Toward Diagnostic Criteria for Left Ventricular Systolic Dysfunction From Myocardial Deformation

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Abstract— **Today, echocardiography is regarded as the clinical gold standard for evaluation of left ventricular (LV) dysfunction. Although a number of quantitative metrics are commonly used in conjunction with specific criteria to diagnose and prognosticate the disease state, part of the assessment of LV function is still qualitative and performed visually. Subjectively derived indices such as the wall motion score index are subject to significant inter-observer variability. Ultrasound-based measures of myocardial deformation (strain) have been available for several years, even in commercially distributed packages, and have the potential to offer a quantitative, objective, and more operator-independent assessment of LV function. However, despite growing evidence on the clinical utility of deformation imaging, a consensus on the meaning, interpretation, and normal ranges of myocardial strain is still lacking, thus preventing routine use of such estimates in clinical practice. In this article, we outline the current status of myocardial strain estimation and address the existing hurdles that must be overcome in order to incorporate this powerful technique into standard clinical assessment of LV function.**

I. Introduction

In current clinical practice, echocardiography is regarded as the gold standard in screening, diagnosis and monitoring of left ventricular (LV) dysfunction. During a routine reading of an echocardiogram, the cardiologist tracks various quantitative features, such as cardiac chamber dimensions, wall thickness, ejection fraction (EF), flow velocities, and valve morphology and function. These indicators provide a snapshot of local LV structure and global function, or deficits therein. Evaluation of regional function, on the other hand, relies primarily on visual assessment. For example, wall motion score indices (WMSI) have been shown to be strong prognostic indicators after a myocardial infarct [1], but WMSI is derived solely from subjective visual estimation of myocardial thickening during systole. Thus, aside from being subject to significant inter-observer variability [2], such measures only consider one (or, at most, two) dimensional deformation, while the actual tissue undergoes a much more complex three-dimensional motion.

Ultrasound-based assessment of myocardial motion and deformation (strain) was proposed more than twenty years ago, and has since undergone extensive development in 2D and 3D echo modes. Myocardial strain estimation offers an objective basis for evaluation of regional LV function throughout the cardiac cycle. In addition to quantifying deformations which may be visible to the expert's eye, such as wall thickening, strain estimation can also quantify motion components that cannot be easily discerned from standard B-mode images, at higher spatial and temporal resolution than metrics such as WMSI. Moreover, strain analysis packages have now been available on commercial echocardiography machines for a number of years from most major vendors, including Philips, GE, Siemens and Toshiba. These software packages typically offer 2D or 3D strain estimates from speckle tracking echo or tissue Doppler imaging.

Despite the extensive supporting literature and widespread availability on a number of different platforms, LV strain estimation is still not a routine component of clinical evaluation. In this article, we discuss the general principles and current status of myocardial strain estimation; then, some existing barriers to use of strain as a standard clinical index are addressed, and some potential pathways to overcoming these hurdles are presented.

II. Current practice in clincial echocardiography

During a standard clinical echocardiographic examination, a trained registered sonographer acquires a set of still images and cine-loops, from which all measurements of heart structure and function are performed by a cardiologist with specific expertise. Acquisitions are done from parasternal, apical, and subcostal acoustic windows, where ultrasound is best transmitted through soft tissues to the heart. From cine-loops of the moving heart, data about chamber dimensions, volumes, and wall thickness are measured. Spectral Doppler is used to quantify blood flow velocity through cardiac valves, and to detect abnormalities in such flows from valve insufficiency or stenosis. The assessment of LV systolic function (the ejection phase of the cardiac cycle) is most frequently performed by measuring ejection fraction, which is calculated as

$$LVEF = \frac{end\ diastolic\ volume - end\ systolic\ volume}{end\ diastolic\ volume}, \quad (1)$$

and expressed as percent. The two volumes in the formula are calculated either in 2D or in 3D, using the modified Simpson's method of the disks from two orthogonal apical views (4-chamber, 2-chamber view). EF values above 55% are considered normal, whereas EF below 55% represents some degree of LV dysfunction [3]. LV wall motion analysis is performed by visual assessment of the magnitude of thickening during systole of each LV segment. The motions of all ventricular segments are assessed by integrating visual information from short- and long-axis views, and a global wall motion score is calculated by summing the individual scores of each segment. LV diastolic function (the filling phase of the cardiac cycle) is also assessed from trans-mitral Doppler flow, mitral valve velocity by tissue Doppler,

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pulmonary veins flow, and by measuring left atrial dimensions. The interpretation of the clinical echocardiographic exam, even if limited to the most clinically used parameters, is labor-intensive, time-consuming, and also subject to inter-observer variability. Adding to it a whole set of elaborate post-processing analysis, which requires additional time and expertise, is understandably difficult to implement practically in a clinical setting. However, evidence is accumulating that myocardial deformation assessment can provide useful information in various clinical scenarios.

