



# Clinical Applications of Strain Echocardiography: A Clinical Consensus Statement From the American Society of Echocardiography Developed in Collaboration With the European Association of Cardiovascular Imaging of the European Society of Cardiology

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| Abbreviations                 |
|-------------------------------|
| <b>2D</b> = Two-dimensional   |
| <b>3D</b> = Three-dimensional |

1. INTRODUCTION

The past two decades have brought significant advances in the quantification of myocardial

|                                                                |
|----------------------------------------------------------------|
| <b>3DE</b> = Three-dimensional echocardiographic               |
| <b>4CV</b> = 4 chamber view                                    |
| <b>AF</b> = Atrial fibrillation                                |
| <b>AI</b> = Artificial intelligence                            |
| <b>AMI</b> = Acute myocardial infarction                       |
| <b>AR</b> = Aortic regurgitation                               |
| <b>ARVC</b> = Arrhythmogenic right ventricular cardiomyopathy  |
| <b>AS</b> = Aortic stenosis                                    |
| <b>ASE</b> = American Society of Echocardiography              |
| <b>AVC</b> = aortic valve closure                              |
| <b>AVR</b> = Aortic valve replacement                          |
| <b>BNP</b> = Brain natriuretic peptide                         |
| <b>CHD</b> = Congenital heart disease                          |
| <b>CMR</b> = Cardiac magnetic resonance imaging                |
| <b>CRT</b> = Cardiac resynchronization therapy                 |
| <b>CTRCD</b> = Chemotherapy-related cardiac dysfunction        |
| <b>EACVI</b> = European Association of Cardiovascular Imaging  |
| <b>EF</b> = Ejection fraction                                  |
| <b>GLS</b> = Global longitudinal strain                        |
| <b>HCM</b> = Hypertrophic cardiomyopathy                       |
| <b>HF</b> = Heart failure                                      |
| <b>HFimpEF</b> = Heart failure with improved ejection fraction |
| <b>HFpEF</b> = Heart failure with preserved ejection fraction  |
| <b>HFrEF</b> = Heart failure with reduced ejection fraction    |
| <b>LA</b> = Left atrial                                        |
| <b>LAScd</b> = Left atrial conduit strain                      |
| <b>LASct</b> = Left atrial contractile strain                  |
| <b>LASr</b> = Left atrial reservoir strain                     |

mechanics. The advent of two-dimensional (2D) speckle-tracking echocardiography (STE) in the early 2000s complemented tissue Doppler-based velocity measures in evaluating myocardial function. In 2011, a collaboration between the American Society of Echocardiography (ASE) and the European Association of Echocardiography, now the European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology, produced a consensus statement focused mainly on the physics and instrumentation issues involved in a variety of emerging techniques to assess cardiac mechanics,<sup>1</sup> particularly myocardial strain. There was relatively little experience with strain assessment in routine clinical practice, leading to few concrete statements for clinical use in specific settings. In the intervening years, though, there has been an explosion of clinical trials leading to thousands of publications documenting the prognostic importance of strain assessment of all cardiac chambers. Contemporaneous data assessing speckle-tracking application in daily clinical practice, suggests an underuse of this technology.<sup>2</sup> Accordingly, the ASE and EACVI have again commissioned a clinical consensus statement on strain, this time meant to focus primarily on areas of documented clinical utility. Each society named a roster of authors, along with additional members of the writing committee from Japan, Korea, and Australia. This document was never intended to provide a comprehensive review of the science and practice of strain imaging. For that purpose, the reader is directed to a recent book from ASE covering all of strain imaging<sup>3</sup> and a host of review articles addressing specific applications of strain imaging, including heart failure (HF),<sup>4</sup> systolic dysfunction,<sup>5</sup> diastolic dysfunction,<sup>6</sup> cardio-oncology,<sup>7</sup> valvular heart disease,<sup>8</sup> congenital heart disease (CHD),<sup>9</sup> right ventricular (RV)

**LLN** = Lower limit of normal  
**LS** = Longitudinal strain  
**LV** = Left ventricular  
**LVAD** = Left ventricular assist device  
**LVEF** = Left ventricular ejection fraction  
**LVGLS** = Left ventricular global longitudinal strain  
**LVMD** = Left ventricular mechanical dispersion  
**MI** = Myocardial infarction  
**MR** = Mitral regurgitation  
**MS** = Mitral stenosis  
**MVC** = mitral valve closure  
**PAH** = Pulmonary arterial hypertension  
**PH** = Pulmonary hypertension  
**PSL** = Pressure-strain loop  
**RA** = Right atrial  
**RASr** = Right atrial reservoir strain  
**ROI** = Region of interest  
**RV** = Right ventricle/ventricular  
**RVEF** = Right ventricular ejection fraction  
**RVFWLS** = Right ventricular free wall longitudinal strain  
**SAHF** = Stage A heart failure  
**SBHF** = Stage B heart failure  
**SD** = Standard deviation  
**SLS** = Segmental longitudinal strain  
**STE** = Speckle-tracking echocardiography  
**STEMI** = ST-segment elevation myocardial infarction  
**TAPSE** = Tricuspid annular plane systolic excursion  
**TDI** = Tissue Doppler imaging  
**TOF** = Tetralogy of Fallot  
**TR** = Tricuspid regurgitation  
**WASE** = World Alliance Societies of Echocardiography

function,<sup>10</sup> left atrial (LA) function,<sup>11</sup> general principles,<sup>12</sup> and extension to three-dimensional (3D) imaging.<sup>13</sup>

For this document, the writing committee was divided on the basis of expertise and interest into small subgroups to address each of the technical and clinical areas. Each subgroup developed clinical advice for application of strain imaging with brief supporting statements. The committee then was presented with these clinical advice points and asked to affirm them or suggest alternatives. The draft document was then reviewed by the respective committees of the sponsoring societies with comments and criticisms requiring responses from the writing committee. Finally, the boards of directors of the ASE and EACVI provided approval for publication of this consensus document.

The purpose of this document is multifold. First, it is meant to guide clinical echocardiographers in the applications of strain with clear supporting evidence for its use. Second, updated clinical advice should encourage the hardware and software industries to develop improved algorithms. Third, it provides guidance to payers as to which applications of strain are most worthy of reimbursement. Finally, gaps in the technology and evidence base are identified in hopes of inspiring new developments and applications in the field. The clinical advice is based on expert opinion, as extensive randomized controlled trials using strain-based measures do not exist within this space. The document itself is organized into modules facilitating updates in specific advice as new evidence is published. The initial section covers technical developments since 2011 with emphasis on the EACVI-ASE Strain Standardization Task Force.<sup>14,15</sup>

The next section addresses the critical issue of establishing normal ranges in strain, particularly left ventricular global longitudinal strain (LVGLS). The bulk of the document discusses clinical applications for strain, including HF, cardio-oncology, ischemia, valvular heart disease, the right ventricle, the left atrium, exercise and dobutamine stress applications, and CHD. Table 1 provides a broad overview

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**Table 1** Endorsed clinical indications for strain utilization

| Clinical scenarios in which strain may be appropriate                 | Type of strain and consensus advice | Clinical value              |
|-----------------------------------------------------------------------|-------------------------------------|-----------------------------|
| Acute and chronic MI                                                  | LVGLS                               | +++ Diagnosis and prognosis |
|                                                                       | RVFWLS                              | +++ Diagnosis and prognosis |
|                                                                       | LASr                                | ++ Prognosis                |
|                                                                       | LVMD                                | ++ Prognosis                |
|                                                                       | LVMW                                | – Not enough evidence       |
| Cardio-oncology                                                       | LVGLS                               | +++ Diagnosis and prognosis |
|                                                                       | RVFWLS                              | ++ Prognosis                |
|                                                                       | LASr                                | ++ Prognosis                |
|                                                                       | LVMD                                | – Not enough evidence       |
|                                                                       | LVMW                                | – Not enough evidence       |
| Valvular heart disease ≥ moderate severity single or multiple lesions | LVGLS                               | +++ Prognosis               |
|                                                                       | RVFWLS                              | +++ Prognosis               |
|                                                                       | LASr                                | ++ Prognosis                |
|                                                                       | LVMD                                | – Not enough evidence       |
|                                                                       | LVMW                                | – Not enough evidence       |
| Undifferentiated cardiomyopathy                                       | LVGLS                               | +++ Diagnosis and prognosis |
|                                                                       | RVFWLS                              | +++ Diagnosis and prognosis |
|                                                                       | LASr                                | +++ Diagnosis and prognosis |
|                                                                       | LVMD                                | ++ Prognosis                |
|                                                                       | LVMW                                | – Not enough evidence       |
| Acute and chronic HF                                                  | LVGLS                               | +++ Diagnosis and prognosis |
|                                                                       | RVFWLS                              | +++ Diagnosis and prognosis |
|                                                                       | LASr                                | +++ Diagnosis and prognosis |
|                                                                       | LVMD                                | ++ Diagnosis and prognosis  |
|                                                                       | LVMW                                | – Not enough evidence       |
| CRT                                                                   | LVGLS                               | +++ Diagnosis and prognosis |
|                                                                       | RVFWLS                              | +++ Diagnosis and prognosis |
|                                                                       | LASr                                | ++ Prognosis                |
|                                                                       | LVMD                                | – Not enough evidence       |
|                                                                       | LVMW                                | – Not enough evidence       |
| Athlete's heart                                                       | LVGLS                               | +++ Diagnosis and prognosis |
|                                                                       | RVFWLS                              | +++ Diagnosis and prognosis |
|                                                                       | LASr                                | ++ Diagnosis and prognosis  |
|                                                                       | LVMD                                | ++ Diagnosis and prognosis  |
|                                                                       | LVMW                                | – Not enough evidence       |
| PH                                                                    | LVGLS                               | +++ Diagnosis and prognosis |
|                                                                       | RVFWLS                              | +++ Diagnosis and prognosis |
|                                                                       | LASr                                | ++ Diagnosis                |
|                                                                       | LVMD                                | – Not enough evidence       |
|                                                                       | LVMW                                | – Not enough evidence       |
| Stress echocardiography                                               | LVGLS                               | ++ Diagnosis and prognosis  |
|                                                                       | RVFWLS                              | ++ Diagnosis and prognosis  |
|                                                                       | LASr                                | ++ Diagnosis                |
|                                                                       | LVMD                                | – Not enough evidence       |
|                                                                       | LVMW                                | – Not enough evidence       |
| Adult CHD                                                             | LVGLS                               | ++ Prognosis                |
|                                                                       | RVFWLS                              | ++ Diagnosis and prognosis  |
|                                                                       | LASr                                | – Not enough evidence       |
|                                                                       | LVMD                                | – Not enough evidence       |
|                                                                       | LVMW                                | – Not enough evidence       |

LVMW, LV myocardial work; +++, clinically endorsed; ++, may be appropriate; –, not currently endorsed.

of the writing committee's suggested high-yield scenarios for when to use strain in day-to-day clinical practice. Finally comes a section on future directions, which we hope will inspire clinicians and engineers to maintain the pace of development in this exciting field.

## 2. BRIEF TECHNOLOGY UPDATES FROM 2011 GUIDELINE

### A. Vendor Dependency and Results of the Strain Standardization Task Force

Beginning around 2010, increasing clinical use of speckle-tracking revealed relatively poor reproducibility when strain was calculated using echocardiographic equipment from different vendors.<sup>16,17</sup> Recognizing the need for standardization, the EACVI and ASE invited technical representatives from interested vendors to participate in a task force aiming to reduce the intervendor variability of strain measurements. The task force convened for the first time at EuroEcho in Copenhagen 2010 and has since then had regular meetings at annual scientific sessions of both societies.<sup>18</sup>

In 2015, a consensus statement was released to communicate technical definitions of various terms, parameters, and methods commonly used in myocardial deformation imaging,<sup>15</sup> such as geometric definitions of the myocardial region of interest (ROI) and its segments; interpretation of the terms *endocardial strain*, *epicardial strain*, and *midwall strain* as deformation of lines along the endocardium, the epicardium, and the middle of the wall; mathematical definitions of parameters measuring motion, deformation, and rotational mechanics; as well as aspects of postprocessing of strain data and the timing of measurements. Although this document focused on the left ventricle, a second statement with focus on the RV and atrial strain measurements was released in 2018.<sup>14</sup>

Currently, the definition of myocardial tracking regions differs substantially among vendors. Although endocardial tracking, combined endocardial and epicardial tracking, and midwall/full-wall tracking are equally feasible and reproducible,<sup>19</sup> evidence is increasing that midwall strain measurements based on full-wall tracking are less susceptible to suboptimal image geometry and abnormal myocardial shapes.<sup>20,21</sup> This approach also appears as the most robust, since the ROI comprises a greater number of myocardial features/speckles that can be tracked. Finally, the vast majority of normative and clinical data use the midwall/full-wall approach. Therefore, this writing committee supports the midwall/full-wall approach as the preferred method moving forward. We further encourage vendors to standardize strain algorithms accordingly.

For longitudinal strain (LS) measurements, a layer-specific strain analysis is technically challenging because of the small number of speckles across the wall and the limited lateral resolution of the image. It does not provide added value as all layers are tightly coupled and shorten roughly the same.<sup>22</sup> Radial thickening and, to a lesser extent, circumferential shortening might provide added information in non-transmural disease, but there is currently no evidence for clinical use.

An intervendor study comparing global LS (GLS) measurements obtained from seven different echocardiography hardware vendors and two additional software vendors revealed intervendor differences in strain values but very good reproducibility in test-retest scenarios with equipment from the same vendor.<sup>23</sup> Consequently, strain has been strongly endorsed as a feasible complementary parameter of left ventricular (LV) function in the updated chamber quantification guidelines. Different strain values per vendor in combination with differing vendor-specific measurement variability, however, resulted in small but relevant differences in the proposed lower limit of normal (LLN) GLS for each vendor.<sup>24</sup> Of note, strain values may shift slightly with different software versions from the same vendor. Therefore, the task

force advises following a particular patient with software from the same company to reduce this potential source of variability.<sup>25</sup>

In a second intervendor study investigating only patients with myocardial infarction (MI) with cardiac magnetic resonance imaging (CMR)-defined scar, segmental LS (SLS) measurements were found to have a markedly higher measurement variability than did GLS,<sup>26</sup> likely related to differences in spatial smoothing of regional strain. Marked intervendor differences in the ability to differentiate scar from normal myocardium were also noted.<sup>27</sup> A recent study showed significant variation between two vendors in the measured relative sparing of measured apical strain commonly used in detection of amyloid, again likely due to differences in spatial smoothing.<sup>28</sup>

Among the studies reporting on normal ranges of GLS, there has been variability among the utility of end-systolic LS vs peak systolic LS.<sup>29,30</sup> Despite this, the writing committee maintains its stance that end-systolic LS (obtained at AVC) be reported as the default parameter for GLS.<sup>15</sup> If alternative timings are used, these need to be explicitly reported to avoid confusion.

Several vendors have released dedicated tracking software for the right ventricle and left and right atria. Compared with a manual adaptation of an ROI of LV software to the differing shape of the right ventricle and left and right atria, the use of dedicated software results in comparable measurement values but significantly improves the measurement feasibility and reproducibility.<sup>31</sup>

In most pathologies, regional dysfunction results in pronounced changes in the time course and shape of myocardial deformation, so that a detailed shape and/or time analysis of SLS curves becomes more relevant than pure peak strain values (Figure 1). Consequently, attention to the correct timing of end-diastole and end-systole is very important when quantifying strain.<sup>32</sup> Regional strain is not supported by the Task Force, because of significant interobserver, intraobserver, and intervendor variability.

Additionally, a third intervendor study has been recently conducted with the aim to quantify differences that may be present in chamber specific functions and contemporary editions of strain packages. Results indicate that there has been a gratifying convergence of strain measurements from major vendors. Furthermore, most vendors do now also support the measurement of midwall/full-wall strain.<sup>33</sup>

Finally, in publishing values of strain, much discussion has surrounded the use of the negative sign prefacing strain values. The Task Force appreciates the theoretical and practical implications of this denomination when presenting strain data and advises as follows:

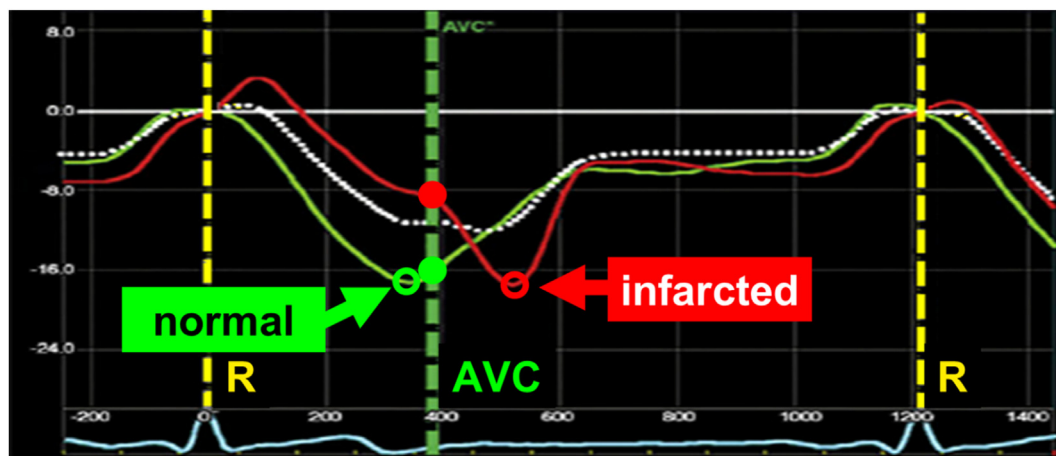
1. If presenting segmental values of strain, the negative sign should be kept for differentiating dyskinetic from normal myocardial contractility.<sup>34</sup>
2. If presenting GLS, it is advised that the negative sign be used.<sup>34</sup>
3. If the negative sign is omitted, then the term *global longitudinal shortening* should be used to correctly refer to the values presented and should be communicated accordingly in the methodology of scientific papers.<sup>34</sup>

### Key Points

- For LS measurements, a layer-specific strain analysis is technically challenging and cannot be expected to provide added value as all layers are tightly coupled to each other and shorten roughly the same.
- In regional disease, timing becomes important, and strain curve shape analysis may be the preferred approach.

### Clinical Consensus Statements

1. GLS is robust and reproducible using most vendors' software and should be used as a complementary parameter of global LV function.



