Echocardiographic Strain Imaging in Coronary Artery Disease
The Added Value of a Quantitative Approach

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KEYWORDS

- Ischemic cardiomyopathy • Coronary artery disease • Speckle tracking echocardiography
- Global longitudinal strain • Left atrium • Right ventricular infarction

KEY POINTS

- Longitudinal left ventricular function by speckle tracking echocardiography provides incremental diagnostic and prognostic information in patients with subclinical and overt coronary artery disease. This technique may be on his way to an ultimate introduction in the clinical practice.
- Longitudinal strain-derived indexes (early systolic lengthening and postsystolic shortening) are further expanding and refining the applications of speckle tracking echocardiography, particularly in patients with coronary artery disease.
- Right ventricular and left atrial function by speckle tracking echocardiography are emerging prognosticators in ischemic cardiomyopathy, deserving great attention in the research field.

INTRODUCTION

Cardiovascular disease remains a leading and partially preventable cause of death worldwide; therefore, the early detection of incipient myocardial ischemia has always been a challenge for the clinicians. Echocardiography is part of the first-line patient assessment tools and may provide crucial incremental information to guide patients' management.[1]

The assessment of regional myocardial function is the cornerstone for the detection of myocardial ischemia by echocardiography. However, it is grounded on visual assessment and requires considerable expertise. Similarly, the quantification of damage after myocardial infarction (MI) relies on left ventricular ejection fraction (LVEF) calculation, which is based on ventricular volumes measurements, known to hold unsatisfactory intra- and interobserver variability, particularly in the context of distorted LV geometry or wall motion abnormalities.[2,3]

Assessment of LV function through strain imaging is currently increasing as an alternative method to identify early myocardial dysfunction before an

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overt reduction in LVEF, thus revealing the so-called subclinical LV dysfunction.[4]

Furthermore, when applied to other cardiac chambers, as the right ventricle (RV) or the left atrium (LA), strain imaging has expanded the quantitative echocardiographic approach and has allowed the detection of myocardial dynamics to a level unreachable before.

The present review focuses mostly on speckle tracking echocardiography (STE) and its application on patients with coronary artery disease (CAD) to improve diagnosis and prognostic risk stratification; the analysis and the technical differences between STE and tissue Doppler methods are beyond the scope of this dissertation.

The analysis of myocardial strain by STE results, after an appropriate learning curve, is feasible and can provide a quantification of the active myocardial deformation.[5]

Strain indicates the tissue deformation (expressed in percentage) during the cardiac cycle, assuming positive strain values for elongation and negative strain values for shortening; strain-rate indicates the speed at which the deformation occurs.

Two-dimensional (2D) strain is progressively being introduced in the clinical practice; 3D-based strain has been proposed as a less time-consuming alternative, but it is not yet implemented in many laboratories and requires further validation as well as the definition of normal reference values.[6]

In particular, global longitudinal strain (GLS) is calculated as the average longitudinal strain from all segments made in standard apical 2-, 3-, and 4-chamber views,[7] with normal value reported between −18% and −25% in healthy individuals[8,9] (**Fig. 1**), whereas circumferential and radial strains are determined from short-axis views.

Although promising and appealing, 2D STE does not come without limitation at the current state. Indeed, strain normal range depends on multiple factors as age, gender, and weight[8]; furthermore, the systolic strain is not entirely independent from loading conditions.[9]

Strain calculation requires good imaging quality and according to the current guidelines its calculation should be avoided if more than 2 myocardial segments are not adequately visualized in a single view.[2] Lastly, intersoftware and intervendor variability must also be kept in mind, especially when assessing segmental strains.[7]

LEFT VENTRICULAR STRAIN AND MYOCARDIAL ISCHEMIC PROCESS

Three layers form the myocardial wall: the inner and the outer layers with oblique fibers and the middle layer with circular fibers. GLS, global circumferential strain, and global radial strain, as measured by STE, reflect the main shortening vectors of these fibers.[10]

