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Myocardial motion in acute ischemia: revealing invisible deformation by echocardiography

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Abstract

Echocardiography has been used clinically to assess regional myocardial wall motion for the diagnosis of acute myocardial ischemia or stress-induced ischemia, but it is often difficult to distinguish hypokinetic motion from normal motion. Myocardial wall motion is affected by loading conditions as well as intrinsic contractility, making it challenging to define a normal range of wall motion. Therefore, hypokinesis is usually diagnosed by comparing target areas with other areas of myocardium considered normal (relative hypokinesis). Myocardial strain analysis by tissue Doppler echocardiography and speckle-tracking echocardiography has enabled objective and quantitative evaluation of regional myocardial wall motion. Peak systolic strain decreases during acute ischemia, but subtle and invisible myocardial motion, such as early systolic lengthening (ESL) and postsystolic shortening (PSS), also occurs, and the analysis of these subtle motions can improve the diagnostic accuracy of ischemia. However, the diagnosis of ischemic myocardium by strain analysis is not widely performed in clinical practice at this time due to several limitations. This article reviews the features of myocardial motion during acute ischemia, the mechanisms of ESL and PSS, the diagnosis of ischemic myocardium using strain analysis, and current approaches and future challenges to overcome the limitations in the detection of relative hypokinesis. This article also explains the use of ESL and PSS to detect myocardial ischemic memory that remains after brief ischemia.

Keywords: early systolic lengthening, echocardiography, ischemia, myocardial strain, postsystolic shortening, relative hypokinesis

Introduction

Objective evaluation of myocardial ischemia is crucial for diagnosing ischemic heart disease and determining a therapeutic strategy. During acute myocardial ischemia, the contraction of the ischemic myocardium quickly deteriorates. Since myocardial contractile dysfunction occurs relatively upstream of the ischemic cascade [1], detecting regional myocardial wall motion abnormalities (i.e., asynergy) via echocardiography has been widely used for the diagnosis of acute myocardial ischemia or induced ischemia during stress testing. In conventional echocardiography, left ventricular (LV) wall motion is assessed by visually observing both endocardial motion and systolic wall thickening, even today. Although some wall motion abnormalities such as akinetic or dyskinetic motion are obvious, it is often difficult to distinguish hypokinetic motion from normal motion. Normal wall thickening is affected by preload and afterload in addition to its intrinsic contractility, making it challenging to define a normal range of wall thickening that can be applied to various situations, including during stress echocardiography. Therefore, hypokinesis is usually diagnosed by comparison with other areas of myocardium considered normal (relative hypokinesis) [2]. However, this evaluation has the problem of being influenced by the subjectivity of the observer. In this review article, we will discuss how relative hypokinesis can be objectively detected during acute ischemia using advanced echocardiographic techniques. The concept of myocardial ischemic memory using subtle myocardial motions that persist after brief ischemia will be also explained.

Detection of the ischemic myocardium by myocardial strain analysis

Tissue Doppler echocardiography and speckle-tracking echocardiography can provide objective and quantitative evaluation of regional myocardial wall motion, which does not depend on visual perception. In particular, by analyzing myocardial strain with speckle-tracking echocardiography, we can now evaluate not only changes in myocardial wall thickness (radial strain) but also changes in myocardial length in the longitudinal and circumferential directions (longitudinal strain and circumferential strain). Three-dimensional speckle-tracking echocardiography can further analyze the area strain (or more precisely, the area change ratio) [3].

Myocardial strain analysis was initially developed to facilitate the detection of ischemic myocardium by quantifying regional myocardial thickening or shortening. The bull's-eye display and territorial analyses of regional peak systolic strains can aid in diagnosing myocardial ischemia [4-6]. Furthermore, histogram

analysis of peak systolic strains enables the quantitative evaluation of relative hypokinesis by analyzing strain distribution across all LV segments [7]. Despite these advancements, such methods have not been widely adopted in routine clinical practice due to several limitations. For instance, peak systolic strain values in the LV myocardium exhibit variation among myocardial segments even in healthy subjects [8]. Additionally, the values obtained from the analysis differ between device vendors [9], complicating the definition of cutoff values for decreased regional myocardial motion. Moreover, defining a normal range at rest for each segment and each device does not guarantee the detection of relative hypokinesis from peak systolic strain values, as these also depend on myocardial loading conditions, similar to wall thickening. Although histogram analysis is theoretically superior and was anticipated to be useful in diagnosing coronary artery disease, it proved to be ineffective in excluding acute coronary syndrome in a multicenter prospective study due to its low specificity [10].