**Figure 1** Time and shape representation of normal compared with infarcted myocardial segmental regional strain curve differences. SLS curves from a normal myocardial segment (green) and an infarcted segment (red). Note the similar peak strain of both curves (open circles). A distinction is only possible via a shape analysis. The infarct segment shows early systolic stretching and reduced end-systolic strain (full circle), while there is a marked postsystolic strain after aortic valve closure (AVC). Reproduced with permission from Mada *et al.*<sup>32</sup>

2. The vast majority of normative and clinical data use the midmyocardial/full-thickness approach, which should be the preferred method moving forward. In general, strain values from the midwall should be reported.
3. It is advised that GLS measurements should by default be reported as end-systolic LS.
4. Radial strain performed poorly in the intervivor studies and is not endorsed for clinical use at this time.
5. GLS values from different vendors have converged in recent years. Although follow-up of a patient should ideally be done with tracking software from the same company and the same release version, in many cases alternative vendors may also be used with care.
6. The performance of different vendors for regional strain measurements varies considerably, and vendor consistency for an individual patient is advised.
7. When presenting segmental strain values, the negative sign should be kept to differentiate dyskinetic from normal myocardial contractility.
8. When presenting global strain values, the negative sign should in general be used.
9. To improve communication with multidisciplinary medical and allied health colleagues, the negative sign may be omitted, but only if fully explained in the methodology using the term *global longitudinal shortening*.
10. When available, the use of dedicated RV and atrial strain software should be preferred over adapting the ROI for LV software.

## B. Tissue Doppler Imaging vs STE

Speckle-tracking echocardiographic assessment of myocardial function, in particular GLS, has been rapidly adopted by clinicians. However, tissue Doppler imaging (TDI), except for early diastolic mitral annular velocity ( $e'$ ) and RV annular velocity ( $S'$ ), has generally remained a research tool. Although STE is convenient to use and provides smooth deformation curves it is important to note that these may be affected by regularization algorithms. During postprocessing it is crucial to compare the tracking result with the underlying myocardial motion to identify regions where the software is not tracking myocardium appropriately.<sup>15</sup> TDI data have excellent temporal and spatial resolution but may appear frequently noisy. However, this superior temporal resolution allows more reliable identification of artifacts, in comparison with strong post-processing algorithms in speckle-tracking, which may smooth out data in areas where tracking has failed.

Therefore, during clinical routine imaging, TDI is advantageous for a fast evaluation of a single region and the comparison of curve shapes among myocardial segments. Furthermore, TDI can measure strain and strain rate. Speckle-tracking allows an easy evaluation of an entire chamber and is the preferred approach for GLS measurements and

other advanced postprocessing, including bullseye displays of different function parameters. It must be remembered, however, that it lacks sufficient temporal resolution for accurate velocity and strain rate measurements when used on standard 2D images from the clinical routine which rarely exceed 70 frames/s. Mastering either technique requires a similar amount of training.<sup>35,36</sup>

Recent advances in imaging technology enable the acquisition of 2D image data at frame rates of  $\geq 500$  frames/s (plane wave imaging, diverging wave imaging). This offers the possibility to perform STE at frame rates that were so far only available from TDI and may result in more accurate strain rate and velocity quantitation with STE.<sup>37</sup> However, this remains in the realm of research and is not clinically endorsed at this stage.

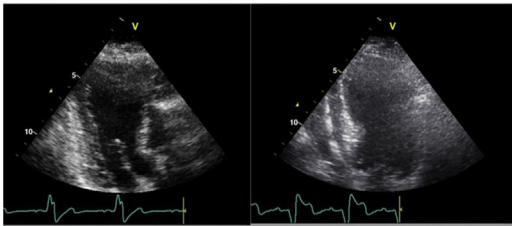
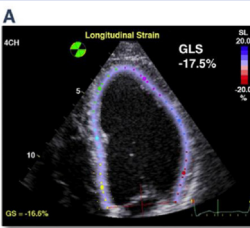
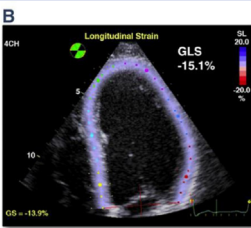
## Key Points

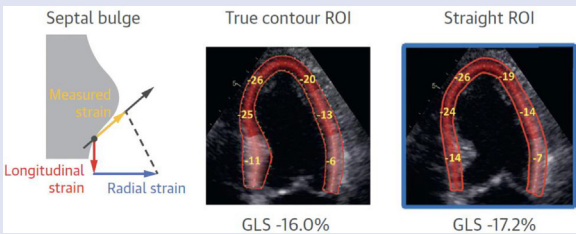
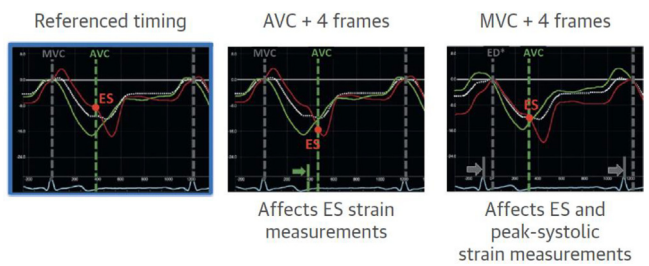
- Deformation imaging based on STE is the method of choice for a rapid and comprehensive functional assessment of the entire ventricle.
- Deformation imaging based on TDI-derived strain is advantageous for rapid evaluation of single ROIs.
- TDI has superior temporal resolution over STE, thus allowing more reliable peak velocity and peak strain rate measurements.
- Researchers and industry are encouraged to continue efforts to increase frame rates of STE.

## C. Clinical Advice for Avoiding Technical Pitfalls in Strain Acquisition

Significant advances in the field of strain imaging have resulted in vendors developing nearly fully automated workflows for strain quantification. These steps have resulted in substantial declines in inter- and intraobserver variability for the quantification of LVGLS, RV free wall LS (RVFWLS), and LA strain.<sup>26,27,31</sup> Despite this there are pervasive technical pitfalls that can affect the accuracy of strain quantification which are related to image quality/acquisition, ROI selection, algorithm-based myocardial tracking errors, user definitions of end-diastole/end-systole, extremes of blood pressure affecting preload/afterload and rhythm associated irregularities during quantification. For a comprehensive list of pitfalls and endorsed tips for avoiding these, refer to Table 2. Briefly, the writing committee brings the

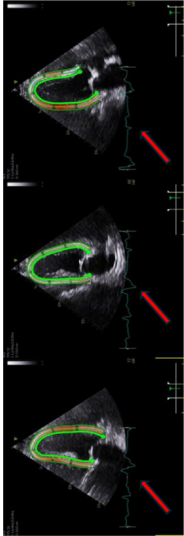
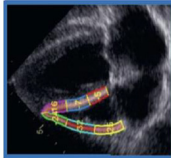
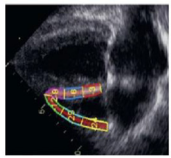
**Table 2** Common pitfalls and corresponding clinical advice for strain acquisition and quantification

| LV strain technical pitfall                                                           | Effect on strain measurement                         | Example                                                                                                                                                                                                                                                                                                     | Clinical advice                                                                                                                                                                                  |
|---------------------------------------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Foreshortening of the LV apical windows                                               | Erroneously increases apical segmental strain values | <div> <div> <p><b>Foreshortened 4CV</b></p>  <p>GLS -20.8%</p> </div> <div> <p><b>Optimal 4CV</b></p>  <p>GLS -16.8%</p> </div> </div> | Avoid using foreshortened LV images for strain quantification and ensure the true apex is visualized during acquisition.                                                                         |
| Poor visualization of myocardium and/or endocardial to blood interface in LV segments | Poor endocardial/myocardial tracking                 |                                                                                                                                                                                                                           | Do not incorporate segments with areas of poor image quality and tracking into global strain calculations (if overall more than three segments are uninterpretable, do not report LVGLS values). |
| Using excessively large myocardial ROI                                                | Underestimating strain values                        | <div> <div> <p><b>A</b></p>  <p>Optimal ROI</p> </div> <div> <p><b>B</b></p>  <p>ROI too large</p> </div> </div>                     | Ensure that only the full myocardial wall is included in the ROI, as inclusion of the pericardium artificially lower strain values.                                                              |

|                                                                      |                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Using excessively small myocardial ROI                               | Overestimating strain values                                                                                                                                                                                                            |  <p>Hypertrophic LV</p> <p>Too thin ROI<br/>GLS -12.1%</p> <p>Optimal ROI<br/>GLS -10.5%</p>                                                                   | Particularly in hypertrophic hearts, ensure inclusion of the full wall in the ROI. Otherwise the ROI reflects rather a layer (here subendocardial, overestimating full-wall strain).                                                                                                                                                       |
| Including local abnormalities in chamber geometry and wall thickness | When a septal bulge or a similar structure is present in other regions of the ventricle, radial strain may become dominant, potentially resulting in a net positive systolic strain when using STE on images acquired from apical views |  <p>Septal bulge</p> <p>Measured strain</p> <p>Longitudinal strain Radial strain</p> <p>True contour ROI<br/>GLS -16.0%</p> <p>Straight ROI<br/>GLS -17.2%</p> | To accurately assess longitudinal shortening in the presence of localized thickening of the LV wall, the ROI should be drawn in a straight, longitudinal direction, avoiding significant local bulges. However, if the wall thickening extends across more than one full segment, we advise including the thickened region within the ROI. |
| Inaccuracies in defining end-diastole and end-systole                | Either increase or decrease strain depending on where the segmental curve peaks/troughs start and finish in the cardiac cycle                                                                                                           |  <p>Referenced timing</p> <p>AVC + 4 frames<br/>Affects ES strain measurements</p> <p>MVC + 4 frames<br/>Affects ES and peak-systolic strain measurements</p> | End-diastole and with it zero strain should correspond to MVC. End-systole should correspond with AVC. If necessary, timing should be manually adjusted on the basis of direct observation of the mitral and AVC or through spectral Doppler evaluation.                                                                                   |
| Using only a single cycle when quantifying strain in AF              | Over- or underestimation of strain values depending on the preceding filling phase                                                                                                                                                      |                                                                                                                                                              | Strain values depend on the length of the preceding filling phase. Consider averaging several cycles, or measure the third of three consecutive cycles with approximately the same length.                                                                                                                                                 |

(Continued)

Table 2 (Continued)

| LV strain technical pitfall                                        | Effect on strain measurement                                                                                                                                                                                                                           | Example                                                                                                                                                                                                                                                                           | Clinical advice                                                                 |
|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Acquisition of strain images during ventricular ectopic beats      | Over- or underestimation of strain values depending on the preceding filling phase                                                                                                                                                                     |                                                                                                                                                                                                 | Avoid performing strain analysis on immediate postectopic beats.                |
| Using the conventional four-chamber view for RVFWLS quantification | Underestimation of RVFWLS values because of differences in RV free wall assessment; the segments of the RV free wall more distant to the interventricular septum undergo the greatest longitudinal deformation and are captured in the RV-focused view | <div><div>Conventional 4CV</div><div>FW LS -20.1%</div><div>RV-focused view</div><div>FW LS -26.2%</div></div> | Advise using the apical four-chamber focused RV view for RVFWLS quantification. |

Images adopted and reproduced with permission from Smiseth *et al.*<sup>11</sup> and Negishi *et al.*<sup>38</sup>

reader’s attention to excellent resources that provide comprehensive overviews on these technical topics for LV strain,<sup>11,38</sup> RV strain,<sup>39</sup> and LA strain<sup>40</sup> quantification.

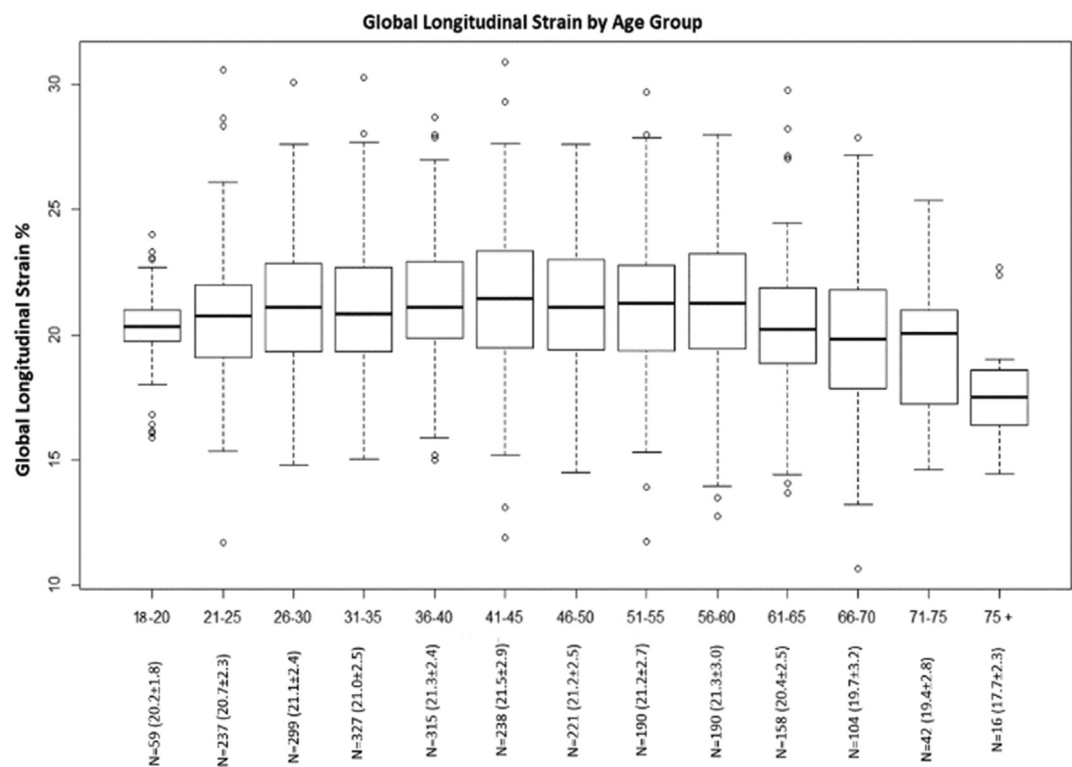
3. NORMAL RANGES OF STE-DERIVED STRAIN

Normal ranges should be defined from large numbers of normal volunteers from the community. The risk of including “convenience samples” of normal echocardiograms from standard echocardiographic practice is that a referral for echocardiography is provoked by some symptom. An individual patient meta-analysis of >2,300 people studied predominantly using the General Electric system (and hence midwall/full-wall strain)<sup>29</sup> provides information about variance (and therefore range) that cannot be identified from traditional meta-analyses (Figure 2). The mean GLS was –21%, with an SD of 2.6%, implying that only 2.5% of normal people have myocardial GLS less negative than –15.9%, and 32% are less negative than –18.4%. As endocardial strain has higher absolute values than myocardial strain, it is not surprising that the lower limit cutoff from the World Alliance Societies of Echocardiography (WASE) study, which used endocardial strain with TomTec, was –17% in men and –18% in women,<sup>41</sup> in contrast to –16% observed by D’Elia *et al.*<sup>29</sup> More recently, Morris *et al.*<sup>42</sup> performed the most comprehensive meta-analysis of LVGLS across 47 studies including 23,208 healthy adults. That study identified –16% as the LLN for LVGLS across major software vendors and demonstrated its prognostic relevance among a large independent sample of at risk for HF and elderly subjects.<sup>42</sup>

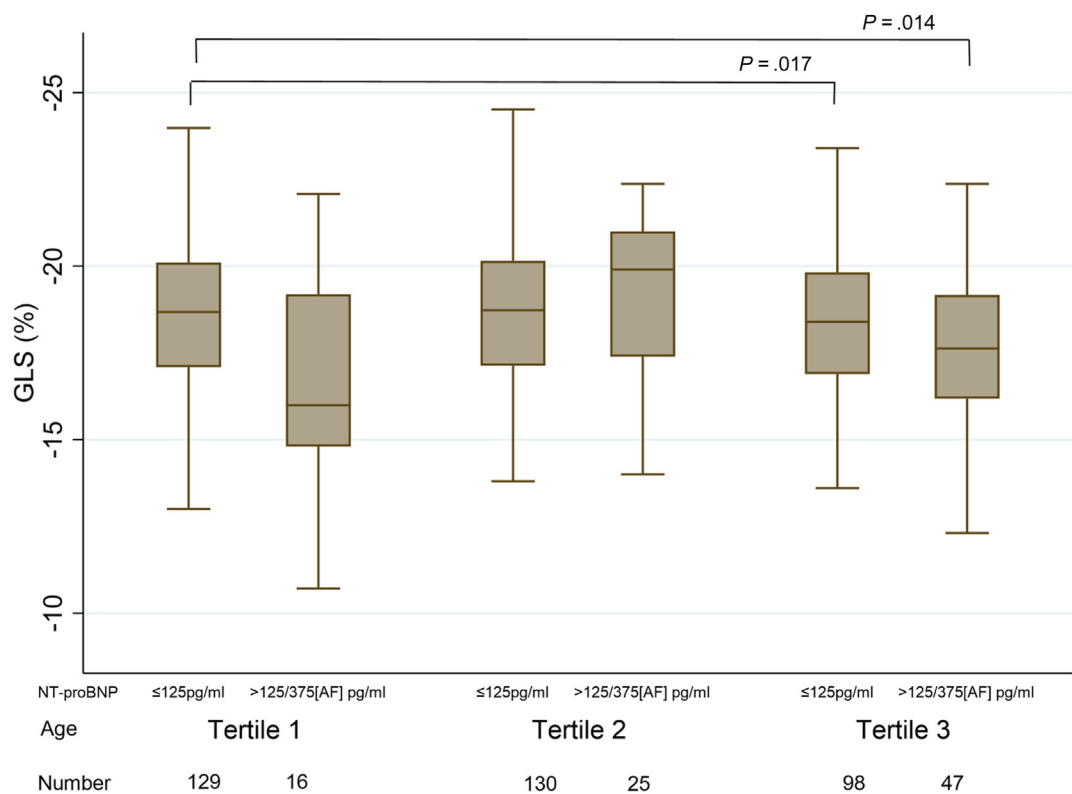
Interindividual variation has been attributed to loading conditions, age, and gender.<sup>43,44</sup> Race does not seem to make a major contribution, with similar limits in different countries reported in the WASE studies.<sup>41</sup> In a group of elderly subjects (age > 65 years) with risk factors, the impact of age was explained by the comorbidities that are associated with increasing age (Figure 3).<sup>45</sup> Normal ranges of strain have been reported in children. However, these are beyond the scope of this document and will be reported in separate dedicated pediatric guidelines.<sup>46,47</sup>

