Assessment of myocardial ischemic memory using three-dimensional speckle-tracking echocardiography: A novel integrated analysis of early systolic lengthening and postsystolic shortening

Ai Kozuma, MSc; Toshihiko Asanuma, MD, PhD; Kasumi Masuda, PhD; Hitomi Adachi, MSc; Seina Minami, MSc; Satoshi Nakatani, MD, PhD

Division of Functional Diagnostics, Department of Health Sciences, Osaka University Graduate School of Medicine, 1-7 Yamadaoka, Suita, Osaka 565-0871, Japan.

Address for correspondence:
Dr. Toshihiko Asanuma
Division of Functional Diagnostics, Department of Health Sciences, Osaka University Graduate School of Medicine,
1-7 Yamadaoka, Suita, Osaka 565-0871, Japan
E-mail: toshi@sahs.med.osaka-u.ac.jp

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Abstract

Background: Persistence of subtle abnormal myocardial deformation such as postsystolic shortening (PSS) after transient ischemia can be used to diagnose a history of myocardial ischemia (myocardial ischemic memory). Furthermore, early systolic lengthening (ESL) has recently attracted attention as another marker of myocardial ischemia. However, it is unclear whether the persistence of such abnormal deformation can be detected by three-dimensional (3D) speckle-tracking echocardiography, which has relatively low spatial and temporal resolution compared with two-dimensional echocardiography. This study sought to evaluate the diagnostic accuracy of myocardial ischemic memory and its spatial extent by 3D speckle-tracking echocardiography.

Methods: The left circumflex coronary artery was occluded for 2 min, followed by reperfusion, in 33 dogs. Their hemodynamic and 3D echocardiographic data were chronologically acquired. Peak systolic strain, early systolic strain index (ESI) as a parameter of ESL, postsystolic strain index (PSI) as a parameter of PSS, and myocardial dysfunction index (MDI) as a combined parameter of ESL and PSS were analyzed in all left ventricular segments.

Results: In the center of the risk area, ESI and PSI significantly increased until 20 min after reperfusion compared with baseline, although peak systolic strain recovered by 20 min. MDI significantly increased for more than 20 min after reperfusion and allowed better diagnostic accuracy of ischemic memory than the other parameters. In the 147 risk segments, abnormal values of MDI remained in 49 segments (33%) at 20 min after reperfusion, whereas abnormal peak systolic strain was observed in only 13 segments (9%).

Conclusions: ESL and PSS persisted after transient ischemia and could be detected by 3D speckle-tracking echocardiography. Integrated analysis of ESL and PSS provided higher diagnostic accuracy of ischemic memory. This method may be useful for detecting transient ischemic insults in patients after the disappearance of anginal attack.

Key words: 3D echocardiography, early systolic lengthening, ischemic heart disease, ischemic memory, myocardial dysfunction index, postsystolic shortening

Abbreviations

AVC = aortic valve closure, dP/dt_{max} = maximum time derivative of left ventricular pressure, dP/dt_{min} = minimum time derivative of left ventricular pressure, ESI = early systolic strain index, ESL = early systolic lengthening, LCx = left circumflex coronary artery, LV = left ventricular, LVEDP = left ventricular end-diastolic pressure, LVSP = left ventricular systolic pressure, MDI = myocardial dysfunction index, PSI = postsystolic strain index, PSS = postsystolic shortening.

It is difficult to prove the presence of myocardial ischemia in a patient after the disappearance of anginal attack because abnormalities visible on electrocardiograms or echocardiograms disappear rapidly. Although the exercise or dobutamine stress test can induce ischemia, its application in unstable patients is limited. Imaging of myocardial ischemic memory has therefore been desirable and its assessment by echocardiography would be useful in the clinical setting.

Postsystolic shortening (PSS), or myocardial shortening that occurs after end-systole, can be easily analyzed by two-dimensional (2D) speckle-tracking echocardiography (1). It is considered a sign of myocardial ischemia (2, 3) and is used as an indicator of ischemic memory because it persists for a while after recovery from transient ischemia in experimental models and clinical studies (4-6). The reason why PSS persists is unclear but seems to be probably due to a short duration of myocardial stunning (1). Besides PSS, early systolic lengthening (ESL), or myocardial lengthening that occurs in early systole, has recently attracted attention as another marker of myocardial ischemia (7, 8) and its utility for indicating ischemic memory is expected. Assessing the spatial extent of such abnormal wall motion persisting within the risk area is indispensable for ischemic memory imaging to estimate the culprit vessel and risk area; however, 2D echocardiography may have a limited capacity for assessing the spatial extent of wall motion abnormalities because it is based on the spatial interpolation (9).

