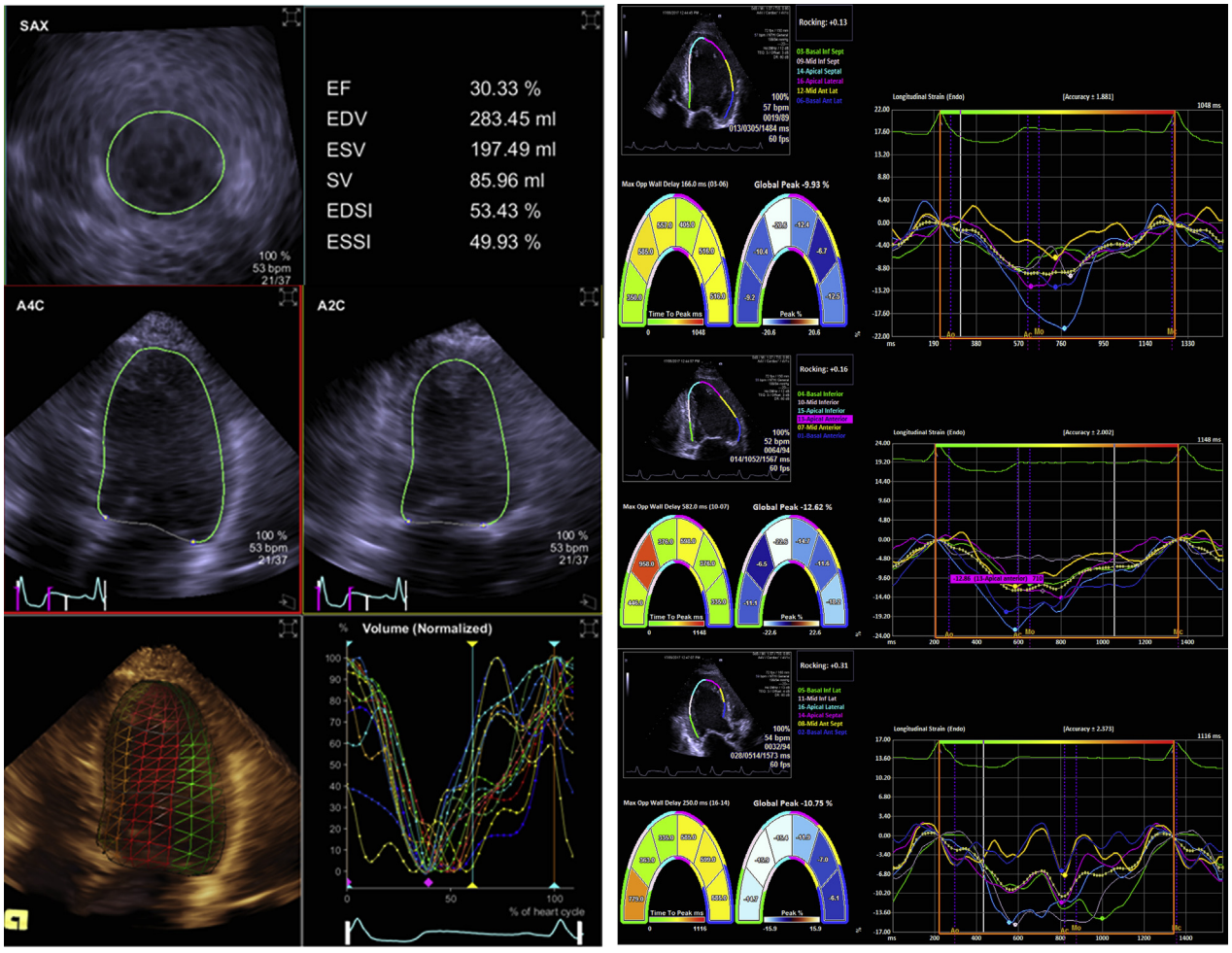
Furthermore, guidance of LV pacing lead placement by speckle tracking is associated with improved outcomes (63,64). Compared with standard placement, pacing a region with greatest mechanical delay (to improve dyssynchrony) and away from areas of severely reduced strain (presumed scar) reduces HF admissions and mortality (HR: 0.48; 95% CI: 0.28 to 0.82, $p = 0.006$) (57).