Features of myocardial motion in the ischemic myocardium

When coronary blood flow is gradually reduced, contraction of the ischemic myocardium is correspondingly impaired, resulting in smaller absolute values of peak systolic strain. Detailed observation during flow reduction reveals that not only is peak systolic strain decreased, but it is also accompanied by a stretching motion in early systole and a shortening motion after end-systole (Fig. 1). These motions are referred to as early systolic lengthening (ESL) and postsystolic shortening (PSS), respectively [11]. ESL and PSS represent relatively small deformations compared to the overall deformation, but they increase in response to a decrease in systolic shortening [12]. No obvious difference in these increases has been noted between longitudinal, circumferential, and radial strain analyses [12]. In the presence of ESL and PSS, contraction appears to be delayed, a phenomenon called tardokinesis. Although such concomitant motions have been observed from myocardial length changes in animal experiments, they have been difficult to detect using conventional echocardiography because of their subtlety. They can now be easily detected using tissue Doppler and speckle-tracking echocardiography.

ESL is defined as myocardial lengthening that occurs after end-diastole (or mitral valve closure). It is typically observed during early systole, but its duration becomes longer as ischemia worsens. Severely impaired myocardial contractility results in holosystolic stretch motion that is no longer limited to early systole (i.e., dyskinesis). ESL is a wasted lengthening that does not contribute to LV inflow because it

occurs after mitral valve closure. When the radial strain, which reflects the deformation of wall thickness, is analyzed, ESL is observed as wall thinning. As representative indices of ESL, the ratio of the strain amplitude of ESL to the maximal strain amplitude during systole [12] and the time from end-diastole to the peak of ESL are used.

PSS is defined as myocardial shortening that occurs after end-systole (or aortic valve closure). It is observed mainly during isovolumic relaxation. PSS is a wasted shortening that does not contribute to LV outflow (i.e., ejection of blood) because it occurs after aortic valve closure. When the radial strain is analyzed, PSS is observed as wall thickening, which is called postsystolic thickening. As representative indices of PSS, the ratio of the strain amplitude of PSS to the maximal strain amplitude during the cardiac cycle (or the absolute value of the peak strain during the cardiac cycle) [12] and the time from end-systole to the peak of PSS are used. PSS presents various patterns: it can be unimodal with an inflection point at end-systole or bimodal with peaks before and after end-systole, and in both cases, the shortening (or the thickening in radial strain) after end-systole reflects PSS (Fig. 2). As discussed below, PSS is seen in the myocardium with contractile dysfunction, but it also affects LV relaxation because it causes LV dyssynchrony during isovolumic relaxation [13].

Since ESL and PSS are subtle myocardial motions, they may be undetectable at low frame rates. To avoid missing ESL and PSS in speckle-tracking echocardiography, higher frame rates should be used as long as the image quality does not deteriorate. In two-dimensional echocardiography, it is recommended to acquire images at a frame rate of at least 2/3 of the heart rate, preferably as high as the heart rate. Proper tracking of the endocardial surface is also important for evaluating ESL and PSS and should always be visually verified. If there are regions of poor tracking, the endocardial tracing line should be adjusted manually.

Mechanisms of ESL and PSS

The mechanisms of ESL and PSS can be understood by envisioning the tug-of-war between the ischemic myocardium and the surrounding myocardium. For simplicity, let us consider a model of three cardiac myocytes aligned in series, where only the middle one is ischemic (although, in real myocardium, we should consider the collective dynamics of myocytes, which consist of complex arrangements) (Fig. 3a-d). When each myocyte contracts during systole, a tug-of-war occurs between the ischemic myocyte and the

nonischemic myocytes. Since the nonischemic myocyte generates greater tension than the ischemic myocytes, the ischemic myocyte is stretched by the nonischemic myocytes, resulting in ESL. When the tension in the ischemic myocyte increases, it can start to shorten, thus ending the ESL.