III. Myocardial Strain: General Principles

A. Defining Strain

Strain (ε) is defined as the change in length of a tissue (L) relative to its baseline state (L_0), i.e. $\varepsilon = (L-L_0)/L_0$. By convention, thickening of tissue then corresponds to positive strain ($\varepsilon > 0$), and thinning corresponds to negative strain ($\varepsilon < 0$). In a 3D Cartesian system, we may then measure strain components along each main axis (denoted ε_{xx}, ε_{yy}, and ε_{zz}); though, when considering the heart, a more convenient set of strains to analyze is based on the natural coordinate system of the LV, namely the radial, longitudinal, and circumferential directions (Fig. 1). Notably, while longitudinal deformation might be visualized in a long-axis apical view, and radial thickening/thinning can be observed in short-axis slices, circumferential deformation (and by relation, LV twist) cannot be assessed by eye. Beyond these three normal strains, the complete strain tensor also includes shear strain components, which together fully characterize tissue deformation. Strain information is therefore a symmetric 3×3 tensor that is computed at every pixel. From this perspective, the complete tensor is complex to interpret and display.

There are many approaches to myocardial strain estimation from echocardiographic data. Broadly, there are three categories, classified by what kind of data is acquired and analyzed. Acquisition of radiofrequency data in the standard echo views permits strain quantification through myocardial elastography [4]. Doppler-based measures of the myocardial velocity and strain rate are referred to as Tissue Doppler Imaging (TDI) [5], [6]. Lastly, motion analysis from standard B-mode images is commonly referred to as Speckle Tracking Echocardiography (STE) [7], [8]. In the following two sections, we will focus only on the two latter techniques, as they are currently the most validated and widespread among commercialized tools.

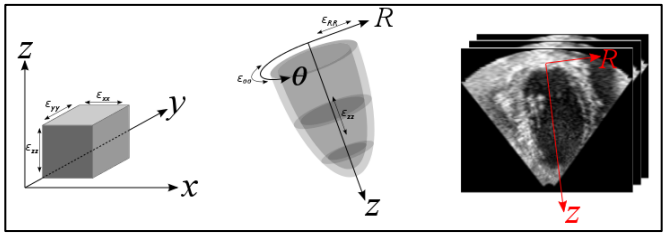

Figure 1. Relationship between the 3D cartesian system and the LV coordiante system. ε* denotes principal strain along each axis.

B. Strain Estimation via TDI

TDI utilizes the Doppler effect with a standard US probe to measure the velocity of the insonified tissue throughout the cardiac cycle. Most commonly, TDI is performed in 2D B-mode views, and produces an estimate of motion (and, by extension, deformation), along the direction of US beam propagation [5]. Two key advantages of TDI are the ability to sustain high-frame rates, without the need for ECG-gating or multiple acquisitions; and to provide visual feedback in real time. By this method, TDI can be used to acquire, for example, longitudinal strains in the LV using a long-axis apical view. However, TDI has several critical limitations. First, the nature of the Doppler effect means that TDI-based strains are strongly angle-dependent, and thus subject to variability depending on the view in which they are acquired. Further, because motion can only be measured along one Cartesian direction, 2D/3D deformations (e.g. circumferential and radial motion in a short axis view) cannot be accurately measured throughout the tissue. At best, several acquisitions in different views are required in order to obtain only partial information about LV motion. Thus, despite widespread availability on commercial machines, and successful application in various research studies, TDI is not widely regarded as a tool useful in routine clinical LV evaluation [9].

C. Strain Estimation via 2D/3D STE

STE is a post-processing technique that is applied offline to standard B-mode echocardiographic images. Optimal acquisition requires good image quality and high frame rates (>25 fps) to avoid undersampling. This is achieved by adjusting sector depth and width to include only the region of interest (ROI). Acoustic artifacts should be avoided, as those also affect speckle tracking accuracy. 2D short and long axis views should be correctly visualized and apical foreshortening, another factor affecting tracking reliability, should be minimized. 3D studies can be much easier, as only one apical view is required for full visualization of the LV.

Strain analysis by STE is a semiautomatic method, which, with variations between different software, first requires the operator to define the myocardium of interest. Subsequently, manual adjustments to the ROI are performed to include the LV wall in the analysis, thus excluding the LV cavity and the pericardium from the sample area. Temporal landmark points (e.g. from spectral Doppler) are set to identify diastolic and systolic phases. After automatic tracking of speckles, a second round of manual adjustments is usually performed by the operator to obtain optimal motion and deformation profiles. Tracking can be performed via a variety of techniques, including block matching [7], [8] and non-linear registration [10].