Three-dimensional (3D) echocardiography can analyze wall motion in all left ventricular (LV) segments by one image acquisition without being affected by the through-plane motion (10) and can evaluate the spatial extent of wall motion abnormalities more accurately than 2D echocardiography (9). The application of 3D speckle-tracking echocardiography would be reasonable for ischemic memory imaging, in which rapid data acquisition for assessing the spatial extent of abnormal wall motion is possible. However, it is unclear whether 3D speckle-tracking echocardiography can detect ischemic memory after transient ischemia with a limited spatial and temporal resolution. Thus, we experimentally investigated the persistence of ischemic memory by 3D parameters in the center of the

risk area and its spatial extent in all LV segments. Furthermore, we studied whether integrated analysis of ESL and PSS could improve the diagnostic accuracy of ischemic memory.

Methods

Animal preparation

All animal studies were approved by the animal experimentation committee and performed in accordance with guidelines for the care and use of laboratory animals at our institution. A total of 33 open-chest female beagles or mongrel dogs (age: 12-24 months, weight: 10.8 ± 2.0 kg) were used in this study. The dogs were anesthetized using intramuscular injection of xylazine hydrochloride (0.5 mg/kg) followed by intravenous administration of pentobarbital sodium (25.9 mg/kg); next, they were intubated and ventilated using a respirator. Oxygen saturation was monitored with a pulse oximeter and maintained within normal ranges. Anesthesia was maintained through continuous infusion of pentobarbital sodium (6 mg/kg/h) and midazolam (0.18 mg/kg/h) throughout the experiment. Immediately after intubation, buprenorphine hydrochloride (4 μg/kg) was administered intramuscularly as an analgesic. The electrocardiogram was continuously monitored, and LV pressure was measured using a 5-Fr micromanometer (Millar Instruments, Houston, TX, USA) inserted through the right femoral artery or the right carotid artery into the LV. Subsequently, vecuronium bromide (1 mg) was administered, and the chest was opened through a left parasternal thoracotomy. The pericardium was opened, and the heart was suspended in a pericardial cradle. The proximal portion of the left circumflex coronary artery (LCx) was dissected free from surrounding tissues, and a vascular occluder was placed. A perivascular ultrasonic flow probe (Transonic Systems, Ithaca, NY, USA) was placed immediately distal to the occluder and connected to a digital flowmeter.

Echocardiography

3D echocardiography was performed using a Vivid E9 system with a 4V transducer (GE Healthcare, Horten, Norway). The transmitting and receiving frequency were set at 1.7 and 3.3 MHz, respectively.

The scan angle was 70º × 70º. The volume rate was 48.2 volumes/s. Full-volume datasets were acquired from 6 continuous cardiac cycles using the electrocardiographic triggering technique. All datasets were obtained through a water bag over the heart, while the respirator was transiently stopped to avoid the stitching noise. A microphone for the phonocardiogram (Fukudadenshi, Tokyo, Japan) was placed on the base of the aorta to determine the timing of aortic valve closure (AVC) (11).

Experimental protocol

The LCx was occluded for 2 min, followed by 30-min reperfusion, and the occlusion and reperfusion were confirmed by flow measurement. The datasets of 3D echocardiography were acquired at baseline, at the end of occlusion, and at 10, 20, and 30 min after the onset of reperfusion. LV pressure was recorded simultaneously with the acquisition of echocardiographic datasets.

Data analysis

LV systolic pressure, LV end-diastolic pressure, maximum and minimum time derivatives of LV pressure (dP/dt_{max}, dP/dt_{min}), and time constant of LV pressure decay during the isovolumic relaxation period (tau) were averaged from 5 consecutive cardiac cycles. The 3D speckle-tracking analysis was performed offline using the EchoPAC BT 13 software (GE Healthcare, Horten, Norway). The LV long axis was aligned in three apical views (four, two, and apical long), and three points on the endocardium (apex and both mitral annuli) were assigned in each view at end-diastole and end-systole. Next, the endocardial and epicardial borders of the LV were automatically tracked for one cardiac cycle. The borders were manually adjusted when it was necessary to optimize the boundary position and tracking. Finally, strain-time curves in 17 segments were displayed. In this study, we used area strain as a myocardial deformation parameter because it has been reported to be superior to other strains for detecting myocardial ischemia (12). End-diastole was defined at the peak of the R-wave (i.e., the reference point of strain measurement), and end-systole was defined at the timing of AVC.