HYPERTROPHY. In patients with nonobstructive hypertrophic cardiomyopathy (HCM), imaging provides information on the differential diagnosis, as well as prognosis (65). Overt LVD is uncommon, but it heralds a dire prognosis. Reduction of GLS to 15% in an HCM patient cohort with normal LVEF was associated with fibrosis (66,67). Reduced GLS is the strongest independent predictor of fibrosis assessed by late gadolinium enhancement on cardiac magnetic resonance imaging; in the presence of late gadolinium enhancement, GLS was 11.8 ± 2.8%, compared with 15 ± 1.7% in its absence (68). Furthermore, reduced GLS has prognostic significance in HCM with preserved LVEF (68–70); GLS was the strongest independent predictor of outcome (ventricular arrhythmia, HF, transplantation, and all-cause death) in a recent study of 400 subjects with HCM who were followed for >3 years (69). GLS <10% portended 4 times the risk compared with GLS >16%, and there was significantly worse event-free survival when subjects were dichotomized by a GLS cutoff of 16% ($p = 0.004$). The differential diagnosis of LV wall thickening secondary to HCM includes athletic LV hypertrophy, hypertensive heart disease, and infiltrations. The pattern of reduction of strain can help to distinguish these conditions, with apical sparing in amyloidosis (71), posterolateral defects in Fabry disease (72), and reduced septal strain in classic HCM.

REGIONAL LVD. Resting measurement of strain is helpful in the detection and assessment of IHD when LVEF is normal and when visible resting wall motion abnormalities are absent. The basis of this information is regional and global deformation. “Bull’s-eye” strain plots provide an accessible display of data. Post-systolic shortening is an important marker of ischemic tissue, so the use of end-systolic rather than peak strain is helpful in IHD.

Animal models of induced coronary ischemia have demonstrated regional strain reductions that