Ischemic changes primarily affect the subendocardial layer, where longitudinal myocardial fibers are more represented.[11] Consequently, CAD and myocardial ischemia are more frequently associated with reduced strain values in the endocardium than in the epicardium. However, in current practice, STE is mostly used to evaluate the entire myocardial wall dynamic (see **Fig. 1**), as the applicability of layer-specific strain is not yet validated and further studies are needed.[12]

Speckle Tracking Echocardiography to Detect Subclinical Myocardial Damage

In terms of diagnostic accuracy improvement for patients with suspected CAD, STE analysis has been proposed as a feasible and reproducible method for the identification of myocardial ischemia during stress echocardiography recognizing functional defects before the development of regional wall motion abnormalities.[13,14]

A study investigated the role of strain imaging in dobutamine stress echocardiography on 102 patients with suspected CAD.[15] Longitudinal strain had similar diagnostic accuracy to wall motion score index; however, if combined with wall motion assessment by an expert reader its accuracy increased to 96% in the detection of regional ischemia.[15]

The routine adoption of speckle tracking during stress echocardiography is still a matter of debate,[16] as there are issues of applicability due to excessive myocardial motion at higher heart rates and the lack of definition of cutoff levels for each major coronary artery region. Joyce and colleagues[17] reported variable diagnostic accuracy using the same cutoff value for the strain parameter in different coronary perfusion regions. The adoption of cut-offs based on “sentinel segments” may be useful, but the heterogeneity of the perfusion territory distal to the stenosis makes it not always accurate.[16]

SPECKLE TRACKING ECHOCARDIOGRAPHY IN PATIENTS WITH STABLE ANGINA AND ACUTE CORONARY SYNDROME

Regional longitudinal peak systolic strain proved to be useful to diagnose CAD and identify the ischemic myocardial areas in patients with stable angina pectoris.[18] GLS may also be useful to identify high-risk patients with left main stem stenosis and 3-vessel CAD in the absence of regional wall motion abnormalities.[19]

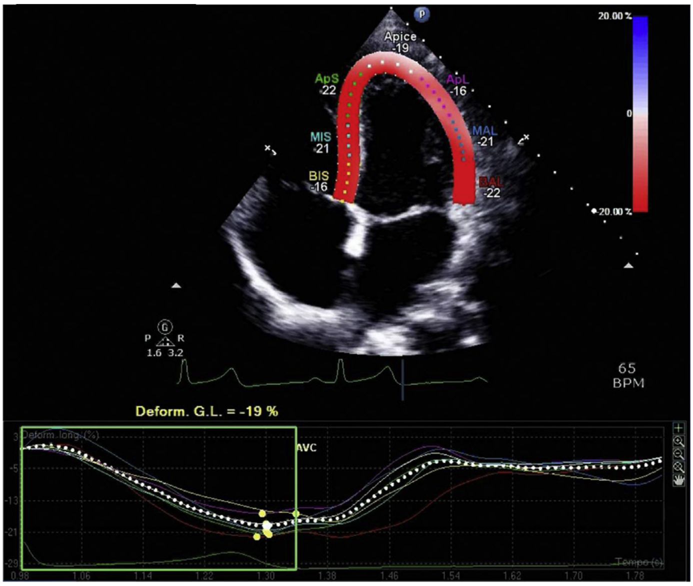

Fig. 1. Example of LV longitudinal strain measurement from the apical 4-chamber view. AVC, aortic valve closure; G.L., global longitudinal strain.