Analysis 1: We first investigated whether myocardial ischemic memory could be detected in the center of the risk area using 3D speckle-tracking echocardiography. The risk area was visually defined

by wall motion abnormality during occlusion. A central segment of the risk area in the midventricular level and an opposite segment were analyzed as representative risk and non-risk segments, respectively (Figure 1). Peak systolic strain was calculated as a parameter of regional systolic function. The early systolic strain index (ESI) as a parameter of ESL was calculated as follows: ESL amplitude/maximal strain amplitude during systole. The postsystolic strain index (PSI) as a parameter of PSS was calculated as follows: PSS amplitude/maximal strain amplitude during the cardiac cycle (Figure 1). When ESL or PSS was not observed, the corresponding index was assigned a value of zero. Combined analysis of ESL and PSS was also performed because both represent abnormal myocardial deformation that occurs in the ischemic myocardium (13). Thus, we designed a new parameter, myocardial dysfunction index (MDI), which was calculated as follows: (ESL amplitude + PSS amplitude)/maximal strain amplitude during the cardiac cycle (Figure 1). The ESL and PSS amplitude overlap each other when the strain value at AVC is positive (i.e., systolic bulging). In this case, the absolute value of negative peak strain after AVC was used as the PSS amplitude to avoid double counting. In the serial change of area strain parameters, each parameter during occlusion and after reperfusion was compared with the value at baseline in the same segment because of regional heterogeneity of normal strain values. The diagnostic accuracy of each parameter to detect ischemic memory at 10 and 20 min after reperfusion was assessed using receiver operating characteristic (ROC) curve analysis, in which sensitivity and specificity were calculated from the values at baseline and after reperfusion.

Analysis 2: Next, we evaluated the spatial extent of ischemic memory using each area strain parameter derived from 3D speckle-tracking echocardiography. Area strains were analyzed in the 16 segments excluding the apical segment. Peak systolic strain, ESI, PSI, and MDI were measured, and a mean ± standard deviation (SD) was calculated per segment at baseline. Values beyond 2 SD of the mean at baseline, which reflects dysfunction, were defined as abnormal in each segment. Risk segments were defined as those with abnormal peak systolic strain at the end of occlusion in this

analysis. To quantify the extent of ischemic memory at 20 min after reperfusion, the percentage of abnormal segments after reperfusion within the number of risk segments (% abnormal segment) was calculated. The percentage of normal segments after reperfusion within the number of non-risk segments (% normal segment) was also calculated for each parameter because ESL and PSS are observed even in the normal myocardium (14). In analysis 2, “ESI and/or PSI” was evaluated as another option in the combined analysis. “ESI and/or PSI” was considered abnormal when either or both were abnormal.

Inter-observer and intra-observer correlations

Ten image clips were randomly selected from among the total clips to assess inter-observer and intra-observer variabilities for peak systolic strain, ESI, PSI, and MDI in the center of the risk area. To determine inter-observer variability, the analysis was repeated by a second observer who was blinded to the values obtained by the first observer. To determine the intra-observer variability, the analysis was repeated more than 2 weeks later by the same observer.

Statistical analysis

Data are expressed as mean ± SD. Multiple comparisons in each hemodynamic parameter against the baseline value were performed by one-way analysis of variance using the Tukey-Kramer post hoc test. Because of the heterogeneity of variance, multiple comparisons of LCx flow were performed by the Games-Howell post hoc test. Multiple comparisons of each area strain parameter against the baseline value were made by one-way repeated measures analysis of variance using the Bonferroni post hoc test in the risk and non-risk segments separately. Multiple logistic regression analysis, in which peak systolic strain, ESI, and PSI were simultaneously added to the equation, was used to determine independent parameters for detecting ischemic memory. ROC curves were analyzed to compare the diagnostic performances for ischemic memory after reperfusion, and comparisons of areas under the curve (AUCs) were performed using the method of DeLong et al (15). Percentages of abnormal (or normal) segments in each parameter were compared using the Chi-square test at first, and differences

in pairs of groups were tested using Ryan's methods (16). The inter-observer and intra-observer variabilities were determined by intraclass correlation coefficients (ICCs). A p-value <0.05 was considered statistically significant. Statistical analyses were carried out using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA), MedCalc version 15.2.2 (MedCalc Software, Ostend, Belgium), and JMP pro version 13.1.0 (SAS Institute, Cary, NC, USA).