Both acquisition equipment and analysis software should have a potentially important impact on GLS, though the EACVI-ASE Strain Standardization Task Force has successfully minimized these differences with less intervender variation than many standard linear and Doppler measurements.<sup>23</sup> As mentioned above, some manufacturers quote GLS as myocardial and others as endocardial strain, the latter having about 1% greater absolute magnitude than the former. Studies performed on different vendors’ machines, for the same patient across sequential studies, should ideally have GLS compared by use of vendor-independent software. Comparison of studies performed with software from one manufacturer should again be ideally measured using the same software version. Furthermore, when considering regional and segmental strains, a study of 58 patients who had regional strain measured on multiple vendors showed that SLS measurements vary significantly among vendors (Figure 4).<sup>22,26</sup>

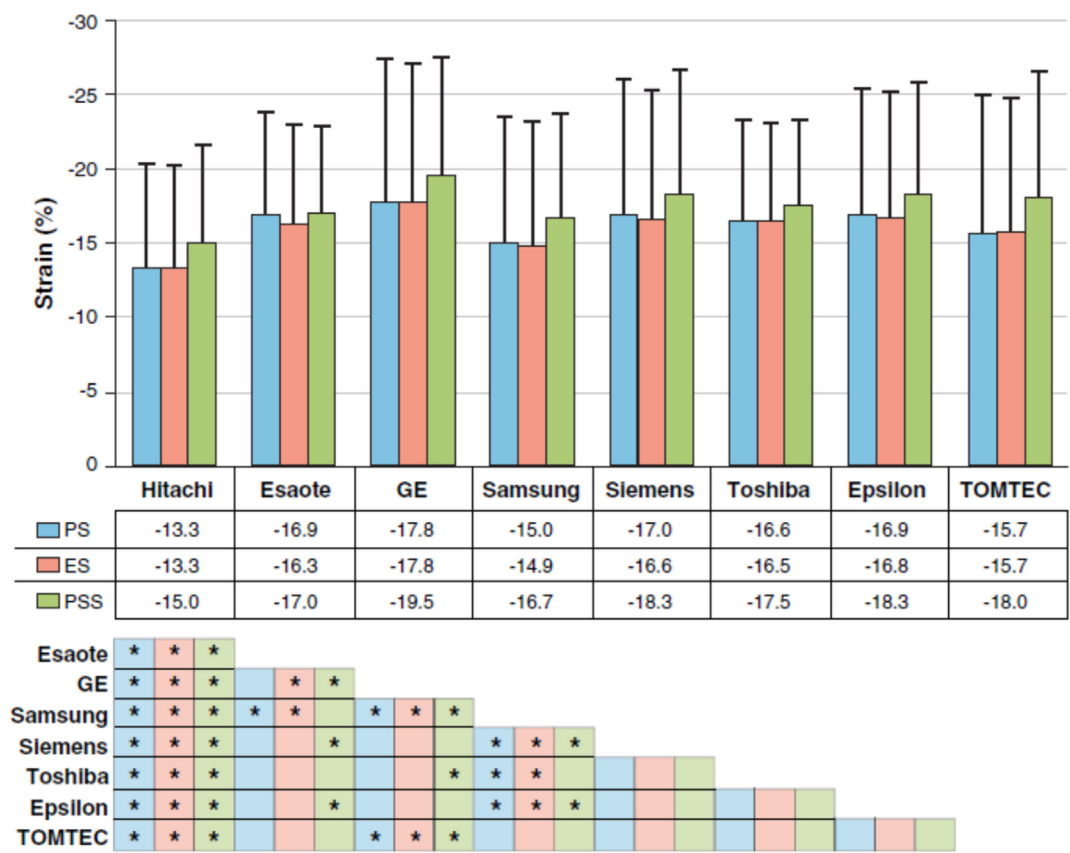
Test-retest variation (the change in a parameter over sequential measurement in a stable person) is the core metric that determines the use of GLS in follow-up.<sup>48</sup> The EACVI/ASE Strain Standardization Task Force elegantly demonstrated in a multivendor study no statistically significant differences in test-retest variability of peak systolic or end-systolic strain measures<sup>23</sup> but this is not the case for segmental strain (Figure 5).<sup>26</sup> This has been best studied in the setting of potential cardiotoxicity, where a meta-analysis has



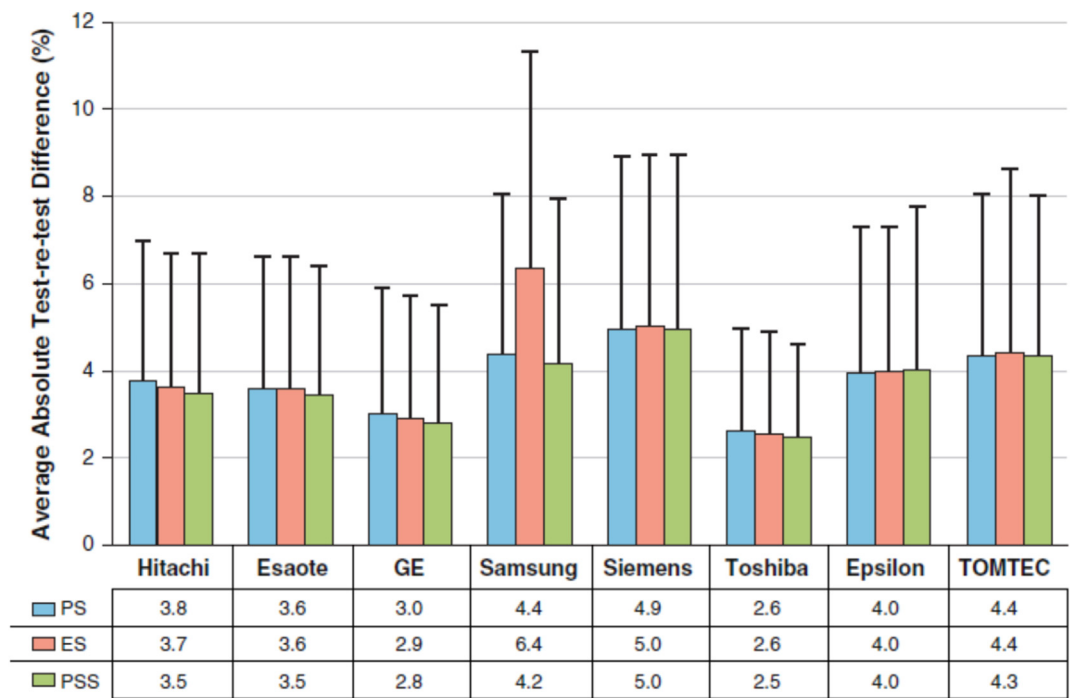
**Figure 2** Normal GLS. Normal range defined by individual-patient meta-analysis from eight recent studies (2,396 subjects; mean age, 42 years; mean weight, 66 ± 12 kg; mean height, 169 ± 9 cm; mean body surface area, 1.7 ± 0.2 m<sup>2</sup>; mean systolic blood pressure, 120 ± 13 mm Hg). GLS by age group; GLS progressively decreases after the age of 60 years but appears to be relatively stable up until this age. *White circles indicate outliers.*<sup>29</sup>



**Figure 3** GLS across advancing age tertiles subcategorized by elevated N-terminal pro-BNP (NT-proBNP). *Whiskers correspond to maximum and minimum values.*<sup>45</sup>



**Figure 4** Differences in regional LV strain measurements with different software. Different measurements of average segmental longitudinal peak strain (PS), end-systolic strain (ES), and postsystolic strain (PSS) LV strain are documented in the same patients. The table shows the significance ( $*P < .05$ ) of pairwise differences between vendors.<sup>26</sup>



**Figure 5** Test-retest differences of segmental longitudinal peak strain (PS), end-systolic strain (ES), and postsystolic strain (PSS) LV strain between different vendors. The minimum detectable differences between two measurements are large in relation to likely pathological changes.<sup>26</sup>

defined a relative change of 10% to 15% to predict the subsequent emergence of toxicity.<sup>49</sup> In a randomized trial of GLS-guided and ejection fraction (EF)-guided management, the initiation of cardioprotective therapy in response to a relative GLS change of 12% led to 5.8% of patients developing cardiotoxicity compared with 13.7% in the EF-guided arm.<sup>50</sup>

The normal range of RVFWLS ( $-26.4 \pm 4.2\%$ ; LLN,  $-18.2\%$ ) has been previously defined in >1,000 normal people. Women had more negative RVFWLS ( $-27.2 \pm 4.8\%$ ; LLN,  $-17.8\%$ ) and younger (age < 50 years) women had the most negative global RV LS (including both free wall and RV septal strain) values ( $-22.9 \pm 3.2\%$ ) compared with men.<sup>51</sup> Furthermore, data from the WASE study using a multinational, multisite cohort and vendor-neutral software demonstrated in 1,913 patients (981 men, 932 women) an overall RVFWLS of  $-28.3 \pm 4.3\%$  (LLN,  $-19.9\%$ ) and women having more negative values than men ( $-29.3 \pm 4.2\%$  [LLN,  $-21.1\%$ ] vs  $-27.3 \pm 4.1\%$  [LLN,  $-19.3\%$ ]).<sup>52</sup>

Normal LA strain has been reported in a meta-analysis of 2,542 healthy adult subjects in 40 studies.<sup>53</sup> Normal LA reservoir strain (LASr) was 39% (95% CI of the mean value, 38%-41%; from 40 articles), LA conduit strain (LAScd) was 23% (95% CI, 21%-25%; from 14 articles), and LA contractile strain (LASct) was 17% (95% CI, 16%-19%; from 18 articles). Meta-regression identified heart rate ( $P = .02$ ) and body surface area ( $P = .003$ ) as contributors to this heterogeneity. Subgroup analyses revealed heterogeneity due to sample size ( $n > 100$  vs  $n < 100$ ,  $P = .02$ ).

Supplemental Table 1 summarizes the normal reference values of global LA strain of the main studies. The normal LASr in healthy individuals is approximately 30% to 60%, with an LLN of 23%.<sup>53-56</sup> There was a significant decrease in all three LA strain parameters with increasing age irrespective of gender in most studies. In some studies, women had slightly higher values in youth, but showed a greater fall in LASr with aging.<sup>56,57</sup>

Three-dimensional strain has the attraction of being able to track through-plane movement but at the cost of lower temporal and spatial resolution than 2D strain. A meta-analysis of normal LV ranges of 3D strain has shown significant variation.<sup>58</sup> Normal ranges of twist, strain area, and other parameters also show unacceptable variability.<sup>59</sup>

### Clinical Consensus Statements

1. Normal LV myocardial GLS is more negative than  $-18\%$ . Borderline GLS is  $-16\%$  to  $-18\%$ . Abnormal GLS is less negative than  $-16\%$ .
2. Normal ranges of GLS are subject to changes in software version. Comparisons in GLS should ideally use the same software vendor and software version, care should be taken when comparing values derived from different vendors. Vendors are encouraged to maintain fidelity as software is updated.

3. The optimal use of LVGLS is in sequential follow-up, by comparison with baseline. Used in this way, a relative change of 10% to 15% is likely to be significant.
4. The use of 3D strain is still in development because of variabilities in software and inconsistent results and is not endorsed for clinical use.
5. Normal ranges of RV and LA strain have been defined and can be used, subject to the same qualifications of load dependence.
6. The LLN for RVFWLS is advised as  $-20\%$  in men and  $-21\%$  in women, and values less negative than these should be considered pathologic.
7. The most relevant LA strain parameter is reservoir strain with upper and lower limits of normal considered to be 23% and 60%. Borderline abnormal is considered between 23% and 30%.
8. Regional strain values show too much test-retest and intervender variability to be used clinically.

## 4. CLINICAL APPLICATIONS OF STRAIN

### A. HF

EF has traditionally been the most important parameter in HF imaging and remains the cornerstone. However, the detection of early disease, serial quantification of function, prediction of outcomes and decision-making about various interventions are all potentially benefited by the addition of strain (Table 3).

**a. Stages A and B HF.** Although a common problem, with a lifetime prevalence of about 20%, HF is not an inevitable consequence of aging but instead has multiple risk factors including hypertension, diabetes and obesity. Patients with these risk factors are considered to have stage A HF (SAHF).

Stage B HF (SBHF), which is essentially asymptomatic LV dysfunction, can be the natural progression of unresolved risk factors.<sup>60</sup> Traditionally, this has been defined based on previous infarction, LV remodeling, and asymptomatic valvular disease, all preludes to the development of HF with reduced EF (HFrEF). With HF with preserved EF (HFpEF) now accounting for more than half of all patients with HF, LV diastolic dysfunction, LA enlargement, and impaired LVGLS should be considered in this definition<sup>61</sup>; they are certainly linked with impaired functional capacity<sup>62</sup> and the prediction of incident HF.<sup>63</sup> These changes do not necessarily occur in unison; the "hypertensive" component appears to be associated with diastolic disturbance and may contribute to metabolic and fibrotic components resulting in impaired GLS with a basal to apex continuum.<sup>64,65</sup>

Impaired GLS is prognostically important in patients with hypertension,<sup>66</sup> diabetes,<sup>67</sup> and obesity.<sup>68</sup> In an echocardiographic examination performed in patients with these disease entities, LVGLS should be reported to provide further prognostic information.

**Table 3** Indications for use of LV strain in HF

|                 | Stage A                           | Stage B                                                                              | Stage C: HFpEF | Stage C: HFrEF | Stage D                        |
|-----------------|-----------------------------------|--------------------------------------------------------------------------------------|----------------|----------------|--------------------------------|
| Risk assessment | Association of strain and outcome |  |                |                |                                |
| Diagnosis       | Distinction of SAHF vs SBHF       | Is it HFpEF (vs noncardiac dyspnea)                                                  |                |                |                                |
| Management      | ICD decision-making               |   |                |                | eCRT implantation VAD vs BiVAD |
| Follow-up       | Cardiotoxicity                    | Recognition and follow-up of increased filling pressure                              |                |                | Adequacy of therapy            |

BiVAD, Biventricular ventricular assist device; ICD, implantable cardiac defibrillator; VAD, ventricular assist device.

Increased LV mass is not specific in terms of etiology; the most common causes are increased afterload (e.g., hypertension, aortic stenosis [AS]), myocardial disease (e.g., hypertrophic cardiomyopathy [HCM]), and infiltrative diseases. LVGLS is significantly impaired in primary myocardial disease and infiltration, and the distribution of abnormal strain may provide important clues to the etiologic diagnosis. For example, regional septal strain impairment may be seen in classical HCM, apical strain impairment in apical HCM, predominant basal to midsegment impairment in hypertensive heart disease, and prominent apical-sparing patterns of strain in cardiac amyloidosis (Figure 6).<sup>65,69</sup>

Although patients with abnormal LVGLS in the setting of hypertension,<sup>66</sup> diabetes,<sup>70</sup> and obesity<sup>68</sup> are at risk for HF,<sup>71</sup> there remains no evidence that screening for SBHF alters outcomes. Studies are needed to show that LVGLS-guided screening is useful for selecting patients for cardioprotective therapy, for HF prevention, and for enhancing the cost-effectiveness of treatment.

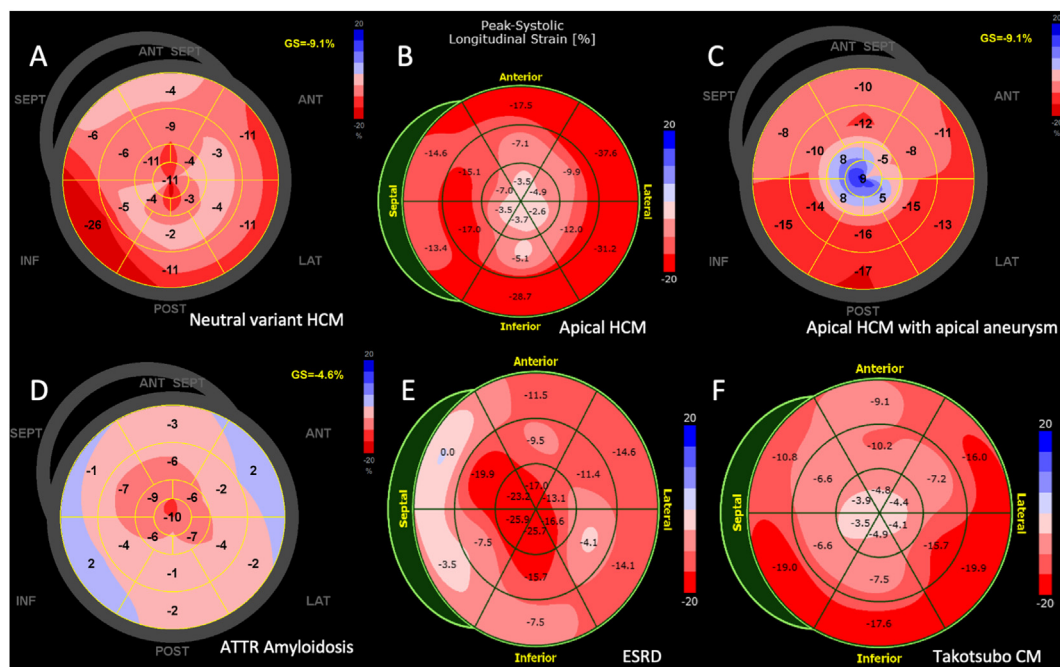
### Clinical Consensus Statements

1. Abnormal GLS (less negative than  $-16\%$ ) or borderline GLS ( $-16\%$  to  $-18\%$ ) in the presence of other echocardiographic abnormalities should be considered a marker of SBHF.
2. GLS should be obtained and reported in patients with increased LV mass, on the basis that an apical sparing of regional LS (mean of the apex  $>2$  times the mean of the rest of the heart) points toward the possibility of cardiac amyloidosis.
3. GLS is currently not advised for the screening of SAHF, but there may be some utility in the recognition and monitoring of treatment of SBHF.