STE deformation measurements have been validated against sonomicrometry and MRI [11], [12]. In general, published validation studies compare either global LV measures (i.e. globally averaged radial or longitudinal strain), or averaged correlations between corresponding segments [13], [14].

D. Strain Display and Characteristics

Analysis results are visualized as strain color maps imposed over an LV bullseye diagram, or as strain curves from each ventricular segment using the standard 17-segment AHA model. Each of the three strain components is displayed and analyzed separately (Fig. 2). In cases where the shear strains are calculated, three additional components are also considered.

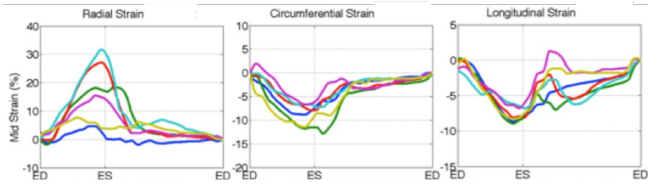

Figure 2. Sample strain curves from a normal subject, derived via 3D STE. Here, only the three principal strain components are shown, from the six mid-level LV segments.

From these charts, a number of measurements and parameters can be derived and assessed depending on the clinical condition studied: peak strain values per each segment, global average strain, time-to-peak strain, and dyssynchrony indices are the most studied parameters.

More detailed analysis of the temporal progression of strain in each segment may also be informative: a salient feature of infarct regions is systolic radial thinning while healthy regions undergo thickening. This paradoxical deformation may not be obvious to an inexperienced observer, but is easily seen by visualizing and comparing the strain profiles in multiple segments.

E. Challenges and Limits of Strain Measures

The demonstrated potential of strain analysis to detect clinical and even sub-clinical LV dysfunction belies several difficulties in attaining reproducible and reliable strain profiles.

One reason for this is the intrinsic heterogeneity of ultrasound as a modality. Because transthoracic echo relies on intercostal and subcostal spaces to view the heart, image quality varies significantly not only between patients, but even within a single image in one patient. Artifacts such as tissue dropout, shadowing and reverberations can introduce significant noise into the image, and thus corrupt strain estimates. As this is an issue of data acquisition, it affects all subsequent post-processing techniques, whether TDI, 2D STE or 3D STE. Thus, in order to achieve more robust strain analysis, most studies have employed a manual step of excluding low-quality segments from analysis [11] [13] [15]. Naturally, the heterogeneity of image quality between patients further amplifies this problem. One study has suggested that this limitation may preclude the use of STE in general patient populations [15].

Another source of heterogeneity is not intrinsic to ultrasound acquisition, but rather to the domain of post-processing methods. Even if we only consider block-matching STE, there is an enormous variability in the specific steps used to calculate regional and global strain values. Factors such as search window size, type of matching measure, and spatial and temporal smoothing all influence the shape and amplitude of the final strain profile. For all these reasons, today strain measures still lack reliability and standard calibration methods.

IV. Clinical Relevance of Strain Measurements

Many studies have demonstrated that the evaluation of LV deformation along different directions can provide important details on the pathophysiology of LV systolic mechanics beyond traditional EF assessment. Even when EF is in the normal range, the distribution and patterns of myocardial strain can be heterogeneous, reflecting a functional remodeling that has been correlated with the presence of cardiovascular risk factors such as hypertension, diabetes, coronary artery disease, and LV hypertrophy [16] [17] [18]. Recently, the application of deformation imaging to population studies led to the recognition of a significant proportion of LV subclinical dysfunction otherwise unrecognized by traditional assessment. Strain measurements, both in subjects with normal EF and in those with cardiac disease, are prognostically relevant, being associated with future cardiovascular events [19], [20]. Furthermore, a recent study demonstrated that LV dysfunction as measured by global longitudinal strain, even in the context of unaffected LVEF, has a distinct association with subclinical brain infarcts [21].

In patients with overt heart disease, the site of damage in the ventricular wall may differently affect specific components of LV function. In patients with ischemic heart disease, LV longitudinal strain has been shown to be specifically affected by subendocardial infarction, whereas transmural infarction is associated with depressed circumferential strain [22], [23].

Although global strain has been demonstrated to carry significant prognostic value in several clinical conditions and is able to identify degrees of subclinical dysfunction that EF cannot detect, a more regional assessment is needed when, like in ischemic heart disease, the disease process involves LV segments but the global function appears unaffected. Longitudinal strain, in particular, is especially sensitive to myocardial ischemia because longitudinally oriented myofibers are predominant in the subendocardium, an area particularly vulnerable to ischemic injury. In fact, LV strain and strain rate have been shown to correlate with the presence of obstructive coronary disease even in normally contracting myocardial segments [24].