Results

Hemodynamic data could not be used throughout the experiment in one dog and after reperfusion in another dog because of malpositioning of the micromanometer. In area strain data, only one basal anterolateral segment at baseline was unavailable because it was automatically excluded by the software due to tracking failure.

Hemodynamics

LV end-diastolic pressure and tau significantly increased, whereas the absolute value of dP/dt_{min} significantly decreased during occlusion. However, these parameters recovered to baseline levels by 10 min after reperfusion (Table 1).

Analysis 1

Area strain curves derived from 3D speckle-tracking echocardiography

A representative example of area strain curves in the risk and non-risk segments are shown in Figure 2. The absolute value of peak systolic strain decreased in the risk segment during occlusion but recovered to the baseline level after reperfusion. In contrast, ESL and PSS that appeared in the risk segment during occlusion could be clearly detected until 20 min or more after reperfusion.

In all dogs, the absolute value of peak systolic strain significantly decreased in the risk segment during occlusion. Although peak systolic strain slightly decreased 10 min after reperfusion, it recovered to the baseline level by 20 min after reperfusion. On the other hand, ESI, PSI, and MDI significantly increased during occlusion in the risk segment, and the significant increase persisted until

20 min after reperfusion for ESI and PSI and for more than 20 min after reperfusion for MDI (Figure 3).

Accuracy of area strain parameters for the diagnosis of ischemic memory

In multiple logistic regression analysis, ESI and PSI were independent determinants for the diagnosis of ischemic memory at 10 and 20 min after reperfusion, but peak systolic strain was not (Table 2). In the ROC curve of each parameter for diagnosing ischemic memory, the AUCs for ESI and PSI were significantly or tended to be higher than those of peak systolic strain. In addition, MDI demonstrated the best AUC among all parameters (Figure 4).

Analysis 2

Percentage of abnormal segments within all risk segments

The total numbers of risk and non-risk segments in all dogs were 147 and 381, respectively. A representative example of area strain curves in midventricular and basal segments is shown in Figure 5A. The absolute values of peak systolic strain decreased, and large ESL and PSS occurred in the inferior and inferolateral segments during occlusion. After reperfusion, peak systolic strains recovered to the baseline level, whereas ESL and PSS persisted in these segments for more than 20 min after reperfusion. In this dog, six segments with abnormal peak systolic strains during occlusion were defined as the risk segments. The number of abnormal segments in peak systolic strain rapidly decreased after reperfusion, but that in MDI and “ESI and/or PSI” persisted within the risk segments even at 30 min after reperfusion (Figure 5B).

In all risk segments, the percentage of abnormal segments for ESI, PSI, and MDI was significantly larger than that for peak systolic strain at 20 min after reperfusion (Figure 6). The percentage of abnormal segments for MDI did not seem to be different from that for ESI or PSI but tended to be larger when the analysis was limited to the apical and midventricular segments (68 segments). Another combined analysis of “ESI and/or PSI” showed the largest percentage of abnormal

segments in all strain parameters, although there was no significant difference. In each parameter, the percentage of normal segments was approximately 90% or higher (Figure 6).

Inter-observer and intra-observer variability

ICCs for all parameters were more than 0.9 in average and more than 0.8 even with the lower limit of 95% confidence interval (Table 3).

Discussion

In the dog model with 2-min coronary occlusion followed by reperfusion, we found that ESL and PSS could be detected after reperfusion by 3D speckle-tracking echocardiography. The new combined parameter MDI increased for more than 20 min after reperfusion compared with baseline and provided better diagnostic accuracy than ESI or PSI alone in identifying ischemic memory. The abnormal values at 20 min after reperfusion persisted in 33% of the total risk segments for MDI and 44% for "ESI and/or PSI", whereas they hardly persisted for peak systolic strain. MDI and "ESI and/or PSI" were abnormal in larger segments (43% and 49%, respectively) when analyzed in the apical and midventricular segments.

Myocardial ischemic memory imaging

Although morphological evaluation of coronary arteries is required to diagnose coronary artery disease, additional evidence of myocardial ischemia is needed to determine the optimal therapeutic strategy in patients with coronary stenosis (17). Myocardial ischemic memory imaging, which visualizes abnormalities provoked by ischemia that are sustained even after the restoration of perfusion, is therefore desirable. Myocardial metabolic imaging is a promising method to detect ischemic memory (18); however, its use is not widespread because of the need for a radiation-controlled area and its expensive cost. If ischemic memory imaging by echocardiography is possible, it would provide great value in clinical practice because it can be promptly performed anywhere. We previously reported that PSS is a sign of ischemic memory and its assessment by

echocardiography can be used for after-the-fact recognition of myocardial ischemic insult (4, 5). However, it was unclear whether the spatial extent of ischemic memory assessed by the persistence of PSS is enough to estimate the culprit vessel and risk area.

