Myocardial ischemia and post-systolic shortening

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ABSTRACT

The assessment of regional wall motion is useful to identify myocardial ischemia because wall motion abnormalities occur relatively upstream in the ischemic cascade. Echocardiography is widely used for this, but the subjectivity of visual observation may hamper accurate evaluation. The analysis of myocardial velocity and strain by tissue Doppler and speckle tracking echocardiography has allowed the quantitative assessment of regional wall motion and facilitated the detection of subtle myocardial deformation that is difficult to identify by conventional methods, such as post-systolic shortening (PSS). PSS is defined as myocardial shortening that occurs after end-systole (or aortic valve closure), and is observed in the myocardium with regional contractile dysfunction. In experimental and clinical studies, it has been reported that the assessment of PSS is superior to that of conventional parameters such as wall thickening or peak systolic strain in detecting acute ischemia and diagnosing coronary artery disease. Moreover, it has recently been found that PSS remains after recovery from brief ischemia despite the rapid recovery of peak systolic strain. The assessment of PSS allows after-the-fact recognition of myocardial ischemic insults and is expected to be used for ischemic memory imaging. In this review, we demonstrate the usefulness of the assessment of PSS in the diagnosis of acute ischemia and ischemic memory, and discuss issues to be solved for the widespread use of this assessment in the echocardiographic laboratory.

Introduction

Myocardial ischemia is a pathophysiological state appearing when myocardial blood flow cannot supply adequate oxygen for myocardial demands. The imbalance between myocardial oxygen supply and demand is followed by metabolic disorders, wall motion abnormalities, electrocardiographic changes, and finally, chest pain. This sequence of events is called the ischemic cascade (1). The downstream events in the cascade need a longer period of time for their occurrence and are not appropriate for early detection of an ischemic event. The assessment of regional wall motion, for which echocardiography is widely used, is useful to identify myocardial ischemia, because wall motion abnormalities induced by ischemia occur relatively upstream in the cascade. Exercise and pharmacological (such as dobutamine or dipyridamole) stress echocardiography is well known to have excellent diagnostic accuracy for identifying ischemia (2).

There are some issues in the assessment of regional wall motion by echocardiography. The subjectivity in the assessment is the most important limitation. Because the assessment of regional wall motion is usually done by visual observation of systolic wall thickening, training and experience are needed for accurate diagnosis. To address this issue, analyses of myocardial velocity and strain derived from tissue Doppler or speckle tracking techniques have been developed. These analyses have allowed the quantitative assessment of regional wall motion and facilitated the detection of subtle myocardial deformation that is difficult to identify by conventional methods, such as post-systolic shortening (PSS).

During the last decade, many studies have demonstrated that the assessment of PSS by these analyses is useful to detect acute ischemia. However, it still has not been widely used in clinical settings. Because the assessment of PSS allows after-the-fact

recognition of myocardial ischemic insults (i.e., ischemic memory) (3, 4), this subtle myocardial deformation has been attracting attention again. In this review, we will attempt to demonstrate the usefulness of the assessment of PSS in the diagnosis of acute ischemia and ischemic memory, and issues to be solved for the widespread use in the echocardiographic laboratory.

PSS

Regional contraction of the myocardium is affected by not only inherent contractility of the concerned myocardium but also tension from the surrounding myocardium. Consequently, when regional contractility deteriorates because of ischemia, the amplitude of shortening during ejection time decreases, and early systolic lengthening (ESL) and PSS are observed in the ischemic myocardium (5).

PSS is defined as myocardial shortening that occurs after end-systole (or aortic valve closure) and is observed mainly during isovolumic relaxation (Figure 1). PSS does not contribute to ejection of blood because it occurs after aortic valve closure. In radial or transverse deformation, the term “post-systolic thickening” is used. Various patterns can be observed in the strain profile of PSS. For example, a biphasic shortening is often seen in the ischemic myocardium, especially immediately after the onset of severe ischemia. The latter shortening represents PSS.

There are several parameters for quantifying PSS. The post-systolic index, which is calculated from a ratio, ([peak post-systolic strain] – [end-systolic strain]) / (peak strain or maximum strain change during the cardiac cycle), is widely used (6, 7). This parameter shows the ratio of the amplitude of PSS to total shortening. Time from AVC to peak post-systolic strain is used as another parameter.