In the chronic phase of ischemic cardiomyopathy, GLS has shown to provide important prognostic information, being independently related to all-cause mortality and combined endpoint in a large cohort of 1060 patients.[20]

Regarding acute coronary syndrome, in the early phase of acute MI, reduced GLS may predict the occurrence of complications.[21] Performed right after the coronary revascularization, GLS seemed useful in distinguishing patients more prone to early recovery and reverse remodeling from those who acutely would merit more intensive monitoring and closer follow-up even after a successful percutaneous coronary intervention.[22] Indeed, GLS correlates with the final infarct size better than LVEF or wall motion score index and has a role in the prediction of major cardiovascular events and overall mortality.[23,24]

Strain parameters are also associated with the amount of myocardial fibrosis and might aid in discriminating transmural scarring from nontransmural to target further revascularization.[25,26] Lastly, although conflicting, some report indicates that GLS can identify stunned myocardium likely to recovery after an acute MI.[27]

Another important diagnostic application of myocardial strain is the identification of significant residual CAD after MI in the presence of existing concomitant wall motion abnormalities. A study investigated the role of dobutamine stress echocardiography in detecting residual ischemia in 105 patients at 3 months after first ST-elevation MI.[17] Not only patients with significant residual coronary disease demonstrated greater worsening in global peak longitudinal systolic strain from rest to peak-dose dobutamine but the authors found a significant drop of the peak longitudinal systolic strain in the segments with significant coronary artery using a sentinel segment approach, confirming the promising value of STE in this setting.[17]

EARLY SYSTOLIC LENGTHENING AND POSTSYSTOLIC SHORTENING OF LEFT VENTRICULAR SEGMENTS

Early systolic lengthening (ESL) is a novel predictor of cardiovascular events defined as the time from onset of the QRS complex to the peak positive systolic strain[28] (Fig. 2). ESL reflects a passive lengthening of an ischemic myocardial region before the beginning of systolic shortening, due to its reduced ability to generate an adequate active force during the pressure increase in the isovolumic contraction phase.

In patients with acute MI, ESL duration provides information about prognosis, infarct size, may identify patients with minimal myocardial damage, and may differentiate between occlusive and non-occlusive CAD.[28,29] It may represent a novel and complementary measure of ventricular damage and a predictor of long-term cardiovascular events in those patients who displayed good overall GLS after ST-elevation MI.[30]

Furthermore, ESL may discern between viable and nonviable segments, with akinetic segments displaying significantly higher ESL values.[30,31]

Postsystolic shortening (PSS) reflects a longitudinal shortening occurring after end-systole at

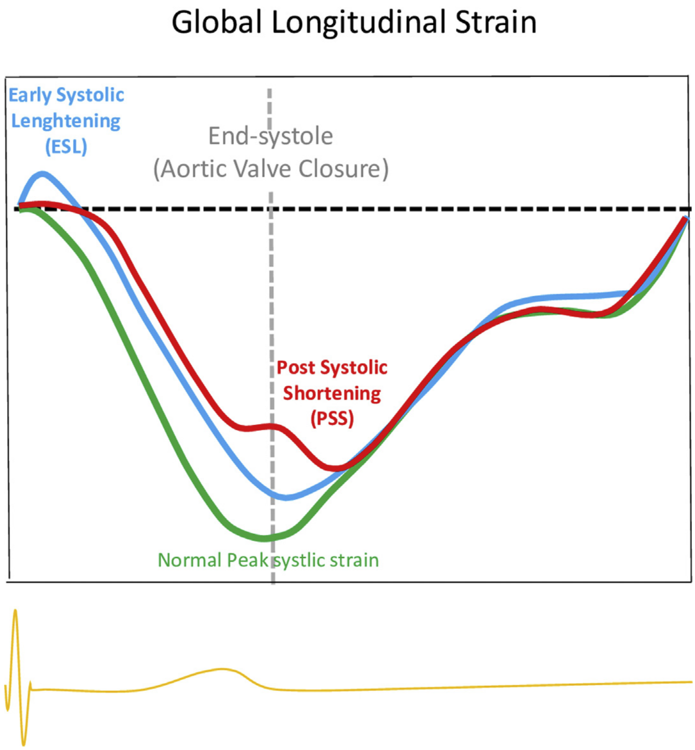

Fig. 2. Illustrative examples of longitudinal strain profile with postsystolic shortening (PSS) and end-systolic lengthening (ESL). PSS is considered myocardial contraction after the point of aortic valve closure, whereas ESL is a lengthening of a myocardial region before the beginning of systolic shortening.