Next, let us consider a similar model for end-systole and beyond (Fig. 3e-h). At end-systole, the ischemic myocyte loses the tug-of-war and cannot shorten as much as the nonischemic myocytes. This means that the ischemic myocyte is still stretched relatively by the nonischemic myocytes. Subsequently, when the nonischemic myocytes relax, the tension on the ischemic myocyte is released, and the ischemic myocyte shortens as if a stretched spring is released, resulting in PSS. PSS in the bimodal strain curve occurs when the contraction of the ischemic myocardium is partly preserved but it cannot sustain its tension until end-systole (e.g., during the hyperacute phase of ischemia) [14, 15]; this type of PSS can also be explained by a similar mechanism. This simple model of three cardiac myocytes indicates that ESL and PSS are essentially passive motions that occur through the interaction between the ischemic myocardium and the surrounding nonischemic myocardium [16] and suggests that ESL and PSS can be detected in the region of "relative hypokinesis".

Another important factor that influences the occurrence of ESL and PSS is the change in LV pressure. An increase in LV pressure during isovolumic contraction can augment wall stress and induce ESL in the ischemic myocardium. Conversely, a decrease in LV pressure during isovolumic relaxation can reduce wall stress and facilitate PSS in ischemic myocardium [16].

It is accepted that ESL is a passive motion, as illustrated by this model, whereas there has been some debate about whether PSS is an active or a passive motion that uses or does not use energy, respectively. It was once hypothesized that PSS occurs as an active contraction during acute ischemia due to the prolonged duration of tension generation, but this mechanism seems unlikely because the action potential duration shortens during acute ischemia [17]. A study that analyzed pressure-segment length loops during acute ischemia concluded that PSS in dyskinetic regions is passive motion, while PSS in hypokinetic regions is active contraction [18]. In contrast, a simulation model by Akaishi et al. showed that PSS can occur when intrinsic contractility is decreased without prolongation, suggesting that PSS in hypokinetic regions is passive [19]. A simulation and animal experiment by Claus et al. also demonstrated that PSS is caused by passive recoil during acute ischemia [16]. My personal view is that most PSS *observed in the myocardium with contractile dysfunction* can be explained primarily by passive recoil. It is important to understand that

reduced contractility can cause ESL and PSS without delaying the intrinsic contractility.

Notably, ESL and PSS are not specific to the ischemic myocardium, as they can occur in any region of reduced contraction. Due to the excitation time lag caused by the impulse conduction system between regions, ESL and PSS can also be observed in the normal myocardium, where the onset of contraction is delayed [20]. When seen in the normal myocardium, the PSS manifests as active contraction. Generally, PSS in the pathological myocardium is accompanied by a decrease in peak systolic strain, and the PSS amplitude is larger and longer than the PSS amplitude in the normal myocardium [21]. Distinguishing between them is often difficult, which complicates the diagnosis of ischemic myocardium using PSS (and vice versa for ESL). Therefore, not only ESL and PSS but also a decrease in systolic strain should be considered for identifying pathological myocardium.

Detection of the ischemic myocardium using ESL and PSS

Tissue Doppler echocardiography has high temporal resolution, allowing accurate evaluation of subtle myocardial motion. With the widespread use of this method, PSS first attracted attention as a diagnostic marker of ischemic heart disease. Voigt et al. showed that the assessment of the PSS by tissue Doppler strain analysis was superior to conventional wall motion assessment for identifying stress-induced ischemia in patients with known or suspected coronary artery disease [22]. Onishi and colleagues demonstrated that PSS assessment using tissue Doppler echocardiography could help diagnose coronary artery disease, even at rest [23] and with higher diagnostic accuracy under dobutamine stress [24]. In speckle-tracking echocardiographic studies, Brainin et al. found that the presence of PSS was an independent determinant of significant coronary artery disease in patients with suspected stable angina, and its assessment was useful in predicting future cardiovascular events [25]. The assessment of PSS can also facilitate risk stratification in patients with non-ST-segment elevation acute coronary syndrome of intermediate or low risk [26]. On the other hand, the assessment of ESL, like PSS, has been useful in the diagnosis of significant coronary artery disease [27]. However, despite these reported benefits, the clinical utility of ESL and PSS is as limited as that of peak systolic strain because, as noted above, ESL and PSS are found even in healthy subjects. Intervendor differences of PSS measurements in regional strain analysis seems to be another limitation [28].