Another area of potential utility of tissue velocity and deformation imaging is LV dyssynchrony assessment in patients with heart failure or after myocardial infarction. Time differences in peak velocity or peak strain between opposing wall segments or an excessive peak velocity or strain dispersion, measured as standard deviation of the TTPS in myocardial segments, have been shown to correlate with the extent of the myocardial damage, and with the response to cardiac resynchronization therapy (CRT) [25] [26].

V. Barriers to Acceptance and Future Work

Despite the published validation studies, the latest expert consensus on 3D STE is that additional rigorous verification

and testing are still needed [27]. Furthermore, there is a lack of agreement about specifically which strain derivatives are most useful clinically (i.e. peak radial strain, peak strain rate, dyssynchrony indices, etc.).

Commercial packages which are frequently used in clinical studies essentially function as black boxes, and the consequent variability in their outputs is well documented [27], [28]-[30]. As there is no standard calibration for any of these methods, it is difficult to establish specific quantitative criteria even for something as simple as "normal" versus "abnormal," let alone specific disease states.

The lack of consensus regarding standardized interpretation of multidimensional strain data is another immense unresolved challenge. Investigators have performed comparison studies between 2D/3D STE and 3D MRI[13]-[15], [31], and sonomicrometry [11], but such comparisons still do not capture the true motion of the underlying tissue, so disagreement is to be expected. Studies that reported more promising results have only compared averaged or global values, for example taking the mean longitudinal strain across the entire LV as a metric of function. The more fundamental question, however, is which metric ought to be compared. As shown in Figure 2, for any chosen component of the complete strain tensor, the LV may be characterized in a number of ways. At the broadest level, on par with EF estimation, is the global average value of the strain, taken over every valid point in the ROI (i.e. after exclusion of low quality regions).

More detailed analysis of the temporal progression of strain in each segment may also be informative: a salient feature of infarcted regions is the demonstration of radial thinning during systole while healthy regions undergo thickening. This paradoxical deformation may not be obvious to an inexperienced observer, but is easily seen by visualizing the strain profiles in multiple segments.

As explained in Section III, the complete strain tensor exists at every pixel in the image. In segmental analysis, many pixels are averaged to decrease noise and a single value for the entire segment is generated. However, if the underlying data is sufficiently reliable, averaging should be avoided (as it could be detrimental), and a truly full-resolution strain map of the LV should be generated. Such high-resolution maps are considerably more complex, but employ the full extent of the acquired data, permitting delineation of more localized phenomena. Visualization of such data is, however, quite challenging because this highly multidimensional information (3 spatial directions, 3-6 strain directions, and time) must still be displayed for the user on a 2D surface (i.e. on paper or a computer screen). Existing visualization methods include bullseye plots [32], as well as various methods of 3D projection in order to reduce the dimensionality. One example is Lopata, *et al*'s technique of averaging along the radial direction to reduce a 3D LV volume to a 3D surface [33]. Such methods are certainly elegant from a technical and theoretical perspective, but they have had understandable difficulty gaining acceptance in the cardiology clinic, as the visualizations are much too diverse and unintuitive. The implication is clear: even if 3D STE strain measures achieve full validation and demonstrate sufficient predictive power, widespread adoption will rely on new methods of presenting the complex data in ways that are both clinically enlightening and intuitive, without reducing the wealth of information to a falsely simplistic single-number index of LV function.

The issue of validation also remains unresolved. As detailed above, numerous studies have attempted to demonstrate the accuracy, reproducibility, and robustness of LV strain measures by various means. Nevertheless, as of this writing, the authors are unaware of any published studies describing the results of the "ultimate" validation procedure, whereby all 3D strain components measured by STE are compared to a gold standard such 3D tagged MRI, on a pixel-by-pixel basis. Such a study, performed in human subjects, would definitively prove the adequacy or inadequacy of the proposed STE technique in estimating true LV strains in humans. Performed exclusively on a large population of healthy subjects, the study would provide a reference or calibration metric for what ought to be considered normal values. By extension, inclusion of specific disease populations (along with properly matched normal controls), would permit us to evaluate whether the method offers any added-value (i.e. greater sensitivity or specificity) over the existing clinical paradigm.

The evidence generated by such investigations will form the foundation upon which broader criteria on the interpretation of echocardiography-based strains may be developed. Only once such guidelines are enacted by the authoritative organizations will strain measurements begin to gain traction in the cardiology clinic.

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