aortic valve closure (see **Fig. 2**). PSS may be found in ischemic viable myocardium reflecting some degree of active contraction, whereas irreversibly injured myocardium remains passive after coronary occlusion.[32] PSS provides information about the ischemic burden[33] and is a predictor of major adverse cardiovascular events and death in patients with acute MI and [34] chronic CAD.[35]

In dobutamine stress echocardiography, diastolic dyssynchrony imaging is a good predictor of CAD,[36] as confirmed by a recent metanalysis.[37]

As a word of caution, PSS may not be ready to be adopted as a stand-alone to identify CAD, as it may be found in healthy individuals in up to one-third of myocardial segments.[38]

RIGHT VENTRICLE FUNCTION

RV involvement in patients with MI is associated with high in-hospital and late mortality, ventricular arrhythmias, advanced atrioventricular block, and mechanical complications.[39–41]

Because isolated RV infarction accounts for less than 3% of all cases of MI, concomitant RV involvement ranges from 14% to 84% of acute MI.[42] Clues of RV involvement in patients with not only inferior but also anterior LV infarcts have been provided by cardiac magnetic imaging studies.[43]

Multiple parameters based on monodimensional and 2D imaging, pulsed-wave (PW) Doppler, and tissue Doppler imaging (TDI) have been described to quantify RV function.[44] Although fully endorsed by the current guidelines, the efficacy of these parameters has been questioned by many investigators in recent years.

The recent application of newer myocardial deformation techniques to the RV could help in overcoming these limitations, allowing the detection of subtle RV dysfunction. RV strain by speckle tracking has proved to be a reliable and accurate tool for the evaluation of RV systolic function when validated against RV ejection fraction by cardiac magnetic resonance in different clinical settings.[45,46] In the latest recommendations for cardiac chamber quantification for the first time a clinical indication for RV strain is included.[2] RV speckle tracking strain is obtained from the apical 4-chamber view, and it could reflect the average value of the RV free wall strain alone or both the RV free wall and septal segments (**Fig. 3**). Currently, the use of RV free wall seems to have the largest body of evidence, but further investigations are needed to clarify this point. Interestingly, a group proposed an approach for a global assessment of RV function using 3 RV apical views, permitting a full reconstruction of the RV