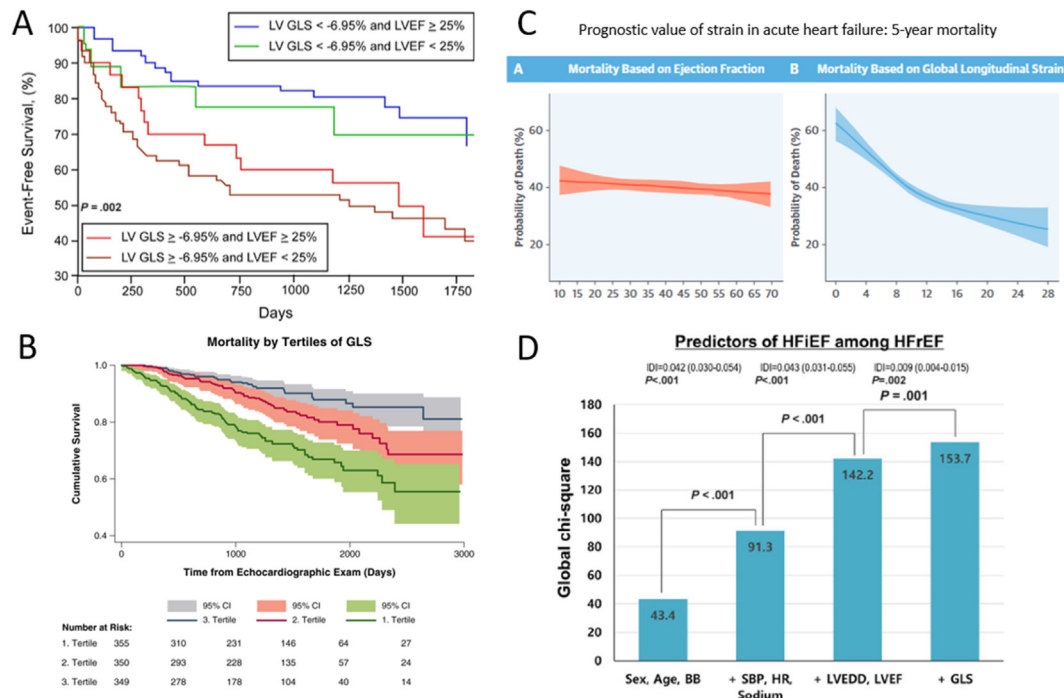
**b. Stages C and D HFrEF.** Although the frequency of HFrEF (LVEF  $< 40\%$ ) is decreasing with rising incidence of HF with improved EF (HFimpEF) and the evolution of novel therapies, HFrEF remains a leading cause of morbidity and mortality worldwide.<sup>72</sup>

LVEF itself is a significant prognostic factor in HFrEF, but it has inherent variability, influenced by image quality, off-axis imaging, and geometric assumptions.<sup>73</sup> Furthermore, LVEF changes over time. The advances in pharmacotherapy for HF, the introduction of cardiac resynchronization therapy (CRT), and the improved recognition of reversible causes of HF have contributed to the improvement of LVEF and outcomes. However, treatment response may vary, and a persistently reduced LVEF over time portends a worse prognosis.<sup>74</sup> Better understanding of the predictors of adverse outcomes in HFrEF may improve the quality of treatment and outcomes.

LVEF and LVGLS show a significant correlation, but for a given EF, LVGLS shows a wide distribution (see [Supplemental Table 2](#)).<sup>75</sup> LVGLS independently predicts outcomes after adjusting for clinical factors and conventional echocardiographic parameters.<sup>76,77</sup> Absolute LVGLS equal to or less negative than  $-6.95\%$  predicted worse long-term adverse events, including death, cardiac transplantation, and HF hospitalization, and each 1% decrease of LVGLS was associated with 15% increased odds for mortality in HFrEF. LVGLS also provides superior prognostic values than LVEF in predicting mortality.<sup>78</sup> Among patients with acute HF, moderate and severe LVGLS reductions correlated with higher mortality, but LVEF was not associated with mortality after multivariable analysis (Figure 7). LVGLS can also be used to predict the trajectory of LVEF in HFrEF. Each 1%



**Figure 6** Use of LV strain patterns to determine etiology of LV hypertrophy and HF. Despite the common 2D echocardiographic LV morphology of LV wall thickening, the strain maps show particular patterns suggestive of (A) neutral-variant HCM with relatively impaired septal function, (B) apical HCM demonstrating apical impairment, (C) apical HCM with apical aneurysm demonstrating apical dyskinesia, (D) transthyretin cardiac amyloidosis demonstrating a relative apical-sparing pattern, (E) end-stage renal disease (ESRD) with a pattern mimicking a relative apical-sparing pattern, and (F) takotsubo cardiomyopathy (CM) with impairment of the mid to apical segments but sparing of the basal segments. ANT, Anterior; ANT\_SEPT, anteroseptal; GS, global strain; INF, inferior; LAT, lateral; POST, posterior; SEPT, septal.



**Figure 7** Prognostic value of LVGLS in HFrEF. **(A)** Worsening LVGLS (less negative than  $-6.95\%$ ; red and brown line) predicted poorer long-term adverse events in patients with chronic HF regardless of whether LVEF was  $\geq 25\%$  or  $< 25\%$  ( $P < .05$  for both). **(B)** In a separate study, the risk for dying among patients with HFrEF increased with decreasing tertiles of GLS, being approximately 3 times higher for patients in the lowest tertile compared with patients in the highest tertile (tertile 1 vs tertile 3; hazard ratio, 3.38; 95% CI, 2.3-5.1;  $P < .001$ ). **(C)** In patients with acute HF, the estimated probability of 5-year all-cause mortality according to LVEF **(A)** and GLS **(B)**. Mortality decreased with decreased strain, but its relationship with LVEF was not prominent. **(D)** Incremental prognostic value of predictors by binary logistic regression model presented as a global  $\chi^2$  value. The addition of GLS offers a significant additional benefit over conventional parameters. BB, Beta-blocker; HR, heart rate; HFIEF, HF with improved EF; IDI, integrated discrimination improvement; LVEDD, LV end-diastolic diameter; SBP, systolic blood pressure. Reproduced with permission from Park et al.<sup>78,79</sup>, Janwanishstaporn et al.,<sup>80</sup> and Merlo et al.<sup>81</sup>

increase in absolute LVGLS (larger negative value, indicating greater contractility) was associated with 10% increased odds for improvement in LVEF above 40%, resulting in HFimpEF (LVEF  $\leq 40\%$  at baseline and improved to  $>40\%$  at follow-up; Figure 7D).<sup>79</sup> But even with LVEF recovery, impaired LVGLS is still a strong predictor for future HF events and deterioration in cardiac function.<sup>80,81</sup> These findings emphasize the need for routine assessment of LVGLS to improve risk stratification in echocardiographic follow-up for patients with HFrEF.

Recently, LASr and RVFWLS were also found to have strong prognostic relevance to adverse outcomes in HFrEF independent of LVEF and LVGLS (see Supplemental Tables 3 and 10).<sup>82-84</sup> In patients with end-stage HF requiring LV assist device (LVAD) implantation, RVFWLS is a better and stronger predictor of right HF after LVAD implantation than tricuspid annular plane systolic excursion (TAPSE).<sup>85,86</sup>

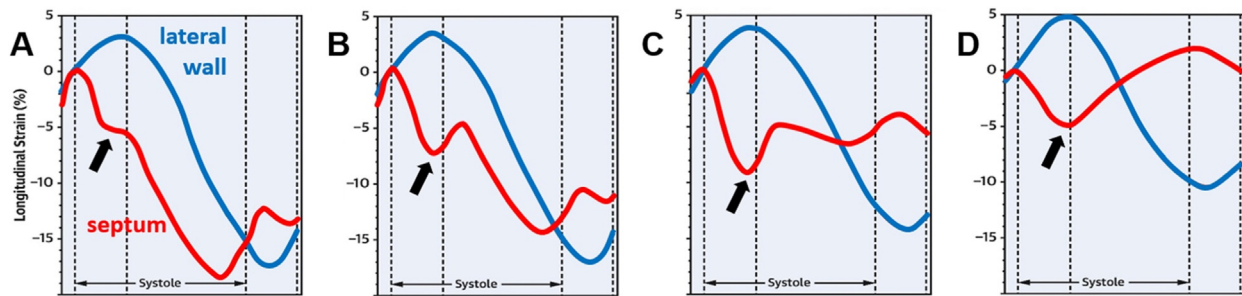
### Clinical Consensus Statements

1. LVGLS should be obtained and reported in patients with HFrEF for prognostication. Worse GLS is a strong predictor of adverse cardiac events.
2. Longitudinal follow-up of LVGLS is advised in patients with HFrEF and HFimpEF to predict future LV remodeling and outcome.
3. Assessment of RVFWLS may help predict RV dysfunction in patients undergoing implantation of LVADs.
4. Assessment of LASr and RVFWLS may provide additional prognostic information in patients with HFrEF.

**c. HFpEF.** HFpEF is a heterogeneous disorder with many etiologies, defined by an EF of  $\geq 50\%$  with some degree of impairment in diastolic, systolic, and microvascular functioning accompanied by reductions in exercise tolerance and symptoms of HF.<sup>87-89</sup> Myocardial deformation mechanics are particularly useful in identifying patients with HFpEF, as traditional echocardiographic LVEF lacks specificity.<sup>90</sup> LVGLS is usually impaired in patients with suspected HFpEF, and characteristic patterns of bull's-eye plots may point to specific etiologies in this patient population.<sup>91</sup> Furthermore, there is growing evidence to support the prognostic value of impaired LVGLS in patients with HFpEF, with incrementally impaired LVGLS portending a poorer prognosis.<sup>78,92</sup>

The translational effect of increased filling pressures and pulmonary vascular resistance, secondary to HFpEF, imparts increasing load on the right ventricle, which may become impaired in the advanced stages of etiologies that predominantly affect the left ventricle.<sup>87</sup> In infiltrative conditions resulting in HFpEF, RV dysfunction may be appreciated earlier in the disease course. Regardless, in HFpEF, RVFWLS is valuable for identifying early RV dysfunction, particularly in conjunction with elevated pulmonary artery pressures,<sup>93</sup> and for ongoing monitoring and prognosis.<sup>94</sup>

Because of the dynamic presentations of HFpEF, provocative maneuvers, such as stress testing, are usually employed in patients with suspected HFpEF. In this situation, strain-based parameters may enhance discriminative value.<sup>95</sup> Despite the emerging incorporation



**Figure 8** Strain-based staging of left bundle branch block (LBBB)-induced LV remodeling. **(A)** Early stage. The septal strain curve (red) shows a slight notch when the lateral wall (blue) starts contracting. **(B)** Progression of LBBB-induced remodeling with more pronounced notching in the septum. **(C)** Reduced septal function. **(D)** Advanced LBBB-induced remodeling. The septum stretches during lateral wall contraction. Septal flash (arrow) can be observed in all four stages because of the early septal longitudinal shortening.<sup>104-106</sup>

of strain-based parameters into the investigation and management of HFpEF patients, significant work is still required to better understand the utility of strain in risk stratifying patients with HFpEF, subphenotyping established diagnoses of HFpEF, and predicting the development of HFpEF within vulnerable populations. The impact and significance of LA dynamics and strain in HFpEF are discussed further in section 4.F.h.

#### Clinical Consensus Statements

1. LVGLS can aid in the diagnosis of HFpEF, helping distinguish this from other causes of dyspnea.
2. Worsening LVGLS and RVFWLS are associated with adverse outcomes in HFpEF. These may be used as prognostic factors.

**d. Cardiomyopathies vs Athlete's Heart.** STE provides valuable incremental information on myocardial function over and above LVEF and TDI. In competitive athletes undergoing strength-based activities, LV wall thickness tends to increase relative to chamber size and may mimic hypertensive or infiltrative phenotypes. LVGLS is usually relatively preserved in competitive athletes compared with equivalent LV wall thickness increase observed in pathologic concentric remodeling (see [Supplemental Table 4](#)).

In endurance-based exercises, increased LV chamber volume with relatively preserved LV wall thickness is observed and is accompanied by preserved LVGLS. This contrasts with reductions in LVGLS observed in inherited or valvular cardiomyopathic conditions with large LV volumes and eccentric remodeling.

Structural alterations are not limited to the left ventricle, and equivalent changes in chamber remodeling have been observed in the right ventricle and left atrium in competitive athletes. RV dilation in conjunction with LV dilation has been well documented in endurance athletes, and RVFWLS is relatively preserved compared with an age-matched general population.<sup>96</sup> This contrasts with age-matched patients with arrhythmogenic RV cardiomyopathy (ARVC) and those with HCM, in whom RVFWLS is frequently abnormal.<sup>97,98</sup>

It is not clear whether LA strain can differentiate the LA enlargement observed in endurance-based and strength-based athletes from LA enlargement seen in cardiomyopathy patients. LASr has been found to be significantly reduced in endurance-based competitive athletes compared with age-matched nonathlete populations in some studies but preserved in others.<sup>99</sup> Compared with cardiomyopathies, LASr was higher in competitive athletes.<sup>100</sup> Using LASr to distinguish adaptive remodeling in competitive athletes from adverse

remodeling secondary to cardiomyopathies or atripathies is not advised.

#### Clinical Consensus Statements

1. LVGLS in competitive athletes tend to fall within the normal to low normal range for the comparative age- and sex-specific general population. If values are less negative than a low normal range, this may be suspicious for an underlying cardiomyopathic process.
2. RVFWLS may provide incremental information in the context of abnormal RV chamber parameters when there is a suspicion of an underlying cardiomyopathic process instead of adaptive physiological remodeling secondary to competitive athlete's heart.
3. There is insufficient evidence at present to support the use of LA strain parameters in differentiating underlying atripathies from remodeling that occurs in competitive athlete hearts.

**e. Myocardial Dyssynchrony.** In contrast to earlier studies that applied nonspecific time-to-peak parameters, evidence is now growing that intraventricular dyssynchrony can be related to better volume response and outcome after CRT if specific deformation patterns are sought.<sup>101</sup> Visual assessment of phenomena such as septal flash and apical rocking might already be sufficient to select CRT patient candidates with higher accuracy than current guideline criteria.<sup>102</sup> However, tissue Doppler and speckle-tracking segmental strain analysis can be used in addition to characterize such specific deformation patterns amenable to treatment by CRT.<sup>103</sup> Data from large, randomized studies using specific deformation parameters for guiding patient management by CRT are currently being performed (ClinicalTrials.gov identifier NCT04225520) and may influence future guidelines.

In dyssynchronous hearts amenable to CRT, septal strain patterns develop an early onset of shortening followed by a notching when the lateral wall starts to contract. More advanced remodeling is characterized by systolic stretching of the septum ([Figure 8](#)).<sup>104,105</sup> Despite left bundle branch block, the septal strain pattern can behave in a pseudo-normal fashion when the lateral wall is dysfunctional (e.g., due to infarct scar).<sup>106</sup>

Segmental strain curves can be combined with estimated LV pressure to obtain a measure of regional work performed per volume unit of myocardium. Analysis of regional myocardial work distribution may contribute to improved patient selection<sup>107</sup>; however, randomized trials involving these analyses are lacking. More information may be found in contemporary consensus statements.<sup>108</sup>

## Clinical Consensus Statements

1. Patient candidacy for biventricular pacing may be enhanced by a careful assessment of intraventricular dyssynchrony. Although visual and M-mode assessment might be sufficient, both TDI-based and speckle-tracking-based segmental strain analysis can be used to quantify intraventricular dyssynchrony.
2. Care must be taken to characterize specific deformation patterns. General time-to-peak comparisons are not sufficient for this purpose.

## B. Cardio-Oncology

In terms of HF, most of the research in cardio-oncology has been conducted in patients treated with anthracyclines, although the cardiotoxicity of tyrosine kinase inhibitors and human epidermal growth factor receptor 2 antibodies (such as trastuzumab) has also been recognized.

The early identification of patients at high risk for developing cardiac dysfunction and failure is important as symptoms are late and at that stage the prognosis is poor.<sup>109</sup> The identification of these patients before their chemotherapy is an attractive option. An abnormal or low normal baseline LVEF has prognostic value in predicting which patients treated with chemotherapy will develop cardiac events.<sup>110,111</sup> The percentage of patients who have abnormal or low normal LVEF is low, between 1% and 10% depending on the population.<sup>110,112</sup>

LVGLS has shown prognostic value in the prediction of overall mortality in a general population of patients undergoing echocardiography.<sup>113</sup> The value of baseline LVGLS in predicting clinical outcomes has also been recognized in a study of patients treated with anthracyclines.<sup>114</sup> One of the most valuable applications of LVGLS may be in patients with borderline LVEF. In a study of 158 patients with a baseline LVEF of 50% to 59% subsequently treated with anthracyclines, Mousavi *et al.*<sup>115</sup> reported that strain added incremental value to the LVEF, with a baseline strain less negative than  $-16\%$  being associated with an increased occurrence of symptomatic HF and cardiac death.

Several studies have reported that LVGLS decreases early during treatment with anthracyclines, trastuzumab, or radiotherapy, even when LVEF remains unchanged. Importantly, these early decreases in LVGLS predict later decreases in LVEF.<sup>116,117</sup> Multiple studies had demonstrated the adverse prognostic value of an abnormal LVGLS at baseline or decrease thereof during chemotherapy. A meta-analysis of nine studies by Oikonomou *et al.*<sup>49</sup> reported that patients with an abnormal LVGLS during chemotherapy had an odds ratio of 12.2 to develop cancer chemotherapy-related cardiac dysfunction (CTRCD). Similarly, patients with a relative decrease of LVGLS after initiation of chemotherapy were 15.8 times more likely to develop CTRCD than patients with unchanged strain. The magnitude of the decrease after anthracycline treatment that is best predictive of later LVEF decreases has been reported as a relative decrease of 10% (change in LVGLS with sensitivity of 78% and specificity of 79%)<sup>117</sup> and 11% (change in LVGLS with sensitivity of 65% and specificity of 94%).<sup>118</sup> Conservatively, a relative decrease of 15% (e.g., 3% absolute decrease from a baseline of  $-20\%$ ) during chemotherapy, is considered to be preclinical cardiac dysfunction.<sup>119,120</sup> In the setting of anthracycline chemotherapy follow-up studies have found reductions in LVGLS that appear to be segmental, with an apical-sparing pattern, persistently reduced LVGLS in a minority of patients, and a greater reduction in strain in those receiving higher cumulative anthracycline doses.<sup>121</sup>

Decreases in radial and circumferential strain have also been noted after anthracyclines; no predictive value of radial strain has been found, while the value of circumferential strain in predicting subse-

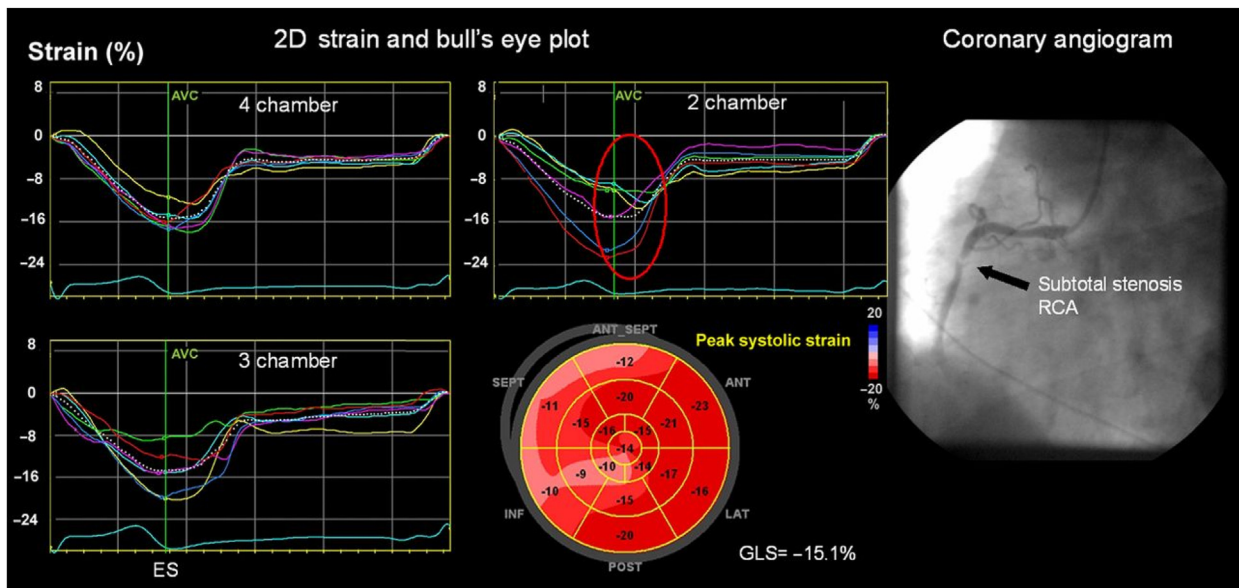
quent LVEF decreases has been reported by some investigators<sup>122</sup> but its routine use in the clinical setting cannot be endorsed.