Regional myocardial deformation can be analyzed with 3D speckle-tracking echocardiography without through-plane motion, which is a limitation of 2D speckle-tracking echocardiography (10, 19). Rapid data acquisition in all LV segments is another advantage of 3D imaging (20). Thus, 3D speckle-tracking echocardiography may be suitable for assessing the spatial extent of ischemic memory because rapid data acquisition after the ischemic episode is desirable for detecting ischemic memory.

Detection of ischemic memory by 3D speckle-tracking echocardiography

Although 3D speckle-tracking echocardiography has advantages for ischemic memory imaging as mentioned above, its low spatial and temporal resolution limits the clinical use (21). This limitation may hamper the detection of small PSS. Inherent contractility in the regional myocardium can be modified by tension from the surrounding myocardium, resulting in the occurrence of not only PSS but also ESL when regional contractility deteriorates during ischemia (1, 13). Recently, the utility of ESL as another marker of myocardial ischemia has been attracting attention (7, 8). We therefore hypothesized that a combined analysis of ESL and PSS improves the diagnostic accuracy for detecting ischemic memory despite the low spatial and temporal resolution of 3D imaging.

In analysis 1, the decrease in peak systolic strain persisted until 10 min after reperfusion in the center of the risk area, whereas the increases in PSI persisted until 20 min after reperfusion. The AUC for PSI to detect ischemic memory was larger or tended to be larger than that for peak systolic strain. This result seems to be similar to that of previous experiments using tissue Doppler and 2D speckle-tracking echocardiography (4, 5) and suggests that the assessment of ischemic memory by 3D speckle-tracking echocardiography is also feasible. Furthermore, ESI and PSI were independent determinants for the diagnosis of ischemic memory and the new parameter MDI provided a

significantly higher AUC than PSI alone. The additional assessment of ESL seems to supplement the underestimation of PSS, which is caused by low spatial and temporal resolution.

ESL in the area strain persisted until 20 min after reperfusion in the present 3D echocardiographic experiment, whereas ESL in the circumferential or radial strain did not persist after reperfusion in the previous 2D experiment (5). Through-plane motion in the 2D short-axis view is prone to be seen in free wall segments (i.e., the area perfused by the LCx) and can hamper the accurate evaluation of myocardial deformation in these segments (10). This may be a cause of the discrepancy because short-axis images were used in the previous experiment.

The mechanisms of persistence in ESL and PSS have not been elucidated completely. However, we believe that persistence is due to a short duration of systolic stunning because abnormal ESL and PSS occur in the myocardium with contractile dysfunction through an imbalance of tension between the damaged and surrounding normal myocardium (13, 22). The combined parameter MDI seems to be reasonable for detecting subtle changes in myocardial deformation caused by systolic stunning. In contrast, slight changes in peak systolic strain may be difficult to detect because its normal variation is relatively large (1).

In the present study, regional wall thickening was not evaluated because area strain was used. We previously reported that the peak radial strain was recovered to the baseline level at 10 min after reperfusion in the same 2-min coronary occlusion models as this study (5, 23). We therefore think that deterioration of wall thickening is also difficult to be detected after reperfusion in such ischemia.

Spatial extent of ischemic memory by 3D speckle-tracking echocardiography

The persistence of ESL and PSS after transient ischemia is assumed to recover inhomogeneously within the risk area because of regional differences in the severity of ischemic insults (24). Even if the abnormalities of ESI and PSI are observed in the central segment of risk area, they may not be visible in the peripheral risk segments. In the present study, the percentage of abnormal segments for MDI was 33% and that for “ESI and/or PSI” was 44%, although that for peak systolic strain was only 9%.

This result suggests that the combined analysis is better for the diagnosis of ischemic memory because its evidence in the multiple segments would increase the diagnostic accuracy.

When the analysis was limited to the apical and midventricular segments, the percentage of abnormal segments for MDI and “ESI and/or PSI” improved to 43% and 49%, respectively. This improvement seems to be due to difficulties in speckle-tracking in basal segments. The EACVI-ASE Strain Standardization Task Force has recently reported a significantly lower accuracy for detecting regional functional abnormalities in the basal segments (25).