Is there a way to overcome these problems? In most previous studies, the systolic strain, ESL, and

PSS were assessed independently. A single echocardiographic parameter seems to be inferior to visual assessment for diagnosing ischemia [29]. However, the decrease in systolic strain and the occurrence of ESL and PSS are found in the relative hypokinetic region, and they are related to each other. Therefore, an analysis that incorporates ESL and PSS in systolic strain may provide a more accurate diagnosis of relative hypokinesis.

Uusitalo et al. showed that the addition of the PSS to visual wall motion assessment via dobutamine stress echocardiography improved the diagnostic accuracy of coronary artery disease over visual assessment alone [30]. Ishigaki et al. demonstrated that integrated analysis of peak systolic strain, ESL, and PSS enhanced the diagnostic accuracy for single-vessel left anterior descending coronary artery (LAD) stenosis over peak systolic strain alone in patients with suspected coronary artery disease but without visual wall motion abnormalities on echocardiography at rest (Fig. 4) [31]. Although the results of Ishigaki et al. are limited to applications for screening because they were obtained by nonstress echocardiography, the addition of ESL and PSS analysis to the systolic strain may have led to their more accurate diagnosis of relative hypokinesis.

Assessment of myocardial ischemic memory

When ischemia lasts for a relatively long time, wall motion abnormalities during the ischemic episode do not go away right after coronary blood flow is restored (i.e., stunned myocardium). But when the ischemia is brief, wall motion quickly returns to normal. Any echocardiographic parameters that remain after brief ischemia can be useful for diagnosing ischemia retrospectively (i.e., myocardial ischemic memory). In brief ischemia models, our group showed that PSS remains stable even after peak systolic strain has mostly normalized [32-34] and that the combined analysis of ESL and PSS provides a better assessment of ischemic memory for a longer time than the use of ESL or PSS alone (Fig. 5a) [35]. These results suggest that ESL and PSS can help with the sensitive detection of relative hypokinesis caused by stunned myocardium. The presence of ESL and PSS in healthy subjects may make this diagnosis difficult, but it seems possible to differentiate ischemic memory cases from healthy cases because ESL and PSS caused by ischemic memory disappear over time. We also reported that PSS can reappear with mild afterload augmentation even after recovery from ischemic memory, which may have potential clinical applications (Fig. 5b) [36].

Notes about the assessment of ESL and PSS

In myocardial strain analysis, peak systolic strain (or end-systolic strain) should be the basis of regional wall motion assessment, just as systolic wall thickening is important in conventional echocardiography. When regional wall motion is clearly hypokinetic, ESL and PSS assessments are not necessary. In mild ischemia, identifying relative hypokinesis with peak systolic strain alone may be difficult, so the addition of ESL and PSS would be useful. Further studies are required to determine the optimal method for integrating ESL or PSS with systolic strain measurements to create a unified diagnostic parameter with enhanced clinical applicability.

Since ESL and PSS are influenced by tension from the surrounding myocardium, these motions may be less likely to arise when the tension in the surrounding myocardium is impaired. According to the study by Ishigaki et al., neither the ESL nor the PSS improved the diagnostic accuracy for LAD stenosis in patients with multivessel disease, which may indicate dysfunction of the myocardium surrounding the LAD region in multivessel disease patients [31]. Onishi et al. also reported a trend toward lower diagnostic accuracy of PSS in patients with multivessel disease than single-vessel disease patients [24]. On the other hand, Brainin et al. showed that regions of PSS increased in patients with multivessel disease, and this result may suggest that PSS assessment is not necessarily useless for multivessel disease [25].

This review article focuses on myocardial motion during acute ischemia. In chronic ischemia, ESL and PSS are also found in the myocardium with contractile dysfunction, which seems reasonable when considering the mechanisms of ESL and PSS. However, since ESL and PSS occur through the interaction with the surrounding myocardium, these motions may be less likely to arise in stiff myocardium with advanced fibrosis [16]. Therefore, the diagnosis of relative hypokinesis in patients with suspected chronic ischemia may require less emphasis on ESL and PSS.