PSS is well known in the ischemic myocardium through the animal experiments with sonomicrometry; however, it has not been assessed by conventional echocardiography because of the difficulty of visual detection of subtle motion. In the late 1990s, Derumeaux et al. reported that, in anesthetized pigs with graded reduction of coronary flow, peak systolic and early diastolic velocities derived from tissue Doppler echocardiography decreased, and a positive wave during isovolumic relaxation increased in the ischemic myocardium (8). It is considered that the increase of the positive wave is due to PSS. Subsequently, the experimental and clinical studies related to PSS have been mainly conducted with tissue Doppler and speckle tracking echocardiography. The reason why there are few reports about PSS with other imaging modalities seems to be that high temporal resolution is needed for identifying PSS.

The mechanisms of PSS

The potential mechanisms of PSS have been reported by some researchers. PSS was initially considered as a delayed but active contraction induced by ischemia. As described above, however, shortening of the ischemic myocardium is affected by not only intrinsic contractility but also tension arising from shortening of the surrounding nonischemic myocardium. Therefore, PSS can be caused by the interaction between the ischemic and surrounding myocardium as passive recoil (5).

It was controversial whether PSS represents active contraction or passive recoil. Skulstad et al. measured left ventricular pressure and segmental lengths by sonomicrometry and analyzed LV pressure (or stress)-segmental length loops before and during coronary stenosis and occlusion in anesthetized dogs (9). In their results, PSS in the dyskinetic segment generated no active stress, but PSS in the hypokinetic

and akinetic segments seemed to be active contraction.

In contrast, Akaishi et al. calculated regional myocardial elastance as an index of contractility using a non-linear elastic model of contraction and found that peak elastance decreased in hypokinetic segments induced by ischemia, but timing of the peak was not delayed compared to the nonischemic condition (5). This result suggests that PSS occurs as a passive phenomenon.

In the study of Claus et al. using a mathematical model describing active force development, elasticity, and segmental interaction, PSS did not need active force development (10). This study concluded that PSS could be explained in a unified way as passive recoil that was the result of elastic segmental interaction (Figure 2). Actually, it seems that most PSS observed during ongoing ischemia is caused by passive recoil. In this mechanism, relative decrease of myocardial strain during ejection time in the ischemic region compared to that in the surrounding nonischemic regions is necessary for PSS. It is known that PSS becomes greater as afterload increases (9). Claus' theory can well explain this phenomenon, because relative decrease of strain in the ischemic region increases with afterload augmentation.

However, PSS without relative decrease of strain in the ischemic region is sometimes observed, especially after recovery from ischemia (3, 4). In simulations described above, timing of electrical activation is not included. The delay of electrical activation induces ESL which can cause PSS by regional preload augmentation (11). Such PSS might occur as active contraction. Further investigation is needed to address this controversy.

Diagnosis of acute ischemia by PSS

The assessment of PSS is valuable in identifying acute ischemia because PSS occurs in the myocardium with regional contractile dysfunction. Tissue Doppler and speckle tracking echocardiography can clearly visualize PSS during ischemia (12-14). The extent of PSS detected by these methods is consistent with the ischemic area (Figure 3).

It is important to determine whether the assessment of PSS can detect acute ischemia more accurately than conventional parameters such as wall thickening or systolic strain. Previous animal experiments have indicated the superiority of PSS. Among myocardial deformation parameters evaluated by strain and strain rate analyses, PSS parameters best differentiated ischemic from nonischemic segments during acute coronary occlusion (15). Moreover, in graded coronary flow reduction, the post-systolic index increased significantly even in the flow reduction in which peak systolic strain did not decrease (16, 17).

The superiority of PSS to conventional parameters in detecting acute ischemia has also been indicated in clinical studies. Kukulski et al. performed tissue Doppler echocardiography before and during elective coronary angioplasty in 73 patients with stable angina and analyzed myocardial strain during coronary occlusion (6). In their results, PSS occurred in the risk area during occlusion, and the post-systolic index in that area increased. In diagnostic accuracy for identifying acute ischemia, the post-systolic index was superior to peak systolic strain.