Comparable findings have been made outside of the breast cancer population, confirming the utility of this STE across the spectrum of cardio-oncology practice. Several studies now report similar findings in the setting of lymphoma.<sup>123,124</sup>

Strain imaging can serve as a sensitive tool for detecting functional abnormalities early, sensitively and with adequate specificity, but the true, long-term consequences of these findings remain to be determined. The Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes (SUCCOUR) randomized study was designed to assess whether a strain guided approach to cardioprotective therapy would outperform an EF-guided approach.<sup>50</sup> It is noteworthy that at 1 year, there was a suggestion of some beneficial effect of the strain guided therapy on CTRCD. A follow-up study was conducted 3 years after enrollment. LVEF recovered in most patients and there were no differences in LVEF or in the number of patients meeting CTRCD criteria in the strain guided or LVEF-guided groups.<sup>125</sup>

Several guidelines and state-of-the-art reviews have recently been published.<sup>126-128</sup> The International Cardio-Oncology Society and the European Society of Cardiology guidelines recognize an isolated relative decrease of  $\geq 15\%$  in GLS as mild CTRCD.<sup>126,127</sup> Similarly, the American College of Cardiology cardio-oncology and imaging councils state-of-the-art paper recognizes a decrease of that magnitude as possible cardiotoxicity.<sup>128</sup> In patients with an isolated decrease in strain, optimizing risk factors and replacing any noncardioprotective ongoing treatment by cardioprotective therapies if feasible is justified.<sup>7</sup> Furthermore, strain imaging can be used to detect subclinical late effects of both chemotherapy and radiotherapy. More important, current cardio-oncology guidelines advocate against the interruption of chemotherapy in the context of preserved LVEF and isolated falls in GLS.<sup>126</sup> Recently, the results of the SUCCOUR magnetic resonance imaging study were published, demonstrating a significant improvement in magnetic resonance imaging-defined LVEF after commencing cardioprotective therapy after the detection of CTRCD as defined by a  $>12\%$  relative reduction in LVGLS.<sup>129</sup> This is an encouraging step forward for the utility of STE in guiding therapeutic decisions.

Adult survivors of childhood cancer have been subjected to the most investigations as they are at significant risk for cardiac morbidity and mortality. Asymptomatic childhood cancer survivors treated by both high dose anthracyclines and mediastinal radiation demonstrate a significant reduction of LVGLS and LV global radial strain in the absence of LVEF abnormalities.<sup>130,131</sup> Additionally, subclinical abnormalities of the right ventricle are demonstrated by using RVFWLS.<sup>132</sup> Important information was collected from the St. Jude Lifetime Cohort Study, a cohort of 1,820 adult survivors of childhood cancer exposed to either anthracycline chemotherapy, chest-directed radiotherapy, or both therapies (median age, 31 years at the time of study; median time from diagnosis, 23 years).<sup>133</sup> In this population, abnormal LVGLS and altered LV diastolic function were more prevalent than reduced 3D echocardiography-derived LVEF and were associated with treatment exposure. Subclinical LV dysfunction was identified in one-third of survivors with normal LVEF. On the basis of these findings, a combined assessment of LVEF and LVGLS plus LV diastolic function may be supported in adult survivors of childhood cancer. However, long-term follow-up studies are needed to establish the predictive nature of these echocardiographic findings for major cardiac events and their clinical relevance.



**Figure 9** Strain imaging in patient with atypical symptoms, no chest pain, and no signs of ischemia in the electrocardiogram. Each trace represents one LV segment. Possible inferior wall hypokinesia on grey scale imaging. Strain imaging showed moderately reduced systolic shortening and marked postsystolic shortening in the inferior wall (red circle). The patient was referred for angiography, which revealed a subtotal stenosis of the right coronary artery (right) and was successfully treated with percutaneous coronary intervention. ANT, Anterior; ANT\_SEPT, anteroseptal; AVC, aortic valve closure; ES, end-systole; INF, inferior; LAT, lateral; POST, posterior; RCA, right coronary artery; SEPT, septal. Reproduced with permission from Smiseth *et al.*<sup>136</sup>

### Clinical Consensus Statements

1. Strain should be performed at baseline in all patients undergoing chemotherapy with anthracyclines.
2. It is reasonable for strain to be measured at baseline in all patients undergoing radiotherapy or nonanthracycline chemotherapy.
3. Strain should be obtained early after chemotherapy with anthracyclines to identify subclinical cardiotoxicity.
4. Patients with baseline strain lower than normal limits should undergo echocardiography with strain at mid treatment.
5. In patients with a relative decline of strain of more than 12%, it is reasonable to consider treatment with cardioprotective therapy, whatever the change in LVEF.
6. Strain imaging should be incorporated in the follow-up echocardiographic examinations performed in survivors of childhood cancer.

### C. Ischemic Heart Disease

**a. Diagnosis and Localization of Infarction.** The reliability of visual estimation of regional wall motion and thickening abnormalities on 2D echocardiography for diagnosis and localization of acute MI (AMI) is dependent on the expertise of the examiner and time elapsed following the ischemic insult. GLS and SLS analysis provides more objective information and better diagnostic accuracy to diagnose significant coronary artery stenosis in patients who have suspected non-ST-segment acute coronary syndrome.<sup>134</sup> Even in patients without apparent regional wall motion abnormalities on visual analysis, GLS and SLS were significantly more impaired in patients who had significant coronary artery stenosis than those without stenosis (Figure 9).<sup>135,136</sup> However, 2D strain analysis has no clear additional value in the setting of acute ST-segment elevation MI (STEMI), as these electrocardiographic findings alone mandate an early interventional strategy.

**b. Detection of Myocardial Ischemia.** LVGLS analysis has the potential to detect latent LV dysfunction that is associated with myocardial ischemia due to significant coronary artery stenosis. A systematic review and meta-analysis of the diagnostic accuracy of LVGLS to predict significant coronary artery stenosis in patients presenting with acute and chronic chest pain (six studies, 781 patients, 397 with significant coronary artery stenosis) revealed that LVGLS measurements at rest have only modest diagnostic accuracy.<sup>137</sup> The cutoff values of LVGLS for prediction of significant coronary artery stenosis varied between  $-17.4\%$  and  $-19.7\%$  with sensitivity of 51% to 81% and specificity of 58% to 81%. A preferential reduction of endocardial layer strain has been reported in patients who had normal wall motion but flow-limiting coronary stenosis ( $\geq 99\%$  diameter stenosis),<sup>138</sup> but these results need to be verified in larger studies.

It has been hoped that application of 2D strain analysis may overcome the subjectivity and need for expertise of stress echocardiographic interpretation. Compared with visual analysis, 2D strain analysis with use of GLS or SLS values at peak stress had a higher sensitivity but a lower specificity, resulting in the similar diagnostic accuracy of the two methods.<sup>139-143</sup> The primary cause of lower specificity could be related to the unreliable myocardial speckle-tracking due to vigorous myocardial contraction and altered loading conditions at higher heart rates, which produces artificially more negative strain values, pointing to the need for higher than usual frame rates. Another limitation of this application of 2D strain analysis is that there are no definite and universal cutoff values for diagnosing significant coronary artery stenosis. Regional heterogeneity of strain values may be exaggerated during stress even in healthy subjects,<sup>144</sup> resulting in difficulty determining optimal regional strain cutoff values. More detailed analysis of regional strain curves, especially assessment and measurement of postsystolic shortening, is likely to be superior to

regional cutoffs, but this has not been proven for clinical practice. Recall also (section 2) that regional strain pattern analysis relies particularly on vendor-dependent analysis software fidelity, which limits its utility.<sup>22</sup>

**c. Assessment of Myocardial Viability.** two-dimensional strain analysis can provide objective information to predict LV functional recovery after AMI. Supplemental Table 5 shows moderate diagnostic accuracy of GLS and SLS to predict LV functional recovery after coronary revascularization, albeit with different criteria for recovery among studies. In postinfarction patients, an increase in LVGLS with low-dose dobutamine was associated with better wall motion at 1 month.<sup>145</sup>

Despite the high success rate of primary percutaneous coronary intervention, LV adverse remodeling occurs in one-third of patients following AMI. Myocardial deformation analysis can be used for the prediction of LV adverse remodeling during follow-up (see Supplemental Table 6). Proposed cutoff values of LVGLS for predicting LV adverse remodeling range from  $-10\%$  to  $-15\%$ , with an area under the receiver operating characteristic curve of 0.73 to 0.88. The findings were consistent with a previous meta-analysis showing that LVGLS was associated with adverse LV remodeling with optimal cutoff values very close to  $11\%$  in most studies.<sup>146</sup> LVGLS also provides significant incremental value over clinical and conventional echocardiographic parameters in predicting adverse LV remodeling in some studies.<sup>147-149</sup> Although LV circumferential strain and LV torsion have also been reported for the assessment of myocardial viability, the evidence is currently too sparse to justify their clinical use.

**d. Risk Stratification After MI.** LVGLS predicts long-term adverse outcomes and provides incremental value over conventional echocardiography parameters in patients with AMI treated by primary percutaneous coronary intervention (see Supplemental Table 7). As the primary end point was different among studies, the absolute cutoff values of GLS varied from  $9.3\%$  to  $15.1\%$ , but all studies consistently showed that decreased LVGLS was significantly associated with adverse outcome. Meta-analysis using a random effects model revealed that for each  $1\%$  reduction in LVGLS, the hazard ratio for adverse outcome was increased by  $34\%$ . The robustness of LVGLS has also been verified after adjusting for conventional echocardiographic parameters, such as LVEF or in the subgroup of patients who had LVEFs  $>40\%$ .<sup>150-152</sup> Less information exists regarding the prognostic role of layer-specific strain analysis and 3D speckle-tracking analysis, and these cannot be advised for routine clinical use at present. A recent study showed that LV midwall GLS is better than endocardial GLS for predicting adverse outcome in patients with acute coronary syndrome.<sup>153</sup>

RV LS also has prognostic value after MI. In 621 patients with AMI who were treated with primary coronary intervention, univariate analysis revealed that RVFWLS was significantly associated with all-cause mortality.<sup>154</sup> RVFWLS had an independent incremental value over clinical variables and LV function parameters including LVEF, E/e' ratio, and mitral regurgitation (MR).

### Clinical Consensus Statements

1. GLS or SLS patterns (as opposed to quantitative values) may assist in evaluation of patients with non-STEMI acute coronary syndrome, especially with negative cardiac biomarkers, no dynamic electrocardiographic changes, and no apparent regional wall motion abnormalities.
2. Two-dimensional strain analysis of LVGLS or SLS may be performed at early phase of AMI after percutaneous coronary intervention for the predic-

tion of functional recovery, LV adverse remodeling, and risk for adverse outcomes.

3. RV strain analysis is feasible if an RV-focused view with good image quality is acquired for the analysis. This may be useful in assessing RV infarction using RVFWLS.

### D. Valvular Heart Disease

The assessment of myocardial function in the context of significant valvular heart disease remains highly challenging. Current guidelines support valve replacement/repair in cases of severe valvular heart disease that cause symptoms or reduced LVEF, but LVEF may be within the normal range in these patients.<sup>155,156</sup> Assessment of LV deformation analysis using echocardiography or CMR provides a more sophisticated approach to study both regional and global chamber function.<sup>157</sup>

**a. AS.** Basal LS less negative than  $-13\%$  has been reported to predict an abnormal exercise response in patients with AS, with sensitivity and specificity of  $77\%$  and  $83\%$ , respectively (area under the curve,  $0.81$ ;  $P < .01$ ).<sup>158</sup> Impaired LVGLS was also associated with a higher LV mass index and relative wall thickness, which supports a direct connection between concentric remodeling and contractile dysfunction. Among recent prognostic studies,<sup>159-161</sup> a study in 163 patients with asymptomatic moderate to severe AS provided evidence that LVGLS less negative than a cutoff  $-15.9\%$  was an independent predictor of adverse events (occurrence of symptoms, aortic valve replacement [AVR], or death). Also, Adda *et al.*<sup>162</sup> demonstrated that longitudinal LV dysfunction was particularly impaired in patients with AS with low flow. Patients with low-flow, low-gradient AS showed a significant reduction in basal LS compared with patients with normal-flow, high-gradient AS ( $-11.6 \pm 3.4\%$  vs  $-13.6 \pm 3.2\%$ ,  $P < .05$ ). The sensitivity and prognostic value of LS have been particularly helpful in asymptomatic patients (see Supplemental Table 8).<sup>163-166</sup> The clinical value of strain data in AS might be more controversial in symptomatic patients, in whom intervention is already indicated.<sup>167</sup> However, using only the apical four-chamber view, LS predicted death in patients with AS and preserved LVEF.<sup>168</sup> In the low-flow, low-gradient subgroup, LS is an important parameter to help manage these patients.

In patients with severe LV hypertrophy and a low-flow state, the LS pattern sometimes offers diagnostic information beyond prognosis. An apical-sparing pattern often suggests transthyretin-related cardiac amyloidosis unrelated to the AS. When this strain pattern is observed, nuclear based scintigraphy studies ( $^{99m}\text{Tc}$ -hydroxymethylene diphosphonate,  $^{99m}\text{Tc}$ -pyrophosphate, or  $^{99m}\text{Tc}$ -3,3-diphosphono-1,2-propanodicarboxylic acid) on the basis of local availability and expertise, should be performed to look for cardiac uptake of the tracer, which is highly diagnostic of transthyretin-related cardiac amyloidosis.<sup>169</sup>

An individual participant data meta-analysis has been performed by the EACVI in patients with severe asymptomatic AS. Eight studies were pooled and thus, it has been demonstrated that LVGLS performed well in the prediction of death (area under the curve,  $0.68$ ). The best cutoff value identified was LVGLS of  $-14.7\%$  (sensitivity,  $60\%$ ; specificity,  $70\%$ ), which increases the risk for death by 2.5-fold<sup>170</sup> in patients with severe asymptomatic AS. Furthermore, a recent meta-analysis of 12 studies demonstrated the prognostic value of LVGLS in the preprocedural assessment of patients with severe AS undergoing transcatheter AVR, with a less negative LVGLS having a

higher risk for all-cause mortality and major adverse cardiovascular events compared with patients with more negative LVGLS.<sup>171</sup>

**b. Aortic Regurgitation.** Current valve guidelines rely on LV diameter and LVEF to guide timing of surgery in patients with aortic regurgitation (AR).<sup>155</sup> More sensitive tools are needed, and LS has been studied in patients with AR. In medically treated patients, LVGLS of  $-18\%$  was the best cutoff for identifying disease progression to symptoms or HF, while a cutoff of  $-14\%$  was predictive of poor outcome in patients undergoing AVR.<sup>172,173</sup> In patients with moderately severe and severe AR, resting LV strain was also a strong independent predictor of the need for early AVR together in addition to other RV functional parameters such as exercise TAPSE and resting RVFWLS. Also, patients with LVGLS less negative than the median value of  $-19.5\%$  were more likely to have a shorter survival, seen mostly in patients who did not undergo AVR. When the authors compared patients with LVGLS more negative than the median value who received AVR with those with preserved LVGLS but who did not undergo AVR, there was a twofold increased mortality ( $-8\%$  vs  $-15\%$  favoring AVR,  $P = .08$ ). Importantly, LVGLS was independently associated with all-cause mortality (hazard ratio, 1.11 per 1% decrease;  $P = .003$ ) after multivariate Cox proportional-hazards model adjustment and provided incremental prognostic value to the existing prediction model. All these studies had relatively brief follow-up and used a variety of end points including 1-year survival, need for AVR, changes in LV dimensions, and alleviation of symptoms. Whether LVGLS might provide superior risk discrimination in patients with chronic AR and preserved LVEF regarding the timing for aortic valve intervention remains unclear. Further large studies with consistent end points are needed.

**c. MR.** In patients with severe primary MR, LVEF may remain in the normal range for long periods of time, even after alterations in contractility develop. The earlier detection of LV contractile dysfunction is of pivotal importance and favors the timely surgical correction of chronic MR, which usually restores normal LV contractile function.<sup>157</sup> LVGLS has been demonstrated in many studies as a more robust and sensitive diagnostic or prognostic tool than LVEF. Like LVEF, LVGLS should be more negative than  $-20\%$  in patients with augmented preload and a decrease in volumetric afterload as occurs in MR patients. As LVGLS decreases, prognosis worsens, suggesting early MR intervention (surgical or transcatheter valve repair; see Supplemental Table 9). In asymptomatic patients with significant primary MR and preserved LVEF who underwent mitral valve surgery, brain natriuretic peptide (BNP) and LVGLS provided synergistic risk stratification, independent of other established factors.<sup>174</sup>

In secondary MR, LVGLS data have been used to demonstrate that surgical and transcatheter mitral valve repair in nonischemic dilated cardiomyopathy improved LV forward flow and induced LV reverse remodeling but did not change LV systolic function.<sup>175</sup> There has been some recent evidence to also support its role in predicting outcomes after transcatheter edge to edge repair.<sup>176</sup>

**d. Mitral Stenosis.** Strain studies in patients with mitral stenosis (MS) have shown significant reductions in LV stroke volume and LVGLS compared with normal subjects. Sengupta *et al.*<sup>177</sup> found that nearly 85% of patients with severe MS have LVGLS in the lowest quartile of the control subjects. LV end-diastolic volume in these patients was the strongest determinant of LVGLS, suggesting that reduced preload results in the perceived impairment in LV contractile performance in MS to a great extent.