FIGURE 5 **Reduced GLS in the Setting of Impaired LVEF**

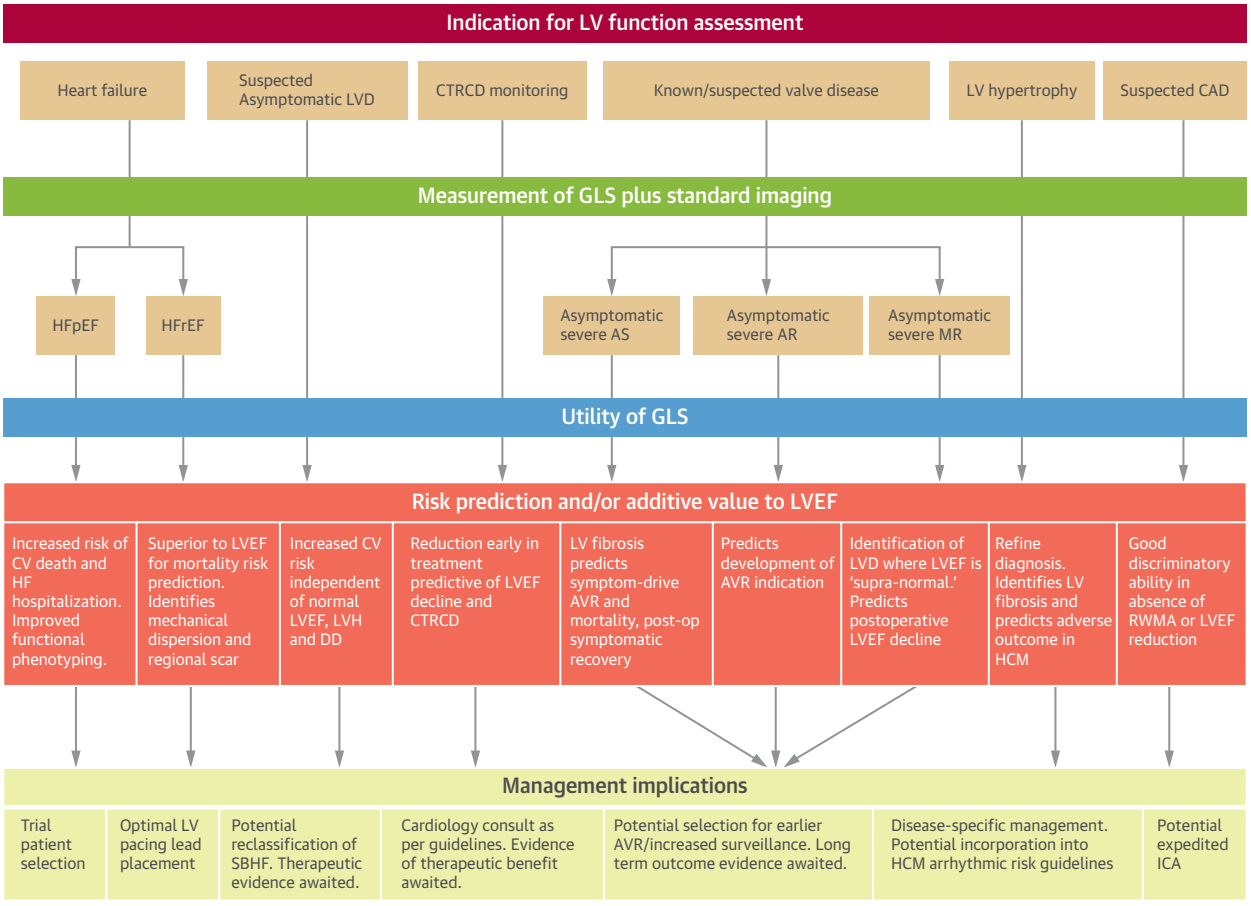


In this patient with symptomatic heart failure with reduced left ventricular ejection fraction (LVEF 30%, **left**), global longitudinal strain (GLS) was reduced to 11%. This figure also shows both spatial and temporal variation in the 4-, 2-, and 3-chamber views. A2C = apical 2-chamber (view); A4C = apical 4-chamber (view); EDV = end-diastolic volume; EDSI = end-diastolic sphericity index; ESSI = end-systolic sphericity index; ESV = end-systolic volume; SAX = short-axis (view); SV = stroke volume.

correlate with region and degree of coronary occlusion (73). In humans with stable CAD, both lesion-specific regional strain and GLS are reduced (74). Evidence of basal segment involvement (strain <17.4%) has a sensitivity and specificity of 79% for detection of extensive CAD (left main or 3-vessel), with discriminatory value exceeding those of apical segments or GLS (75). Relative apical-sparing has been observed in left main stenosis compared with 1- or 2-vessel disease despite similar GLS (74). Selective strain imaging of myocardial layers in the longitudinal orientation is also associated with underlying CAD (visual angiographic stenosis ≥50%) (76).

Although CAD is inherently a regional disease, abnormal GLS (mean 16.5%, 95% CI:15.8 to 17.3) detects moderate to severe CAD with 74% sensitivity and 72% specificity and good discriminatory value (area under the receiver-operating characteristic curve 0.81) (77). The addition of resting GLS to exercise electrocardiography and conventional echocardiographic indices in patients with low-intermediate risk chest pain (with normal LVEF) improves prediction of severe CAD and may therefore

CENTRAL ILLUSTRATION Prognostic and Management Implications of Abnormal Strain Measurement in Common Clinical Scenarios



Potter, E. et al. J Am Coll Cardiol Img. 2018;11(2):260–74.

AR = aortic regurgitation; AS = aortic stenosis; AVR = aortic valve replacement; CAD = coronary artery disease; CTRCD = cancer therapeutics–related cardiac dysfunction; CV = cardiovascular; DD = diastolic dysfunction; GLS = global longitudinal strain; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HCM = hypertrophic cardiomyopathy; ICA = invasive coronary angiography; LV = left ventricular; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MR = mitral regurgitation; post-op = post-operative; RWMA = resting wall motion abnormality; SBHF = stage B heart failure.

have a role in work-up of this common presenting symptom (74).

Non-ST-segment elevation acute coronary syndromes remain a diagnostic challenge because occluded vessels, especially in the posterior circulation, may not produce ST-segment elevation. In acute presentations, the presence of significant CAD (≥50% diameter stenosis on invasive coronary angiography) is predicted by both peak systolic segmental strain and GLS (area under the receiver-operating characteristic curve of 0.86 and 0.89, respectively). A GLS <21% had a negative predictive value of 92% for exclusion of significant CAD (78). Lesion-specific regional circumferential strain is able to identify coronary occlusion within an hour of presentation with high sensitivity and specificity (79).

Following AMI, GLS may improve risk prediction for all-cause mortality and cardiovascular composite endpoints when LVEF is in the intermediate range (80). Reduced GLS can predict infarct size; a GLS <15% independently predicts infarct mass ≥30 g with sensitivity and specificity of 83% and 93%, respectively (81).