In a study of 60 patients who underwent dobutamine stress echocardiography by Celutkiene et al., a velocity wave during isovolumic relaxation, which represents PSS, was observed in the ischemic region and increased during stress (18). The peak velocity of PSS was the most accurate parameter of induced ischemia (sensitivity 73-100% and specificity 82-97%) compared to systolic and early diastolic velocities

(sensitivity 52-77% and 63-68%, specificity 63-77% and 59-81%, respectively).

Voigt et al. evaluated strain and strain rate parameters during dobutamine stress in 44 patients with known and suspected coronary artery disease and compared the diagnostic accuracies of the deformation parameters with that of perfusion scintigraphy performed simultaneously (7). PSS was observed during stress in all ischemic segments, and PSS parameters such as post-systolic index were better for identifying stress-induced ischemia than maximal strain and strain during ejection time (Figure 4, 5). The assessment of PSS by strain rate imaging improved the diagnostic accuracy compared to conventional visual wall-motion reading (sensitivity from 81% to 86%, specificity from 82% to 90%).

In the other study assessed by the analysis of tissue Doppler displacement, a PSS parameter at peak dobutamine stress predicted the presence of coronary artery disease with sensitivity of 89% and specificity of 77% (19). The sensitivity for single-vessel disease was 93% and that for multi-vessel disease was 78%.

In contrast, there are studies showing PSS not to be superior to systolic stain in assessing ischemia. For example, Bjork Ingul et al. reported that the post-systolic index was inferior to end-systolic strain in the receiver-operating characteristics curve analysis of dobutamine stress echocardiography for diagnosing coronary artery disease (20). Some potential reasons are considered.

Temporal resolution of the strain analysis affects the diagnostic accuracy of PSS. When echocardiographic images are acquired at the low frame rate, PSS often fails to be detected because of its relatively short duration. The frame rate of speckle tracking echocardiography is generally lower than that of tissue Doppler echocardiography. In the results of Bjork Ingul et al., the area under the curve of the post-systolic index

derived from the speckle tracking method was smaller than that derived from the tissue Doppler method (20). Therefore, a high frame rate should be selected for the accurate detection of PSS in the speckle tracking method.

Because the heterogeneity of contraction among myocardial regions induces PSS as shown by Claus, et al. (10), it can be observed in not only ischemic but also nonischemic heart diseases such as hypertrophic and dilated cardiomyopathies, hypertensive heart disease, pulmonary hypertension, left bundle branch block, and even in healthy subjects. PSS has been reported to be observed in approximately one-third of myocardial segments in healthy subjects (21). The presence of physiologic PSS can complicate the accurate identification of pathologic PSS. This nonspecificity hampers its widespread use in the echocardiographic laboratory. Thus, it is indispensable to distinguish between pathologic and physiologic PSS. In general, pathologic PSS has a larger amplitude and longer duration than that in healthy subjects (21, 22). Criteria for pathologic PSS, proposed by Voigt, et al., are shown in Table (21). Relative decrease of myocardial strain during ejection time seen in concurrence with PSS is important for the differentiation in ongoing ischemia. However, the cutoff value of the post-systolic index in each myocardial segment is still unclear, especially in speckle tracking echocardiography, and this needs to be determined for use in clinical settings.

Because the amplitude and duration of PSS become greater during ischemia even in the segment with physiologic PSS, comparison of the strain profile during the ischemic episode and that before the episode is desirable for accurate diagnosis. Therefore, analysis of PSS is considered advantageous in stress echocardiography. In the analysis of myocardial strain, subtle change of the strain amplitude during ejection time is difficult to detect because its normal variation is relatively large; however, that

of timing in peak strain is relatively easy to detect.

It may be difficult to detect ischemia in the myocardium damaged previously using PSS. The simulation and experimental models of Claus et al. demonstrated that PSS did not occur in chronic infarction (10). This result suggests that the increase of myocardial stiffness can diminish PSS caused by passive recoil.