**e. Tricuspid Regurgitation.** Severe tricuspid regurgitation (TR) carries a poor prognosis, driven primarily by impaired RV systolic function. Although the data are limited, several studies support the incremental prognostic value of RVFWLS over traditional parameters of RV systolic function such as fractional area change and TAPSE. Prihadi *et al.*<sup>178</sup> demonstrated an incremental less negative RVFWLS over fractional area change and TAPSE in predicting all-cause mortality in 896 patients with significant functional TR using a cutoff less negative than  $-23\%$ . A subsequent study performed in 115 consecutive patients undergoing isolated surgery for severe functional TR found that a preoperative RVFWLS less negative than  $-24\%$  was predictive of all-cause mortality and unplanned cardiac readmissions over 5-year follow-up after surgery.<sup>179</sup>

## Key Points

- Because LVGLS is a continuous parameter, in valvular heart disease establishment of absolute cutoffs is less meaningful than recognizing that as strain magnitude decreases, prognosis worsens in a continuous manner.
- There should be supranormal LVGLS if LV contractile function is normal in patients with valvular disease that results in increased preload and reduced volumetric afterload (AR, TR, and primary MR).

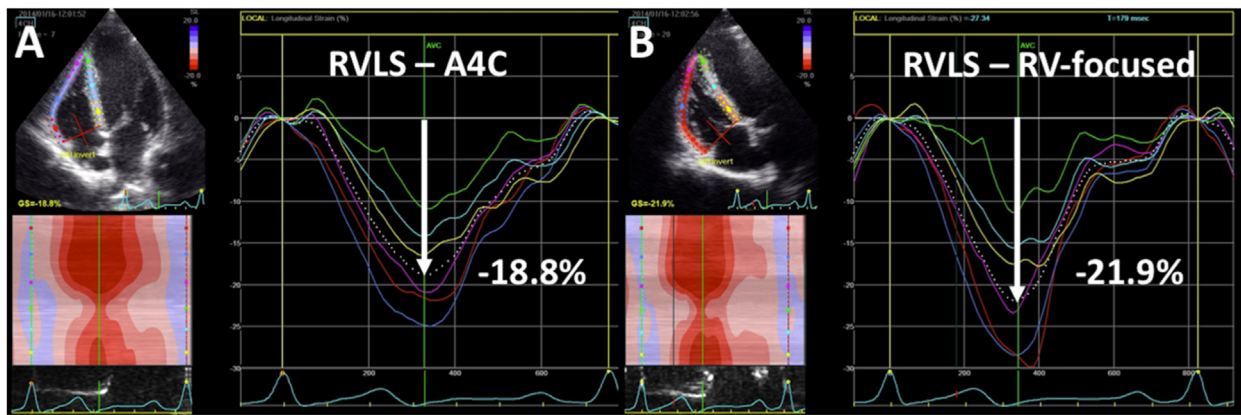
## Clinical Consensus Statements

1. LVGLS is a useful prognostic factor in AS, particularly asymptomatic patients and in the low-flow, low-gradient subgroup. A recent meta-analysis suggests that LVGLS less negative than  $-14.7\%$  increases the risk for death by 2.5-fold in severe asymptomatic AS.
2. Less negative LVGLS has been associated with worse outcomes in both medically and surgically managed patients with AR, although the optimal cutoff has not been defined.
3. In patients with severe primary MR, LVGLS should be supranormal with adverse prognosis observed when strain is less negative than  $-20\%$ . Patients with LVGLS less negative than  $-20\%$  should be carefully monitored and mitral valve intervention may be appropriate as clinically indicated.
4. Strain is less well established in patients with functional MR, with no well-established cutoff to guide timing of intervention.
5. RVFWLS may be used in patients with significant TR to risk stratify before intervention, with values less negative than  $-23\%$  suggestive of poorer outcomes.

## E. RV Strain

Although RV LS can be measured using TDI,<sup>180</sup> most evidence comes from 2D STE. The most accurate and reproducible measurements are obtained from the apical RV-focused view, which optimally lays out the RV free wall (Figure 10).<sup>181</sup> RV speckle-tracking requires good image quality at 60 to 90 Hz without foreshortening, dropout, or reverberations.<sup>14</sup> RV LS is less confounded by overall heart motion, translation, and loading conditions compared with other measures of RV longitudinal function such as TAPSE and TDI-derived S' velocity.<sup>182</sup>

As for the left ventricle, most evidence relates to RV strain in the longitudinal direction, which is the advised parameter.<sup>24</sup> The RV free wall is too thin to allow accurate computation of transversal (radial) strain despite some support for this,<sup>183-185</sup> and this parameter is not advised for clinical use.<sup>14</sup> Similarly, as there are no



**Figure 10** Demonstration of different RV strain value acquisition from variations of RV transthoracic windows. Obtaining RV strain measures from the apical RV-focused view is more accurate. Here is an example of incrementally higher RV GLS obtained from an apical RV-focused view compared with an apical four-chamber (A4C) view.

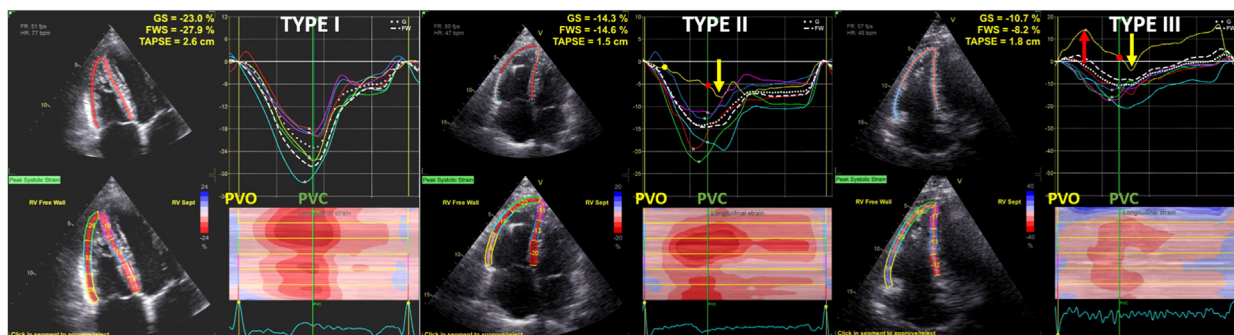


**Figure 11** Workflow for obtaining accurate RV strain measurements. Following the order of steps from 1 to 8 and optionally deselecting the septum to produce RVFWLS will result in accurate and reproducible RV strain parameters. *Long*, Longitudinal; *PVC*, pulmonary valve closure; *RVOT*, RV outflow tract.

oblique fibers in the right ventricle, torsion contributes little to overall RV contraction.

**a. Image Acquisition and Postprocessing of RV LS.** The endorsed view for RV STE obtained from the standard apical four-chamber view is obtained by counterclockwise rotation and medial angulation to maximize the RV diameter. In this view, the LV apex is centered in the imaged sector, while showing maximal RV dimensions (both longitudinal and transverse), and the entire RV free wall

are evident throughout the cardiac cycle (Figure 11).<sup>14</sup> This view should show the interatrial septum but not the aortic valve (too anterior) or coronary sinus (too posterior). Of note, strain values obtained from the RV-focused view are greater in magnitude than those obtained from standard apical four-chamber views,<sup>181</sup> emphasizing the importance of view standardization for patient follow-up and setting normal reference values (see section 3).<sup>14</sup> The ROI should include both the RV free wall and interventricular septum, with width adjusted to the thickness of the RV free wall (approximately 5 mm



**Figure 12** Strain patterns of the basal segment of the RV free wall (yellow curve) in patients with confirmed arrhythmogenic cardiomyopathy affecting the right ventricle. Type I, normal deformation of the basal segment, which is synchronous with the other RV segments; type II, delayed onset (yellow dot) and reduced extent of the end-systolic deformation (red dot) with evident postsystolic shortening (yellow arrow); type III, prominent early systolic stretching (red arrow) with shallow values of end-systolic strain (red dot) and most of the deformation occurring after the closure of the pulmonary valve (yellow arrow). GS, Global strain; FWLS, free wall longitudinal strain; PVC, pulmonary valve closure; PVO, pulmonary valve opening.

normally and larger with RV hypertrophy). Assessment of RV strain is easier and more reproducible with dedicated RV strain software.<sup>31</sup>

The RV free wall includes three segments (basal, mid, and apical), which have equal lengths at end-diastole. The septum is similarly segmented. For reporting RV LS, the average of the free wall segments is advised and should be labeled as RVFWLS. If septal segments are included in the strain average, this should be noted clearly, as global RV LS (labeled RV four-chamber LS), which includes both free wall and septal segments, is usually smaller in magnitude than three-segment RVFWLS.<sup>186</sup>

Finally, in addition to amplitude parameters, temporal parameters such as the time to peak strain (R wave to peak RV shortening) can also be assessed. RV mechanical dispersion can be calculated as the SD of time to peak strain in a six-RV-segment model,<sup>187</sup> which is more robust than using the RV free-wall segments only.<sup>188</sup> Note that the evidence base for RV dispersion is much smaller than for the left ventricle.<sup>189</sup>

**b. Clinical and Prognostic Value in Different Cardiac Conditions.** There is an increasing body of literature for the clinical and prognostic value of RV strain in various cardiac conditions (see Supplemental Table 10).<sup>190,191</sup>

**Pulmonary Hypertension and Heart Failure**—RV function is a major determinant of prognosis in patients with pulmonary hypertension (PH), irrespective of etiology,<sup>192</sup> with strain playing an increasing role in prognostication. In pulmonary arterial hypertension (PAH), RV strain was significantly worse than in patients without PH<sup>193</sup> and correlated with invasive pulmonary pressure and vascular resistance,<sup>193–195</sup> BNP and 6-minute walk distance,<sup>194–196</sup> and occurrence of cardiovascular events during follow-up (see Supplemental Table 10).<sup>196–203</sup> Moreover, improved RV strain parameters were associated with improving pulmonary pressure and vascular resistance<sup>194</sup> and 6-minute walk distance<sup>204</sup> with treatment. Finally, a good correlation between RVFWLS and RVEF by CMR has been reported.<sup>195,203,205</sup>

An increasing body of literature demonstrates the utility of RV strain for outcome prediction in patients with both acute and chronic HF (both HFrEF and HFpEF; see Supplemental Table 3). RVFWLS is also predictive of RV failure following LVAD implantation.<sup>206</sup>

**Ischemic Heart Disease**—In survivors of STEMI, RV strain is prognostic and independently associated with adverse clinical outcomes

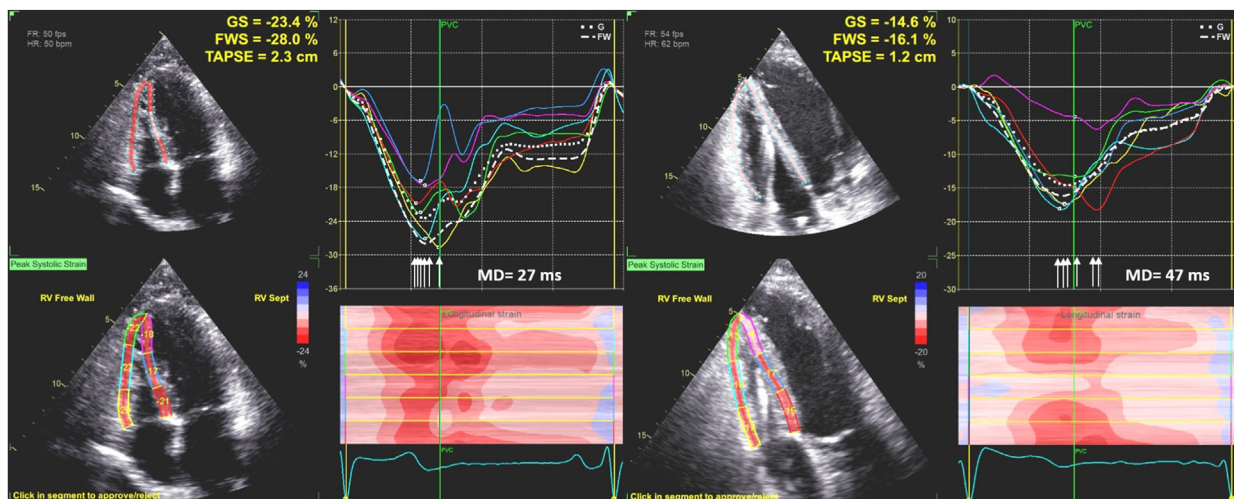
incremental to clinical, infarct size and other LV and RV functional parameters. Similar results were also reported in patients with ischemic cardiomyopathy (see Supplemental Table 10).

**ARVC**—In patients with ARVC, RVFWLS can detect early (subclinical) regional RV dysfunction before conventional echocardiography<sup>188,207</sup> with three characteristic deformation patterns identified: type I, normal deformation; type II, delayed onset of shortening, reduced systolic peak strain, and mild postsystolic shortening; and type III, systolic stretching with large postsystolic shortening (Figure 12).<sup>208</sup> Finally, RV strain-derived mechanical dispersion can stratify the arrhythmogenic risk of patients with ARVC (Figure 13).<sup>187</sup>

**Systemic Sclerosis**—RVFWLS can detect occult regional and global RV dysfunction regardless of RV systolic pressure and systemic sclerosis phenotype.<sup>209</sup>

**c. Future Perspectives.** Much reference data for RV strain has been obtained from conventional apical four-chamber views using LV software adapted to the right ventricle. It is important to determine the intervendor consistency of measurements obtained from the RV-focused four-chamber view and software specific to the right ventricle. Majority of data diagnostic and prognostic for RV strain have been obtained in single center-studies, mandating future multicenter, prospective studies. Finally, RVFWLS samples only a limited amount of the RV myocardium, resulting in an incomplete evaluation of the right ventricle. Although 3D echocardiography has the potential for strain analysis of the entire right ventricle,<sup>210</sup> technical and geometric issues currently limit this to the investigational realm.

Recently, the ratio of RVFWLS to pulmonary artery systolic pressure ratio has been validated as a measure of RV–pulmonary artery coupling against RV end-systolic elastance/arterial elastance obtained invasively with conductance catheterization<sup>211</sup> and found to be independently prognostic in patients with PAH,<sup>212</sup> severe TR,<sup>213</sup> HFpEF,<sup>93</sup> and secondary MR in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure With Functional Mitral Regurgitation (COAPT) trial.<sup>214</sup> Similarly, myocardial work index quantified by integrating RVFWLS with invasively measured RV pressure can predict decompensation in heart transplant recipients.<sup>215</sup> These studies confirm the pathophysiologic linkage among TR, RV and LV function, and pulmonary artery systolic pressure to each other.



**Figure 13** Example of RV mechanical dispersion in arrhythmogenic cardiomyopathy. RV mechanical dispersion (MD) in an asymptomatic mutation carrier (*left*) and an arrhythmogenic cardiomyopathy patient with recurrent arrhythmias and implanted intracardiac defibrillator device (*right*). White vertical arrows indicate the timing of maximum myocardial shortening in each segment of the right ventricle. MD is more prolonged and clinically significant in the *right* panel. FR, Frame rate; GS, global strain; FWLS, free wall longitudinal strain; HR, heart rate; Sept, septum.

## Key Points

- To obtain accurate and reproducible measurements of RV LS by 2D STE, an RV-focused apical four-chamber view acquired between 60 and 90 frames/sec should be used.
- An echocardiographic examination bed with a cutout at the level of the cardiac apex makes it easier to position the patient on the left side, to obtain a proper RV-focused apical view as described above.
- Both the dedicated RV software packages and the adaptation to the right ventricle of software packages developed for the left atrium provide the same measurements of RV LS, provided that the ROI of the latter is manually adapted to the right ventricle, and its thickness reduced to 5 mm. Assessment is easier and more reproducible with the dedicated RV software.<sup>31</sup>

## Clinical Consensus Statements

1. Among the parameters obtained by measuring RV longitudinal deformation, the free wall LS is the parameter with the most robust documentation of its diagnostic and prognostic value in a variety of clinical conditions, and in the general population of patients referred for echocardiography.
2. Normal values of RVFWLS are sex-specific but do not change with age (see section 2).
3. RVFWLS should be measured and reported (when technically feasible) in patients with evidence for RV enlargement, regional or global dysfunction, moderate or greater TR, or PH.