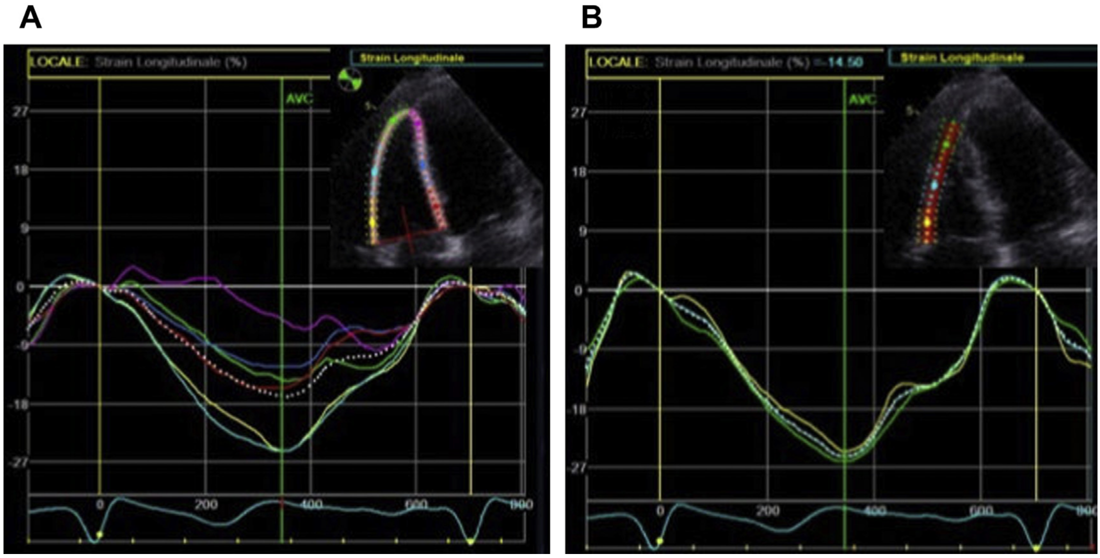

Fig. 3. Assessment of RV systolic function by 2D longitudinal strain from an apical 4-chamber view. Strain curves obtained automatically by tracing the endocardial margin of RV free wall and septal segments (*A*) or of the RV free wall alone (*B*). Each curve represents one RV segment. An average ventricular longitudinal strain along the cardiac cycle is depicted (*dashed curve*).

in an 18-segment model and a calculation of a "true" RV global longitudinal strain.[47] To date, wide agreement regarding normal values is lacking; a recent meta-analysis suggested $-27 \pm 2\%$ as the normal range, but an RV free wall strain cut-off of -20% to -21% seems to be able to detect abnormal RV function.[48,49]

Few studies have investigated the relationship between RV speckle tracking strain and CAD. Among these investigations, acute MI has been discussed more than chronic ischemic heart disease. In patients with MI, RV strain has proved to be the best tool providing information about global and targeted regional function, with good feasibility and reproducibility.[50] Global longitudinal strain of the RV showed a better sensibility and specificity for prediction of major adverse cardiovascular events than standard RV function parameters.[51,52] It also provides important prognostic information about the arrhythmic risk and sudden cardiac death in patients with acute MI[39] due to interwoven scar tissue and viable myocardium constituting substrates for reentry arrhythmias. There is little evidence regarding outcomes associated with RV strain in chronic ischemic heart disease. In a study by Chang and colleagues[40] conducted on 208 patients with stable angina, impaired RV strain was significantly related to worse cardiovascular outcomes and new onset of arrhythmia. The same group successfully demonstrated the usefulness of RV strain for the detection of occult RV dysfunction in patients with chronic right coronary artery stenosis.[41] Lastly, RV strain provides prognostic value also in stable outpatients with chronic heart failure. In a cohort of 171 consecutive patients with stable LV dysfunction (41% with ischemic cardiomyopathy), a lower magnitude of RV strain predicted adverse events after adjustment for age, cause of heart failure, and LVEF.[53] Although it has been accepted that RV dysfunction complicates and increases long-term mortality, whether RV strain is an independent predictor of adverse events in patients with CAD or a consequence of the progression of LV dysfunction still requires verification. Currently, preliminary results indicate that the RV itself plays a pivotal role in maintaining hemodynamic and rhythmic stability, but further prospective studies are needed.

LEFT ATRIAL FUNCTION

In recent years, the role of LA mechanical function has emerged to be of clinical value in several clinical settings including the ischemic heart disease.[54–57] LA function, in close interdependence with LV function, plays a crucial role in maintaining optimal cardiac performance. LA modulates LV filling through its 3 phases: reservoir, conduit, and booster pump. The reservoir function corresponds to the LV systole; the conduit function results from the blood transiting from the LA to the LV during early diastole (passive emptying); and finally the booster pump function in late diastolic phase corresponds to the LA contraction. The contribution of LA phasic function to LV filling depends on LV diastolic properties. With abnormal relaxation, the relative contribution of LA contractile function to LV filling increases, whereas the conduit function decreases. As LV filling pressures progressively increase, the limits of atrial preload reserve are reached, and the LA serves predominantly as a conduit.[58]