Conclusions

Advanced echocardiographic techniques enable detailed assessment of regional myocardial wall motion and the detection of subtle and otherwise invisible deformations. A decrease in peak systolic strain, along with the occurrence of ESL and PSS, suggests that the region is relatively hypokinetic (or more compromised) compared to the surrounding regions. While these motion patterns are not specific to

ischemia, they may be indicative of ischemia if the region corresponds to the dominant area of the coronary artery. With the ongoing advancements in artificial intelligence (AI) technologies, assessments of ischemic myocardium, including ESL, PSS, and myocardial tissue characteristics, will become more automated. Nonetheless, a deep understanding of these complex myocardial motions and their pathophysiological basis remains essential, even in the era of AI.

Conflict of interest

Toshihiko Asanuma declares that he has no conflict of interest.

Animal studies

All institutional and national guidelines for the care and use of laboratory animals were followed.

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Figure captions

Fig. 1 Area strain curves derived from three-dimensional speckle-tracking echocardiography at baseline and during mild, moderate, and severe coronary flow reduction in a canine model. The risk area is shown in green, and the normal area is shown in red. In the risk area, the absolute value of peak systolic strain (orange circle) gradually decreases, and early systolic lengthening (ESL) (yellow arrow) and postsystolic shortening (PSS) (pink arrow) gradually increase as the coronary flow reduction worsens. AVC = aortic valve closure

Fig. 2 Postsystolic shortening (PSS) in unimodal and bimodal strain curves. The strain curves are displayed as radial strain. PSS shows up as thickening after an inflection point at aortic valve closure (AVC) in the unimodal strain curve (green and cyan in a) or as a second peak after AVC in the bimodal strain curve (red in b) [15]

Fig. 3 The mechanisms of early systolic lengthening (ESL) and postsystolic shortening (PSS). This figure illustrates how ESL and PSS arise during ischemia using a simplified model. **ESL:** (a) Three cardiac myocytes are connected in series at end-diastole. (b) The middle myocyte is ischemic and has reduced contractility. (c) During systole, the ischemic myocyte generates less tension than the nonischemic myocytes, creating a tug-of war effect (red arrows). (d) The ischemic myocyte is stretched by the nonischemic myocytes, resulting in ESL (blue arrows). **PSS:** (e) Three myocytes are connected in series at end-diastole. (f) In the absence of ischemia, each myocyte is assumed to have equal contraction at end-systole. (g) In the middle myocyte being ischemic, the ischemic myocyte loses the tug-of war and cannot shorten as much as the nonischemic myocytes at end-systole, resulting in relative stretching of the ischemic myocyte (red arrows). (h) Nonischemic myocytes relax, releasing tension on the ischemic myocyte, which then shortens like a released spring, producing PSS (blue arrows). For simplicity, the effect of left ventricular pressure is not considered

Fig. 4 Incremental value of early systolic lengthening (ESL) and postsystolic shortening (PSS) in diagnosing single-vessel left anterior descending coronary artery (LAD) stenosis. T_{ESL} and T_{PSS} represent the time from end-diastole to peak ESL and from end-systole to peak PSS, respectively. (a) In multivariable logistic regression models, the addition of T_{ESL} and T_{PSS} to the peak systolic strain significantly increased the model power. The tables present the odds ratios and 95% confidence intervals. (b) According to the receiver operating characteristic curve analysis, the integrated analysis of all three

parameters significantly improved the diagnostic accuracy for single-vessel LAD stenosis compared with peak systolic strain alone [31]. AUC = area under the curve

Fig. 5 Myocardial ischemic memory revealed by subtle myocardial motion analysis. (a) Myocardial ischemic memory associated with early systolic lengthening (ESL) and postsystolic shortening (PSS) in a two-minute coronary occlusion-reperfusion canine model (analysis by area strain). In the risk area, the absolute value of peak systolic strain (green circles) decreases, and ESL (blue arrows) and PSS (red arrows) occur during occlusion. After reperfusion, peak systolic strain recovers to the baseline level, but the ESL persists for 20 minutes after reperfusion, and the PSS persists for more than 20 minutes [35]. (b) Reappearance of myocardial ischemic memory with afterload augmentation in a two-minute coronary occlusion-reperfusion canine model (analysis by radial strain). In the risk area, peak systolic strain decreases and PSS (yellow arrowhead) occurs during left circumflex coronary artery (LCx) occlusion. Although the peak systolic strain returns to the baseline level and the PSS disappears 60 minutes after reperfusion, the PSS reappears in the risk area after mild afterload augmentation with phenylephrine infusion [36]. AVC = aortic valve closure