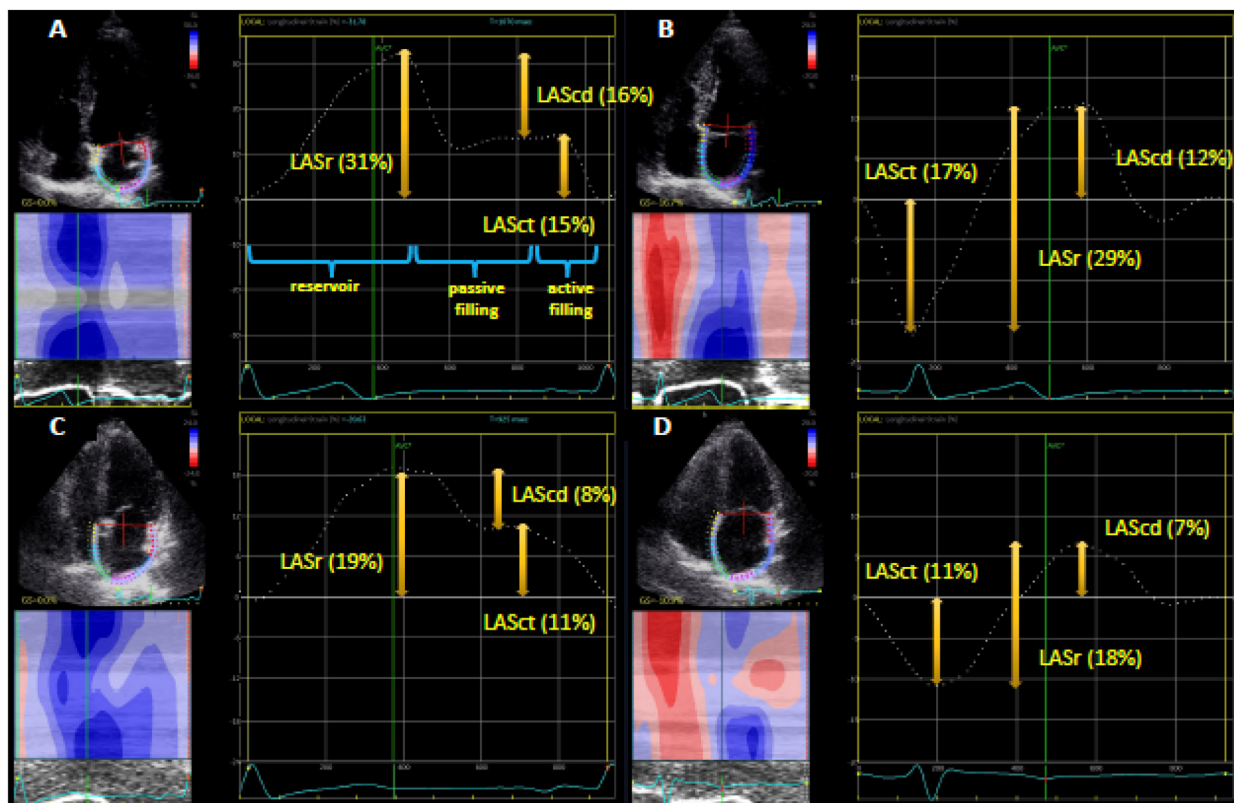
## F. LA and Right Atrial Strain

**a. LA Strain.** LA dynamics includes three mechanical phases that modulate LV filling: reservoir (in LV systole), conduit (pre-A-wave diastole), and active contraction (late diastole). LA strain is determined largely by LV strain and modulated by the ratio of LV and

LA volumes. Nevertheless, it also integrates information on filling pressures and LA myocardial properties.<sup>216</sup> LA strain measurements have been successfully validated against LA pressure and pulmonary capillary wedge pressure in multiple studies,<sup>217,218</sup> and LA strain has shown prognostic value in several clinical settings.<sup>219,220</sup>

**b. Quantification of LA Strain.** LA strain is preferentially measured by speckle-tracking. To do this, LA endocardial borders are traced manually or automatically on high-quality 2D images obtained at a frame rate between 50 and 90 frames/sec. The EACVI/ASE task force endorses using the LA strain value obtained from non-foreshortened apical four- and two-chamber views, although apical four-chamber strain alone is also commonly performed and shown to be useful.<sup>14</sup> Dedicated LA strain software should be used when available, to reduce measurement variability.<sup>31</sup>

Two different temporal gating approaches are available to quantify LA strain by STE. **Figure 14** shows findings in a normal subject (Figures 14A and 14B) and a patient with HF (Figures 14C and 14D). The first approach (Figures 14A and 14C) takes the electrocardiography-derived QRS onset as the starting point (R-R gating) and measures two key LA deformations: the first (LASr, corresponding to LA reservoir) peaks at the end of LV systole (corresponding to AVC), and the second, LASct, occurs late and corresponds to LA contraction. The difference between LASr and LASct represents LAScd. The second gating approach (Figures 14B and 14D) uses the electrocardiographic P wave as the starting point (P-P gating), enabling the measurement of two deformations, the first down-sloping, which corresponds to LASct, and the second up-sloping, which corresponds to atrial relaxation and reservoir function. The peak LA strain in this gating is approximately conduit strain, so the sum of LAScd and LASct represents LA reservoir function (LASr). Note that the atrial parameters are smaller for P-P gating than R-R gating, as the starting length of the atrium is smaller after atrial contraction, so the percent change in length is greater. P-P gating cannot be applied to patients with atrial fibrillation (AF). Moreover, most published studies used R-R gating, making it the de facto



**Figure 14** Examples of LA strain acquisitions across varying timing methods. LA strain findings in a normal subject (**A**, **B**) and a patient with HF (**C**, **D**). One approach to timing (**A**, **C**) takes the electrocardiography-derived QRS onset as the starting point (R-R gating). The second gating approach (**B**, **D**) uses the electrocardiographic P wave as the starting point (P-P gating). See text for details.

preferred method for measuring LA strain. The Strain Standardization Task Force consensus publication demonstrates that values obtained with R-R gating can be translated into corresponding findings using P-P gating and vice versa.<sup>14</sup> It is also possible to approximate reservoir strain from changes in LA volume throughout the cardiac cycle.<sup>221</sup>

**c. Strengths and Weaknesses of LA Strain.** The strengths of LA strain include its pathophysiologic value and the validation with invasive measurements of LA pressure and LV filling pressures. The principal weakness relates to difficult strain measurement in some LA regions, such as the LA roof in the apical four-chamber view (interference from pulmonary vein outlet)<sup>222</sup> and the apical two-chamber view (interference from enlarged LA appendage). In general, however, the tracing of LA borders is easy, with feasibility of biplane strain demonstrated in 94% of 84 healthy subjects<sup>223</sup> with acceptable reproducibility for clinical use demonstrated in limited data.

**d. AF.** AF is associated with thromboembolism, HF, and substantial health care costs, mandating awareness of LA structural and functional risk factors for AF development. LA enlargement is a clear predictor of AF development and recurrence after cardioversion, but this geometric abnormality is a late marker of disease progression. Accordingly, research has recently focused on early functional changes that occur before structural changes. Impairments of reservoir function can be detected with LA strain imaging even before atrial dilatation occurs. LA fibrosis, thought to be a hallmark of structural remodeling that contributes to the AF substrate, increases LA stiffness and worsens LA reservoir and contractile function.<sup>224</sup>

**e. New-Onset AF and Progression in At-Risk Patients.** New-onset AF is relatively common in patients at high cardiac risk or receiving electrical devices (see [Supplemental Table 11](#)). In patients with HF, LA strain could be used to predict the risk for AF development.<sup>225</sup> In patients receiving pacing devices, LA size, LA strain, and electromechanical conduction were associated with development of incident AF.<sup>226</sup> Sade *et al.*<sup>227</sup> also demonstrated that the change in LA strain at the time of atrial contraction, either systolic or late diastolic, predicted new-onset AF in patients receiving resynchronization therapy. A recent study demonstrates that right atrial (RA) strain is more predictive of AF recurrence than is LA strain.<sup>228</sup>

**f. After Rhythm Control of AF.** Electrical cardioversion and catheter ablation are effective to restore sinus rhythm in AF, but unfortunately, AF recurs in 26% to 52% of patients (see [Supplemental Table 11](#)). Enlarged LA volume, long AF duration, and advanced age are known predictors of AF recurrence. LA strain is also a strong predictor of AF recurrence after cardioversion or catheter ablation,<sup>229-232</sup> as well as an important predictor of LA reverse remodeling during long-term follow-up.<sup>233</sup> However, because of the lack of data regarding vendor variability,<sup>234</sup> no cutoff values for LASr have been proposed for recurrent AF after catheter ablation. More recent evidence supporting the predictive value of incrementally impaired RA reservoir strain (RASr) for recurrent AF after cardioversion has emerged.<sup>235</sup>

**g. Cryptogenic Stroke.** In patients with ischemic stroke, the cause is unknown at the time of discharge in a quarter of patients, in whom

silent paroxysmal AF may be an important cause.<sup>236</sup> Although implanted cardiac monitoring significantly increases the detection of silent AF, this is often not applied in routine practice. LASr has been reported to predict AF in patients with cryptogenic stroke. Pagola *et al*<sup>237</sup> demonstrated that LA strain may predict paroxysmal AF over a 3-year period of Holter monitoring.

### Clinical Consensus Statements

1. LASr, in addition to conventional 2D and Doppler echocardiographic parameters, provides information on early detection of functional change and fibrosis of the LA with reasonable reproducibility. However, LASr is not routinely advised but may be appropriate to predict new-onset AF in at-risk patients as well as recurrence after rhythm control.

**h. Diastolic Function and HFpEF.** The left atrium is not a passive transport chamber but is highly dynamic and responds by stretching to protect the pulmonary circulation from high pressures. For this reason, the left atrium plays a major role in incident HF, diastolic dysfunction and HFpEF.<sup>238</sup> LA size represents the chronic burden of LV filling pressure and is associated with prognosis in HF. LASr has been proposed as an alternative approach for LV filling pressure assessment,<sup>218</sup> and it is closely related to exercise tolerance and N-terminal pro-BNP level.<sup>239,240</sup> LASr is a powerful independent prognostic parameter in HFpEF.<sup>239,241</sup> In the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial, however, although LASr in HFpEF was associated with adverse outcomes, concomitant impairment of LV function largely explained the association of LA dysfunction with clinical outcome.<sup>242</sup> For noninvasive estimation of LV filling pressure, LASr does play an additive role to conventional Doppler parameters and LA volume index. There is evidence to support its robust correlation with elevated filling pressures. In a single-center prospective study of 139 patients, LASr < 23% had superior prediction of invasive LV filling pressures as measured by pre-A-wave LV catheterization measures.<sup>243</sup> A large multicenter international study of 322 patients demonstrated that LASr of <18% was determined as the optimal cut-off for elevated filling pressures when predominantly using end-expiratory pulmonary capillary wedge pressure as the reference standard.<sup>244</sup> Because of the validation across multiple sites, the writing committee believes that using LASr < 18% would provide the optimal balance of sensitivity and specificity for determining elevated filling pressures.

**i. RA Strain.** RA dynamics are similarly characterized by three separate phases: RA reservoir, conduit, and contraction. Normal reference values of RA strain have been generated in a healthy population of 200 subjects in a single-center study.<sup>245</sup> The normal value of RA GLS (corresponding to reservoir strain or RASr) was  $44 \pm 10\%$ . Some studies have evaluated RA strain in patients with PAH, TR, and pulmonary embolism.<sup>246</sup> In a recent meta-analysis for normal ranges of RA strain, Krittanawong *et al*<sup>247</sup> identified 4,111 subjects from 21 studies and found a mean RASr of 44%, RA contractile strain of 17%, and RA conduit strain of 18%. However, these studies were performed across different vendors, and the impact of this variation on the findings is yet to be determined. Further investigations are therefore needed to support the use of RA strain in the clinical setting.

### Key Point

- RA strain can be measured using R-R gating in the RV-focused apical four-chamber view.

### Clinical Consensus Statements

1. LA strain should be measured using R-R gating in the apical four-chamber view in suspected cardiomyopathic or arrhythmic conditions.
2. Impaired LASr of <18% is associated with elevated LV filling pressures.
3. Currently, RA strain is not advised for clinical practice.

### G. Exercise and Dobutamine Stress Echocardiography

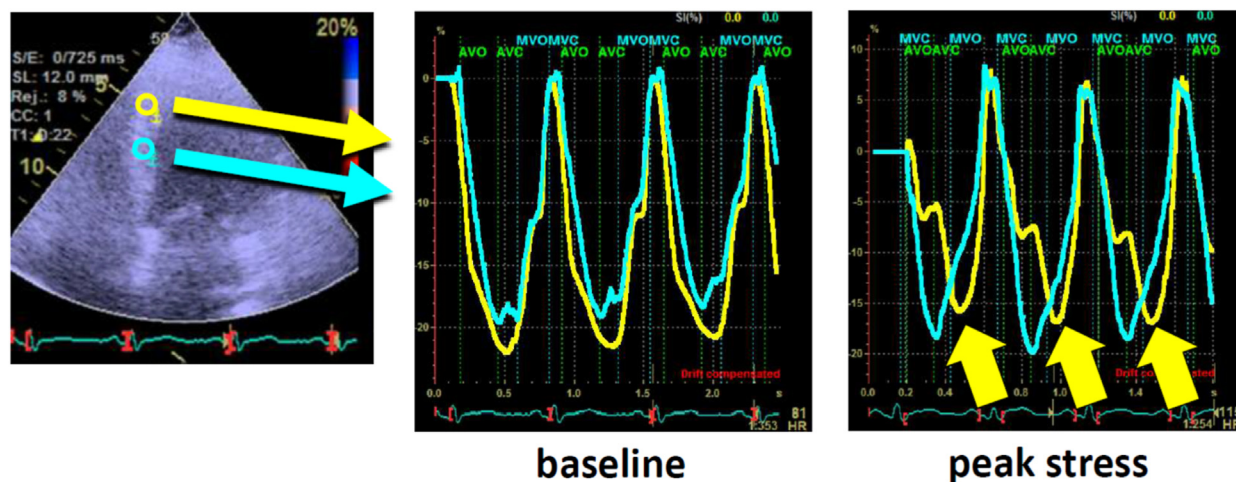
The recognition of regional wall motion abnormalities is the cornerstone of detection of coronary disease by echocardiography. Abnormalities present at rest denote the presence of scar or dysfunctional but potentially viable myocardium (the latter defined by augmentation of function in response to pharmacologic stimulation, usually by dobutamine). Ischemia is denoted by regional dysfunction in response to stress. Unfortunately, all these regional changes are subjective; they may be subtle to identify and are dependent on expertise.<sup>248</sup> In addition, assessment of regional function shows interobserver variability related to both the severity and extent of the regional abnormality, as well as image quality.<sup>249</sup> Access to a reliable and objective means of assessing regional function has been sought for decades, and there was hope of deformation imaging filling this role. This remains a work in progress.

**a. Coronary Artery Disease.** Most of the evidence regarding normal strain and strain-rate responses to stress have been gathered with dobutamine. Deformation imaging with exercise is inherently noisier than pharmacologic stress, and quantitation become more difficult. It requires a much higher frame rate than usual (likely >100 Hz) to maintain sufficient temporal resolution with tachycardia. Strain has a nonlinear response to stress with no further increment or decline at dobutamine infusion rates >20  $\mu\text{g/kg/min}$ . In contrast, strain rate continues to increase to peak dose dobutamine, in proportion to LV  $\text{dP/dt}$ , and is therefore the optimal quantitative deformation marker for this purpose. Unfortunately, while the temporal resolution of tissue Doppler strain rate is high enough to use for this purpose, this technique is cumbersome with virtually no clinical uptake. The temporal resolution of current speckle-tracking is inadequate for reliable measurement of strain rate. The ASE/EACVI task force on strain standardization has shown differences in test-retest variability and measured values<sup>250</sup> that lead to significant concern about the ability of myocardial deformation to reliably quantify regional function.<sup>26</sup>

Despite difficulties in quantifying myocardial function during stress, deformation imaging can still recognize ischemia on the basis of changes of the deformation waveform.<sup>251</sup> The hallmark of ischemia is delayed relaxation which is reflected in the most useful parameter of postsystolic shortening (quantified from strain curves as postsystolic index; Figure 15).<sup>3</sup> Its measurement is based on a reliable recognition of the start and end of systole, which may require manual override of automated timing. Nevertheless, using a single parameter is likely to prove inferior to assessing the shape of the curve.<sup>3,26</sup> Postsystolic shortening is a sensitive but nonspecific marker for ischemia and may also be seen in a regional scar. A particularly interesting aspect is that it may persist following resolution of ischemia: the phenomenon of ischemic memory.<sup>252</sup>

### Clinical Consensus Statements

1. Two-dimensional strain analysis at rest or during stress echocardiography may be appropriate for predicting significant coronary artery stenosis, especially in patients with good image quality. However, there is no specific quantitative cutoff, and the best results are obtained by analysis of the strain



**Figure 15** Postsystolic shortening during stress echocardiography. Tissue Doppler acquisitions taken during dobutamine stress echocardiography of the mid (turquoise curves) and distal (yellow curves) septum. At baseline, both segments show systolic shortening of normal amplitude. At peak stress, the ischemic segment (yellow) develops postsystolic shortening (yellow arrows).<sup>3</sup> AVC, Aortic valve closure; AVO, aortic valve opening; MVC, mitral valve closure; MVO, mitral valve opening.

and strain-rate waveforms for which, in contrast to TDI, STE generally has an inadequate frame rate.

## b. Valvular Heart Disease

Improving the sensitivity and risk stratification of stress echocardiography through the addition of strain measures is an emerging paradigm for advanced assessment of asymptomatic severe valve disease. However, there is a paucity of data in this area, with only a few studies addressing its value in patients with severe MR. Magne *et al.*<sup>253</sup> demonstrated that a lack of 2% improvement in LVGLS at peak stress in patients with asymptomatic severe primary mitral valve regurgitation was predictive of poorer 3-year event-free survival and was incrementally superior to LVEF contractile reserve for prognostication.

## Clinical Consensus Statements

1. Although attractive on theoretical grounds, the use of stress deformation in valvular heart disease has technical challenges and inadequate evidence to support clinical application.

## H. Applications of Strain in CHD

Globally, CHD affects approximately 8.2 per 1,000 newborns with >90% of patients in the United States and Europe living into adulthood.<sup>254-256</sup> This reflects significant advances in medical therapies and surgical interventions. Despite this, arrhythmias, subclinical myocardial dysfunction and overt HF are common causes of significant morbidity and mortality among the CHD and adult CHD populations.<sup>254-256</sup> STE plays a role in early detection, quantification, and monitoring of ventricular dysfunction in various pressure and volume loading congenital malformations.<sup>257</sup> One of the difficulties with interpreting strain measures in these scenarios is the impact of loading conditions, which may make their interpretation more challenging. The following clinical advice is not intended to be a comprehensive description of the role of STE with every type of congenital heart defect but an effort to provide some guidance as to the suggested clinical utility of STE in those conditions where the evidence is more robust.

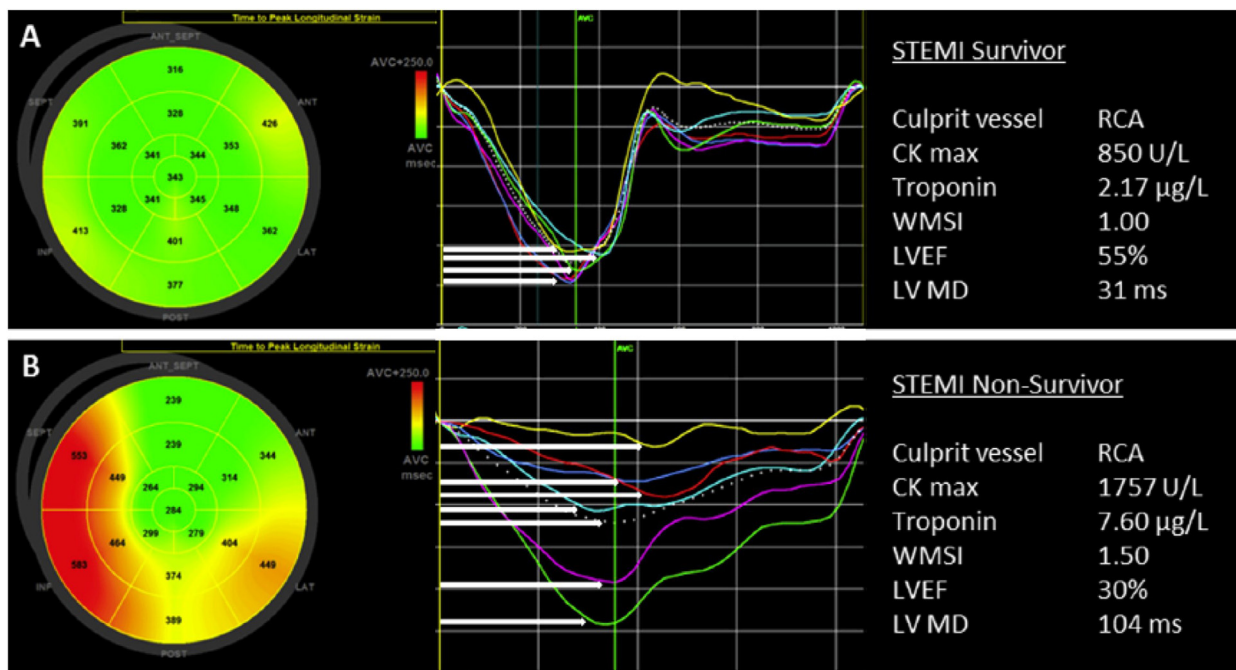
One of the main utilities of strain imaging in CHD is for the quantitative assessment of RV function, such as in patients after tetralogy of Fallot (TOF) repair, in those with a systemic right ventricle, and patients with PH. TOF repair often results in severe pulmonary regurgitation leading to chronic RV volume loading.<sup>258</sup> Monitoring RV function is clinically important. RV global, segmental, and RVFWLS measurements can be used to quantify RV function, and value as outcome predictors has been demonstrated.<sup>259-263</sup> Furthermore, in patients with repaired TOF, decreased LVGLS, reflecting adverse ventricular-ventricular interactions, has been associated with adverse outcomes.<sup>264</sup> A recent systematic review and meta-analysis further supports the utility of LV and RV strain as predictors of major adverse cardiovascular events in CHD.<sup>265</sup> Thus, serial monitoring of RVFWLS in combination with LVGLS is advised.