The estimation of LA function can be obtained by several methods, including the assessment of changes in LA volume during the cardiac cycle, analysis of transmitral flow by PW Doppler, and evaluation of LA myocardial velocities by TDI. Despite these methods, the quantification of LA function remains a challenging issue because their application requires a skillful acquisition technique and calculations that are not routinely performed. To date, direct evaluation of LA function is also feasible with STE. This technique permits assessment of longitudinal myocardial LA deformation, which provides additive value concerning LA function when compared with conventional echocardiographic measurements and seems easier to apply.[59] In line with the current American Society of Echocardiography/European Association of Echocardiography consensus,[60] the LA endocardial border is manually traced in the 4- and 2-

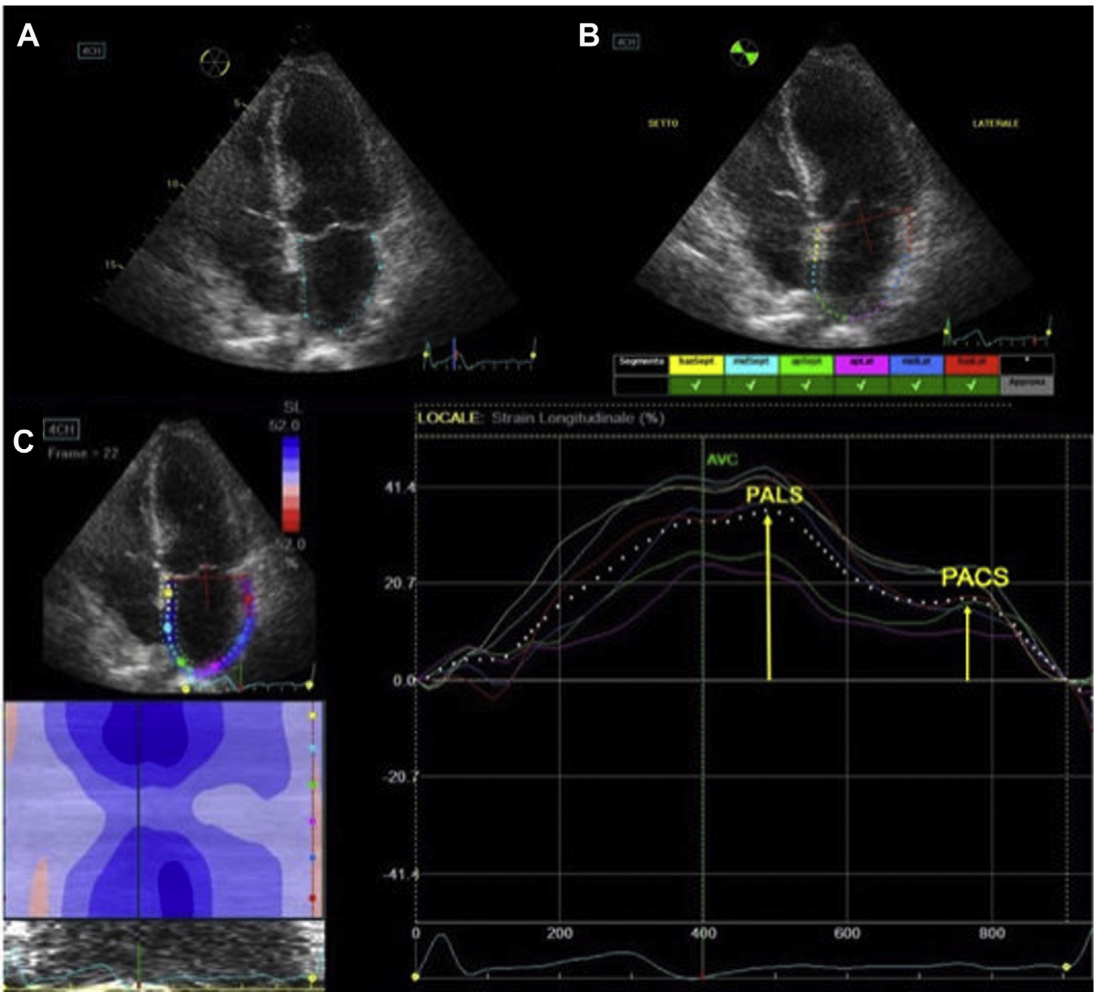

Fig. 4. Comprehensive LA function by 2D longitudinal strain from an apical 4-chamber view. (*A*) LA endocardial region of interest tracing. (*B*) The LA is divided into 6 segments: basal septal (basSept; *yellow*), midseptal (midSept; *light blue*), apical septal (apSept; *green*), apical lateral (apLat; lilac), mid lateral (midLat; *blue*), and basal lateral (basLat; *red*). (*C*) Strain curves during a cardiac cycle using the onset of the QRS complex as the starting point. Each curve represents one LA segment. An average atrial longitudinal strain along the cardiac cycle is depicted (*dashed curve*). AVC, aortic valve closure; PACS, peak atrial contraction strain; PALS, peak atrial longitudinal strain.

chamber views, thus delineating a region of interest composed by 6 segments. Then, after segmental tracking quality analysis and eventual manual adjustment of the region of interest, longitudinal strain curves are generated by the software for each atrial segment. Peak atrial longitudinal strain (PALS) is measured at the end of the reservoir phase, and peak atrial contraction strain (PACS) is measured just before the start of the active atrial contractile phase (Fig. 4).

There is increasing evidence demonstrating the value of PALS in acute and chronic ischemic heart disease. In patients with acute MI treated with primary percutaneous coronary intervention, PALS provides additional prognostic value beyond baseline risk factors and LA maximal volume.[61] Because of increased LV chamber stiffness and LV filling pressures occurring in acute LV ischemia, LA pressure may be increased. To maintain adequate LV filling, a preserved LA reservoir function is crucial. In contrast, in patients with noncompliant LA and reduced reservoir function, LV filling may be significantly impaired, increasing the risk of worse prognosis. LA reservoir function by STE was also related to adverse outcomes in stable outpatients with chronic heart failure and reduced left ventricular ejection fraction (HFrEF). In a cohort of 286 consecutive patients with stable HFrEF (64% with ischemic cardiomyopathy), patients with lower PALS showed worse event-free survival than those with higher PALS.