Which direction of strain (i.e., longitudinal, transverse, circumferential, and radial) should be analyzed for the assessment of PSS is a remaining question in speckle tracking echocardiography. This answer may partly depend on vendor differences in the speckle tracking algorithm (23). Longitudinal strains in apical views are usually analyzed in clinical settings. However, it is empirically known that the acquisition of reliable longitudinal strain profiles is often difficult in apical segments. This may hamper the diagnostic accuracy of ischemia in which the left anterior descending coronary artery is a culprit vessel.

Not only PSS but also ESL occurs in the ischemic myocardium. It has recently been reported that assessment of ESL is useful to detect myocardial ischemia (24). Comparison between PSS and ESL in the diagnostic accuracy for detecting ischemia is needed in further studies.

Detection of ischemic memory by PSS

Acute chest pain often resolves before a patient can present to the hospital, which makes a proper diagnosis difficult. In such patients, imaging technology that allows detecting ischemic memory would be of tremendous utility. It has been reported that the suppression of fatty acid metabolism due to myocardial ischemia persists after relief from ischemia (25, 26). Such metabolic imaging is promising for the assessment of

ischemic memory but must be performed in a radiation-controlled area. In contrast, ischemic memory imaging by echocardiography would have greater utility in the clinical setting and could even facilitate bedside examination.

When severe ischemia occurs in a transient fashion, myocardial dysfunction can persist despite normalization of blood flow; this phenomenon is known as myocardial stunning. In myocardial stunning, the functional, biochemical, and microstructural abnormalities that occur following ischemia are reversible, and contractile force is gradually restored. Systolic dysfunction in myocardial stunning can be used as a measure of ischemic memory, but this phenomenon has not been considered to be induced by relatively mild ischemia. However, a subtle abnormality such as PSS may persist after brief ischemia, even when a contractile abnormality is not observed.

To verify this hypothesis, we performed tissue Doppler echocardiography in a dog model with 15-min or 5-min coronary occlusion followed by reperfusion and evaluated the chronological changes of peak systolic strain and post-systolic index (3). In our results, peak systolic strain decreased significantly in the risk area during occlusion. This decrease in the peak systolic strain in the 15-min group did not completely recover to the baseline level even 120 min after reperfusion (i.e., conventional myocardial stunning), whereas the decrease in the 5-min group recovered immediately after reperfusion. The post-systolic index increased significantly during occlusion, but the increased post-systolic index in the 5-min group remained until 30 min after reperfusion, despite the rapid recovery of peak systolic strain (Figure 6). We also tested another model, in which ischemia was induced by dobutamine stress during nonflow-limiting stenosis (i.e., demand ischemia), and we found that the increase in the

post-systolic index persisted even at 20 min after dobutamine stress. These results suggest that PSS remains longer than the decrease in peak systolic strain after recovery from ischemia, and the assessment of PSS can be used to detect ischemic memory. Moreover, we analyzed strain and strain rate parameters derived from speckle tracking echocardiography in the 2-min occlusion/reperfusion model and evaluated which regional myocardial deformation parameters could demonstrate ischemic memory (4). We found that only PSS-related parameters persisted after recovery from 2-min occlusion. Although the strain rate during early diastole, which is a parameter of regional diastolic function, was expected to be another parameter of ischemic memory, it was not found to be so (Figure 7).

Recently, the myocardial layer-specific analysis became feasible. In the 2-min occlusion/reperfusion model, the analysis of the circumferential endocardial layer was better than that of the epicardial layer to detect ischemic memory (27).

In clinical settings, Ishii et al. investigated whether delayed relaxation could be detected after treadmill exercise in 117 patients with stable angina caused by significant coronary stenosis (28). They analyzed the rate of change in the strain during the first one-third of diastole (strain imaging diastolic index [SI-DI]) using speckle tracking echocardiography. SI-DI decreased significantly in the risk area even at 10 min after the exercise, and the decrease of SI-DI was observed in 85% of the segments within the risk area. They also evaluated the chronological changes of SI-DI in 35 patients with stable angina in whom elective percutaneous coronary intervention was performed (29). Peak systolic strain decreased significantly during coronary occlusion and recovered to near-normal pre-occlusion values after reperfusion. In contrast, SI-DI decreased significantly during occlusion, but the significant decrease remained even at 24 h after

reperfusion. In both studies, the decrease of SI-DI seemed to be mainly caused by PSS, as shown in their figures (Figure 8). In the other study, PSS displayed by velocity vector imaging could be detected 20 min after exercise in patients with exercise-induced ischemia (30).