Systemic RV physiology can be present after atrial switch for complete transposition of the great arteries and congenitally corrected transposition of the great arteries and in patients with hypoplastic left heart syndrome undergoing Fontan palliation procedures.<sup>266</sup> Systemic RVs are at high risk for developing RV dysfunction and RV failure. There is evidence supporting the use of RV GLS for monitoring RV systemic function.<sup>267-269</sup> For these conditions RV GLS is the speckle-tracking echocardiographic parameter that should be used over RV free wall strain given the importance of the septal contribution to systemic cardiac output.<sup>270</sup>

PH associated with CHD can result in RV dysfunction and RV failure.<sup>271</sup> There is increasing evidence that RV strain parameters in patients with PH secondary to CHD have prognostic significance.<sup>272,273</sup> Additionally, monitoring RV and LVGLS in patients with Eisenmenger syndrome and other causes of PH has been suggested as contributory to outcome prediction.<sup>274</sup>

Furthermore, there has been some evidence to support the role of an LVGLS less negative than  $-18\%$  as a superior prognosticator over purely LVEF in Ebstein's anomaly patients for transplant-free survival and reduced HF exacerbations.<sup>275</sup>

Speckle-tracking analysis of atrial function within the heterogeneous CHD cohort is an emerging area of interest. However, additional investigations are needed before any clinical advice can be made.



**Figure 16** Assessment of LVMD with 2D STE. LVMD was calculated as the SD of the time of onset of the QRS complex on the electrocardiogram to the peak LS in 17 segments of the left ventricle. The bull's-eye plots with the regional time to peak LS and the regional curves of time to peak LS from the apical four-chamber views are shown. The arrows indicate the time starting at the R or Q wave of the electrocardiogram until the peak LS. The patient in **(A)** had an inferior MI and preserved LVEF and short LVMD, whereas the patient in **(B)** had a larger inferior MI, resulting in lower LVEF and longer LVMD. ANT, Anterior; ANT\_SEPT, anteroseptal; CK, creatine kinase; INF, inferior; LAT, lateral; LVEF, LV EF; POST, posterior; RCA, right coronary artery; SEPT, septal; STEMI, ST-elevation MI; WMSI, wall motion score index. Reproduced with permission from Abou *et al.*<sup>276</sup>

## Key Points

- LVGLS has demonstrable prognostic value in some patients with CHD.
- Currently, there is no accepted normative RV strain values for systemic RV, post-TOF repair, or Ebstein's anomaly patients.

## Clinical Consensus Statements

1. The clinical role of LV and RV strain assessment has not been established for most congenital heart lesions.
2. RVFWLS can be used for quantifying RV function in patients after TOF repair. Serial RV measurements can be used to monitor RV function.
3. RV GLS can be used in the follow-up of patients with systemic right ventricles and in patients with PH secondary to CHD.
4. LA and RA strain measurements are emerging techniques in CHD with no robust evidence to support their clinical utility at the current time.

## I. Mechanical Dispersion

LV mechanical dispersion (LVMD) is a measure assessing the temporal heterogeneity of myocardial contraction and quantifies the variation in the timing of peak systolic LS across all segments of the left ventricle during one cardiac cycle. It is calculated as the SD of the time from peak of the R wave on the electrocardiogram to peak systolic LS in all LV myocardial segments (see Figure 16).<sup>276</sup> LVMD has

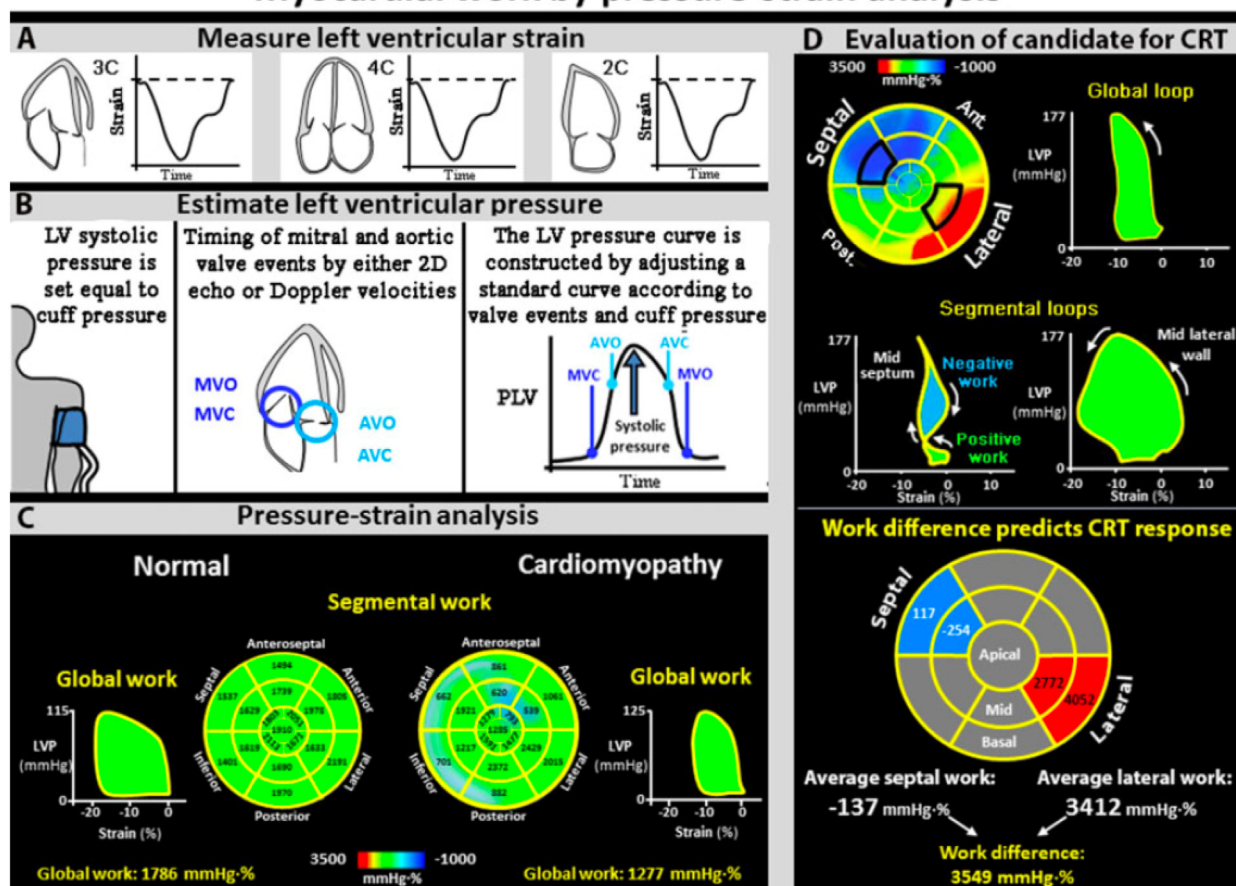
been related to arrhythmic events and may be helpful in identifying patients at increased risk, who might benefit from defibrillator implantation.<sup>277</sup> As this parameter is calculated as an SD among all LV segments, LVMD lacks spatiotemporal information and is therefore not optimal for predicting CRT response. Nevertheless, it can still be used in CRT patients to identify those at higher risk for arrhythmic events.<sup>278</sup> Additionally, elevated LVMD has some demonstrable value as a predictor of the need for pacemaker implantation for patients with severe AS undergoing TAVI.<sup>279</sup>

LVMD is associated with risk for ventricular arrhythmias and sudden cardiac death after AMI.<sup>280</sup> LVMD remained significantly associated with the end point in subgroups with LVEFs <35% and ≥35%. Further investigation has also supported the importance of assessing LVMD for the prediction of all-cause mortality and sudden cardiac death in patients with AMI.<sup>281</sup>

A comprehensive meta-analysis of patients with prior MI and those with nonischemic cardiomyopathy by Kawakami *et al.*<sup>277</sup> reaffirmed the incremental risk for ventricular arrhythmic events (hazard ratio, 1.19 [95% CI, 1.09-1.29] for every 10-ms increase in LVMD). Alternatively, increases in LVMD have been associated with the presence of coronary artery disease and in some selected populations all-cause mortality.<sup>282,283</sup>

LVMD is elevated in patients with bundle branch blocks and conduction delay, but outcome prediction is not well established in these conditions.<sup>284</sup> Furthermore, there is significant variability in LVMD across vendors, and the present consensus suggests that serial

## Myocardial work by pressure-strain analysis



**Figure 17** Myocardial work by pressure-strain analysis. **(A, B)** Schematically how echocardiography and brachial artery cuff pressure are used to obtain a noninvasive LV pressure (LVP) curve are shown. **(C)** LV PSLs from a normal subject and a patient with cardiomyopathy. Global and segmental LV PSLs are displayed as well as segmental bull's-eye plots. The patient with cardiomyopathy has reduced area of the PSL, which means reduced global LV work. **(D)** Myocardial work in a patient with HF and left bundle branch block (LBBB) who is evaluated for CRT. The *upper half* illustrates work distribution. The small area of the septal PSL indicates that very little work is done by the septum. Furthermore, during parts of systole the septum is stretched, which means negative work, as indicated by counter-clockwise rotation of the loop. The lateral wall segments show compensatory hypercontraction and a large loop. The lower half illustrates use of LV lateral wall-to-septal work difference to identify responders to CRT. For this calculation, it is sufficient to measure in only a single plane, the apical four-chamber (4C), and use only the basal and mid segments in septum and lateral wall. The work difference is calculated by using the average value from two segments. Reproduced with permission from Smiseth et al.<sup>296</sup> 2C, Two-chamber; 3C, three-chamber; Ant., anterior; AVC, aortic valve closure; AVO, aortic valve opening; MVC, mitral valve closure; MVO, mitral valve opening; PLV, left ventricular pressure; Post., posterior.

evaluations of LVMD should be performed using the same vendor software to maintain consistency and accuracy.<sup>285,286</sup> Normative values of mechanical dispersion have been reported in predominantly white populations with varying upper limits of normal across age ranges.<sup>284,287</sup> Generally, younger patients had lower LVMD, with LVMD increasing incrementally with age.<sup>287</sup>

Although mechanical dispersion can be measured in the right ventricle and left atrium, their clinical utility is not advised at this stage as further research is still required.

### Clinical Consensus Statements

1. Elevated LVMD after MI has been associated with ventricular arrhythmias and adverse outcome.
2. Elevated LVMD is not suited for detecting dyssynchrony amenable by CRT but may be helpful in assessing the need for defibrillator therapy after MI and in other cardiomyopathies.

3. When monitoring LVMD changes across a patient's studies, a single vendor should be used to avoid significant intervendor variability.
4. Mechanical dispersion of other chambers is not endorsed for clinical utility, as further evidence is required for these values.

## 5. FUTURE DIRECTIONS

### A. Three-Dimensional Strain

The accuracy of 3D speckle-tracking analysis mainly relies on the image quality and temporal/spatial resolution of 3D echocardiographic (3DE) data sets. Although one-beat acquisition of 3DE full-volume data sets is possible, further technological advancements will be required to obtain high temporal and spatial resolutions.<sup>288</sup> Volume rates of 30 to 50 Hz are likely needed.

In addition to the measurement variability of 3DE strain with the use of different ultrasound vendors' machines and software initialization of an ROI on the myocardial border is a potential source of observer variabilities for 3DE strain measurements. Similar to automated 2D strain analysis, fully automated 3DE strain software, has the capability for automatic determination of myocardial borders and 3DE speckle-tracking analysis, which may overcome some of these variability problems.

Myocardial curvature analysis and LV shape analysis are potential fields of research because it may provide prognostic information,<sup>289</sup> but at the present time, there is insufficient basis for clinical use.

Three-dimensional echocardiography has a potential advantage over 2D echocardiography for the assessment of irregularly shaped chambers, such as the right ventricle. Prognostic value of 3DE derived RVEF by 3D software aimed for the right ventricle has been demonstrated.<sup>290,291</sup> However, 3D RV strain is currently measured only by some software,<sup>292,293</sup> and the incremental value of 3D RV strain over RVEF for outcome prediction has not been demonstrated extensively.<sup>294</sup>

### Clinical Consensus Statements

1. Three-dimensional strain analysis is not currently advised for routine use, because of lower spatial and temporal resolutions. Fully automated 3D strain software may allow clinical adoption of this technique into routine practice in the future.

## B. Multilayer Strain

Multilayer strain analysis theoretically has the potential for detecting early stages of LV dysfunction. Nevertheless, a report from the EACVI-ASE Strain Standardization Task Force concluded there is no technical argument in favor of a certain myocardial layer for global LV functional assessment because of significant bias among different ultrasound vendors and interdependence of layer-specific GLS measurements.<sup>19,22</sup> Furthermore, it could not demonstrate differential LS changes in myocardial layers in normal vs infarcted myocardium, independent from the type of software (full-wall tracking/tracking isolated layers).<sup>15,19</sup> Given the thin walls of the chambers and the limited lateral resolution of echocardiographic imaging, layer-specific assessment of the right ventricle, left atrium, and right atrium is not feasible.

### Clinical Consensus Statements

1. Superiority of layer-specific strain over full-thickness strain has not been demonstrated and thus cannot be endorsed for clinical utility at the current time.
2. Layer-specific strain analysis is not endorsed for the right ventricle, left atrium, or right atrium.

## C. Myocardial Work

Pressure-strain loops (PSLs) have been suggested to account for the effects of afterload conditions on myocardial deformation.<sup>295</sup> The method provides measures of LV performance by both, generating PSLs and derived myocardial work indices (see [Figure 17](#)).<sup>296</sup> Segmental myocardial work indices correlate with myocardial metabolism as assessed by <sup>18</sup>F-fluorodeoxyglucose positron emission tomography.<sup>295,297</sup> Wasted work, constructive work, and work efficiency can be distinguished.<sup>298</sup> PSL analyses have shown promise in the detection of myocardial dysfunction in ischemia, AS, AR, and cardiomyopathies<sup>299-302</sup>; determining responses to CRT; and differentiating hypertensive myopathy.<sup>298,303</sup> Moreover, normal ranges of myocardial work indices have been published.<sup>304</sup> Currently, however, there is still a lack of convincing prognostic outcomes as well as a significant overlap of abnormal work indices with previously published normal ranges. There

is also no clear standardization, and outputs may vary significantly depending on determined valve timings.<sup>305</sup>

Finally, some interest has been directed at the off-label application of PSL analysis to the right ventricle to estimate RV myocardial work. Significant differences in PH and HF cohorts have been demonstrated, with some suggestions of prognostic value. However, the consequences of using proprietary LV PSL algorithms to evaluate RV geometry and pressures are not well established.<sup>215,306,307</sup>

### Clinical Consensus Statements

1. Noninvasive echocardiography derived myocardial work indices are not advised for routine clinical use, because of a lack of evidence for standardization and reliable cutoff values in the presence of pathology.
2. In select cases where blood pressure is significantly altered, myocardial work indices may be appropriate as an alternative measure to GLS.
3. RV myocardial work cannot be advised for clinical application at this time.
4. Continued research is encouraged to establish standardization and clinical application of myocardial work indices.

## D. Artificial Intelligence and Deep Learning

The application of artificial intelligence (AI) algorithms to strain analysis is undergoing rigorous investigation through various approaches. Regardless, all AI algorithms require clearance by the regulatory authorities.

Several commercial packages have now been cleared by the regulatory authorities for clinical use.<sup>308</sup> Proprietary algorithms have been developed for novice guidance acquiring echocardiographic images which may aid in expanding access and skillsets to underserved areas for the future performance of strain imaging.<sup>309</sup> Outcomes of an AI quantification of strain compared with manual strain using an algorithm that can automate more than 60 standardized measurements from an echocardiogram,<sup>310</sup> found correlation ranged from 0.76 to 0.84 with root mean square error ranging from 2.6% to 2.8%. Identification of wall motion abnormalities from the suspected MI cohort had area under the receiver operating characteristic curves averaging 0.80 (range, 0.69-0.90; see [Supplemental Table 12](#)).<sup>310</sup> More recently, deep learning pipeline algorithms have demonstrated good interreader variability compared with human operators, with a large British collaborative recently demonstrating that their Unity-GLS neural network had a better correlation with expert consensus GLS ratings ( $r = 0.91$ ) compared with individual expert readings ( $r = 0.85$ ).<sup>311,312</sup>

In the latest round of the intervender strain trials, several commercial AI algorithms will undergo comparison testing. Demonstrating agreement across all approaches to strain will be critical to acceptance of AI estimates clinically. Currently, it is evident that rapid advancements in AI algorithms in the near future are promising for the complete automation of clinically relevant strain measurements.

### Clinical Consensus Statements

1. AI-guided strain measurements may be used clinically, but only after demonstrating agreement with existing algorithms and obtaining regulatory approval. Such algorithms may improve reproducibility and are likely to progress dramatically in coming years.

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## REVIEWERS

This document was reviewed by members of the 2024-2025 ASE Guidelines and Standards Committee, 2024-2026 EACVI Scientific Documents Committee, and ASE Board of Directors.

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## DEDICATION

The Writing Committee dedicates this document to the memory of Drs. Roberto Lang and Maurizio Galderisi, who sadly passed away during its writing. Both were towers in our field and dear friends, and they are deeply missed.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.echo.2025.07.007>.

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