BARRIERS TO THE INCORPORATION OF GLS INTO CLINICAL PRACTICE

EVIDENCE BASE. Myocardial strain provides prognostic information that is independent of and incremental to standard parameters in a range of clinical scenarios. Improvements in myocardial strain have been demonstrated in hypertensive heart disease, obesity, and metabolic syndrome following treatment with spironolactone (45). However, there is an urgent need to link the adoption of strain to improving outcomes by informing decisions.

Current guidelines for the assessment of chemotherapy-related cardiotoxicity advocate formal cardiology evaluation on the basis of GLS cutoffs at baseline because responding to a GLS reduction relative to an individual's baseline measurement is better justified than the use of an absolute cutoff (32). The recognition of clinically significant abnormal values is more difficult because the parameter is influenced by age, sex, and loading conditions, not only afterload but also preload (82). Indeed, abnormal GLS has been variably defined on the basis of underlying pathology and outcomes (**Table 1**). In proposing a GLS cutoff, it would be prudent to select a lower threshold than the normal reference range to maximize specificity for adverse outcomes across common disease or at-risk groups. A sex influence appears consistent in healthy populations, but the impact on outcomes in disease states is not well established. In addition, sex- and age-based reference ranges quoted in some data have large CIs (19) (**Table 1**).

TECHNICAL CONSIDERATIONS. The feasibility of GLS has been improved by the wide availability of post-processing algorithms. However, as with the adoption of all new technologies, inertia needs to be overcome by education and training. Although the learning curve for an echocardiographer to obtain appropriate images is small, it warrants a process of validation and audit (12). User education is needed for general physicians and general practitioners, who typically share the care of multimorbid and community-based patients with stage B HF and HFpEF; strain has much to offer for these patients.

The previous variability in measurements among various manufacturers was a significant barrier to the adoption of this method because it prevented adoption of a standardized normal range, and it meant that the use of different echocardiography machines from one visit to the next provided (or obscured) differences. Although the use of the same manufacturer is advisable from visit to visit, this cause of variability has been substantially reduced since the conclusion of a concordance process (16).

CONCLUSIONS

The measurement of global systolic function is essential in risk assessment and management of all patients with cardiac disease. GLS improves detection of systolic dysfunction beyond LVEF and has revealed additional pathological features in scenarios where diastolic dysfunction has been considered the singular or defining abnormality. Reduced GLS has a consistent independent association of GLS with adverse outcomes, and its use now is well justified for the purpose of risk evaluation (**Central Illustration**). In general, however, the evidence is still being developed to link GLS measurements with changes in management (**Central Illustration**). The role that GLS holds in current cardio-oncology recommendations is the exception, and even there, further work on a consensus definition of abnormal absolute values and/or relative changes in GLS and their application in individual disease states is needed. Nonetheless, in addition to cardio-oncology, the value of strain in optimizing LV lead placement exemplifies how the technique can bring unique information to enhance existing management. Its promise in the diagnosis of HFpEF and the recognition of stage B HF will extend the contribution of GLS outside of specialist centers because these disease burdens are ubiquitous in the wider community.

The escalating prevalence of obesity and DM and the aging of the population are projected to increase the burden of subclinical LVD. Early detection of LVD and initiation of cardioprotective therapy hold promise in the effort to reverse the HF epidemic, but large-scale randomized trial evidence is awaited. Routine GLS measurement in this setting will increase the proportion of patients identified as having disease. The adoption of strain imaging therefore raises questions not only around its incorporation into HF staging, but also regarding how imaging resources are allocated to large numbers of patients who are "at risk" but who have no present indications for imaging. Health economic considerations will need to include evaluation of the entire disease management pathway.

Although LVEF will remain a cornerstone of LV function assessment, the addition of GLS enables detailed phenotyping and improved risk assessment and is a tool for present and future therapeutic advancement.

ADDRESS FOR CORRESPONDENCE: Dr. Thomas H. Marwick, Baker Heart and Diabetes Institute, Melbourne, P.O. Box 6492, Melbourne, Victoria 3004, Australia. E-mail: tom.marwick@baker.edu.au.

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KEY WORDS global longitudinal strain, heart failure, left ventricular dysfunction, left ventricular ejection fraction

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