In the assessment of ischemic memory using PSS, some issues need to be addressed for clinical use. The time period during which PSS can be detected after brief ischemia is still unclear. Because the persistency of PSS depends on the duration and severity of ischemia (3), remaining PSS could be detected for several hours after severe supply ischemia. However, in cases of demand ischemia induced by an exercise stress, it seems to persist only for less than 30 min (28, 30). This duration may be considered too short as ischemic memory, but it would still be valuable in stress echocardiography. A rapid heart rate during peak stress makes difficult the detection of PSS under the limited frame rate of speckle tracking echocardiography. Moreover, echocardiographic images are poor during peak stress, especially in exercise. The later assessment would facilitate the acquisition of robust strain profiles.

Differentiation between pathologic and physiologic PSS is still an important issue here as described above. The cutoff value of the post-systolic index for ischemic memory is unclear. We would recommend that echocardiography for diagnosing ischemic memory should be performed twice in 10- or 15-min intervals because PSS as a sign of ischemic memory would decrease over time whereas normal PSS would remain at the same level.

The reason why PSS persists after brief ischemia is unknown. The persistency of PSS may reflect subtle systolic stunning that cannot be detected by conventional systolic parameters, and a reversible metabolic disorder can be one possible mechanism

of this phenomenon. PSS is considered a motion that reflects regional contractile dysfunction, but it is still controversial whether regional relaxation disorder is related to the occurrence of PSS. Further investigation is needed to address these issues.

Conclusions

In summary, the analysis of myocardial velocity and strain by tissue Doppler and speckle tracking echocardiography has allowed the detection of subtle myocardial deformation, such as PSS, that is difficult to identify by conventional methods. Assessment of PSS is valuable in diagnosing acute ischemia because it improves diagnostic accuracy although there are some issues to be solved. The detection of PSS that persists after brief ischemia would be invaluable for ischemic memory imaging.

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FIGURE LEGENDS

Figure 1. Post-systolic shortening

Longitudinal myocardial strain profiles in 6 segments of the 2-chamber view in a patient in whom percutaneous coronary intervention has been performed on the right coronary artery. In this case, regional wall motion abnormalities were not pointed out in the visual assessment. However, in myocardial strain derived from speckle tracking echocardiography, peak systolic strain decreases, and post-systolic shortening (PSS), which is myocardial shortening that occurs after aortic valve closure (AVC), is shown in the inferior segment (yellow line). Early systolic lengthening (ESL) is also demonstrated in the inferior segment.

Figure 2. The mechanism of post-systolic shortening

Post-systolic shortening is termed post-systolic thickening (PST). The difference in myocardial thickening between ischemic and nonischemic regions cumulatively produces the restoring forces (F_R) during systole, but left ventricular cavity pressure (P) counteracts the restoring forces (**a-c**). The pressure decreases rapidly after aortic valve closure (AVC), and the restoring forces cause thickening in the ischemic region (i.e., PST) and thinning in the nonischemic region (**d-e**). After the thickness in both regions becomes equal, thinning occurs in the ischemic region (**f**). (Claus P, et al. Ultrasound Med Biol 2007; 33; 1963-70)

Figure 3. Risk area derived from myocardial contrast echocardiography and post-systolic shortening displayed by velocity vector imaging

In a dog with left circumflex artery occlusion, the risk area is shown as the area that is not filled by contrast microbubles (**left**). Post-systolic shortening (PSS) is demonstrated as inward velocity vectors after aortic valve closure (**right**). The area indicating PSS corresponds closely with the risk area. (Masuda K, et al. J Am Coll Cardiol Img 2008; 1: 210-20)