[62] Mechanism linking LA function with outcome in this clinical setting is not fully understood. Chronic exposure to high LV filling pressures will cause an increase in LA volume, and it may be hypothesized that a decreased LA function is just a marker of a sicker LV.[63]

Because LA reservoir and conduit function reflect underlying LV function, there is some skepticism about the utility of LA strain compared with other markers of LV strain. The reciprocating changes in LV and LA volumes within the nearly constant total cardiac volume suggest that any measure of LA function will be highly influenced by LV longitudinal function. Thus, any longitudinal elongation of the atrium must correspond to the deformation of the ventricle.[64–66] This phenomenon has been reported by Ersbøll and colleagues,[67] who demonstrated that PALS provides a composite measure of LV longitudinal systolic function and maximum LA volume before mitral valve opening and as such, contains no added information when these readily obtained measures are known.

In contrast, PACS is less dependent on LV function, and changes to atrial pump function do not depend primarily on changes to the LV but may be due to the development of an underlying "atriopathy."[68] Currently, data about the prognostic role of PACS in the ischemic cardiomyopathy are lacking. Further research will allow us to understand this relationship better.

SUMMARY

Echocardiographic strain imaging is useful for the evaluation of acute and chronic ischemic heart disease. It may soon affect the guideline-based management of patients with ischemic heart disease. GLS of the LV holds both a diagnostic and prognostic value in patients with stable angina, acute coronary syndrome, and subclinical CAD; ESL and PSS of LV segments are innovative and not entirely validated markers of ischemia. Left atrium PALS reflects LV diastolic dysfunction and has a prognostic value in ischemic cardiomyopathy. Although less validated than the left counterpart, RV strain measures are useful for the diagnosis and risk stratification of patients with RV ischemic involvement. Even though we are getting closer, further accumulation of evidence is needed for the definitive introduction of strain parameters in clinical practice and guidelines for patients with ischemic heart disease.

DISCLOSURE

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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