Figure 4. Post-systolic shortening induced by dobutamine stress echocardiography

In a patient in whom myocardial ischemia is confirmed by stress perfusion scintigraphy (arrow), longitudinal strain and strain rate profiles derived from tissue Doppler imaging are shown in the ischemic (apical) and nonischemic (basal) regions. Strain profiles are almost the same in both regions before dobutamine stress (**left**), but post-systolic shortening (ε_{ps}) emerges in the ischemic region during stress (**right**). The beginning of myocardial shortening (t_{bos}) and the end of shortening (t_{eos}) are delayed during stress. AVC = aortic valve closure, AVO = aortic valve opening, MVC = mitral valve closure, MVO = mitral valve opening. (Voigt JU, et al. Circulation 2003; 107: 2120-6)

Figure 5. ROC curves for identifying dobutamine-induced ischemia

$\varepsilon_{ps}/\varepsilon_{max}$, i.e., the post-systolic index, shows the best area under the curve (AUC) for identifying ischemia compared to other parameters such as maximal strain (ε_{max}) and strain during ejection time (ε_{et}). *$p < 0.05$ vs. other parameters. (Voigt JU, et al. Circulation 2003; 107: 2120-6)

Figure 6. Peak systolic strain and post-systolic index after brief coronary occlusion

In dogs with 5-min coronary occlusion followed by reperfusion, peak systolic strain

significantly decreases in the risk area during occlusion, but the decrease recovers immediately after reperfusion (**A**). The post-systolic index increases significantly during occlusion, and the increase remains until 30 min after reperfusion, despite the rapid recovery of peak systolic strain (**B**). *$p < 0.05$ vs. baseline. (Asanuma T, et al. J Am Coll Cardiol Img 2009; 2: 1253-61)

Figure 7. Ischemic memory of post-systolic shortening (dog)

Speckle tracking images and strain profiles in a dog with 2-min occlusion of the left circumflex artery followed by reperfusion. **Top panels:** End-systolic circumferential strain is color-coded in the inner half of the myocardium. The orange color in the risk area disappears during occlusion (yellow arrowheads), indicating end-systolic strain is near zero. **Middle panels:** Circumferential strain profiles in the risk area (orange line) and the nonischemic area (blue line) are shown. Post-systolic shortening (PSS) is demonstrated in the risk area during occlusion. Although systolic strain recovers to the baseline level by 10 min after reperfusion, PSS persists until 30 min after reperfusion (red arrows). **Bottom panels:** Circumferential strain rate profiles in the risk area (orange line) and the nonischemic area (blue line) are shown. The strain rate during early diastole (pink arrows) decreases in the risk area during occlusion, but this decrease does not persist after reperfusion. AVC = aortic valve closure. (Asanuma T, et al. J Am Coll Cardiol Img 2012; 5: 1-11)

Figure 8. Ischemic memory of post-systolic shortening (patient)

Speckle tracking images and strain profiles in a patient with 90% stenosis of the left anterior descending artery (LAD) at baseline, 20 and 50 s after LAD occlusion (**A**), and

2 min, 30 min, and 24 h after reperfusion (**B**). **Top panels:** Transverse strain at the first 1/3 of diastole is color-coded (warm colors represent positive values, and cold colors represent negative values). Blue was assigned in the risk area 50 s after occlusion but yellow was assigned within the risk area after reperfusion, indicating strain values remain high even at the first 1/3 of diastole. **Bottom panels:** Post-systolic shortening (PSS) was clearly demonstrated 2 min and 30 min after reperfusion in the apical anterior and mid anteroseptal segments. Even 24 h after reperfusion, PSS persists in the apical segment. AVC = aortic valve closure. (Ishii K, et al. J Am Coll Cardiol 2009; 54: 1589-97)

Table. Criteria for pathologic post-systolic shortening

- Transient PSS (occurrence during and resolution after ischemia)
- Clearly reduced systolic function or systolic bulging ($\varepsilon_{ET} > -7\%$)
- Moderately reduced function ($-7\% > \varepsilon_{ET} > -18\%$) and

  -PSS exceeding 20% of ε_{total} or

  -shortening continues from systole or PSS peak occurs more than 90 ms after AVC

AVC = Aortic valve closure, PSS = post-systolic shortening, ε_{ET} = ejection time strain, ε_{total} = total strain during heart cycle. (Voigt JU, et al. J Am Soc Echocardiogr 2003; 16:415-23)