Although myocardial dyssynchrony is small in normal subjects (26), ESL and PSS are observed even in the normal myocardium, and their frequencies are different among segments (14). Physiological ESL and PSS values may reduce the specificity for detecting ischemic memory. However, most physiological ESL and PSS values were not considered abnormal because the cut-off values were determined on the basis of more than 2 SDs of the mean at baseline per segment in the present study. The cut-off values per segment in healthy subjects should be determined in a future study.

Clinical implications

The duration of ischemic memory is important for clinical application. Although the persistence of PSS can be observed for a couple of hours after recovery from severe demand ischemia (4), the duration of ischemic memory derived from speckle-tracking echocardiography may be shorter than that derived from myocardial metabolic imaging (18). We recently reported that mild afterload augmentation allowed the reappearance of PSS that had disappeared after transient ischemia (27). Afterload increase maneuvers such as handgrip stress may enable the revelation of concealed ischemic memory.

For stress echocardiography, image acquisition during peak stress is mandatory. However, high heart rates and poor image quality during peak stress cause difficulties in speckle-tracking analysis (28). PSS persists for a while after the cessation of dobutamine stress in dogs with non-flow limiting

stenosis (4). The assessment of ischemic memory by quick 3D acquisition shortly after peak stress may be practical for stress speckle-tracking echocardiography.

Study limitations

MDI derived from 3D speckle-tracking echocardiography has not been directly validated by sonomicrometry in the present study. However, we believe that MDI is valuable for detection of ischemic memory by 3D speckle-tracking echocardiography because occurrence of ESL and PSS during ischemia has been confirmed by the sonomicrometry study (13) and area strain values derived from 3D speckle-tracking echocardiography have also been validated (29).

We tested only one model with LCx occlusion because a dog's LV is mainly perfused by LCx. The diagnostic accuracy of ischemic memory in the smaller risk area is still unclear. The volume rate used in this study was a slightly higher than that in clinical settings because a dog's heart is smaller than a human's heart. Lower volume rates may affect the detection of ESL and PSS. However, heart rates are usually lower in patients than in dogs, which is favorable for the clinical application of this study.

Our data were acquired from trans-epicardial echocardiography in open-chest dogs. Feasibility and diagnostic accuracy in patients may be lower than those in the present study.

Conclusions

Not only PSS but also ESL persisted after transient ischemia and they could be detected by 3D speckle-tracking echocardiography. The new combined parameter, MDI provided higher diagnostic accuracy for detecting ischemic memory than ESL or PSS alone. MDI allowed detection of ischemic memory in more than 30% of all risk segments, whereas "ESL and/or PSS" enabled it in more than 40%. Integrated analysis of ESL and PSS by 3D speckle-tracking echocardiography may be useful for detecting transient ischemic insults in patients after the disappearance of anginal attack.

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Figure legends

Figure 1: Area strain analysis

(A) Bull's eye map of area strain at early systole during the left circumflex coronary artery occlusion. In analysis 1, a central segment of the risk area at the midventricular level and an opposite segment were analyzed as representative risk and non-risk segments. (B) Time-strain curve during one cardiac cycle. Peak systolic strain (ε_S), the early systolic strain index (ESI) as a parameter of early systolic lengthening (ESL), and the postsystolic strain index (PSI) as a parameter of postsystolic shortening (PSS) were analyzed. ESI was calculated as follows: ESL amplitude (ε_{ESL})/maximal strain amplitude during systole ($\varepsilon_{S\,MAX}$). PSI was calculated as follows: PSS amplitude (ε_{PSS})/maximal strain amplitude during the cardiac cycle (ε_{MAX}). The combined parameter, myocardial dysfunction index (MDI), was calculated as follows: $(\varepsilon_{ESL} + \varepsilon_{PSS})/\varepsilon_{MAX}$. AVC = aortic valve closure.

Figure 2: Area strain curves

Representative area strain curves in the risk segment (green line) and the non-risk segment (blue line). In the risk segment, the absolute value of peak systolic strain (green circles) decreased during occlusion and ESL (blue arrows) and PSS (red arrows) occurred. Peak systolic strain recovered to the baseline level after reperfusion. In contrast, ESL persisted until 20 min after reperfusion and PSS could be clearly detected for more than 20 min. Abbreviations as in Figure 1.

Figure 3: Serial changes of area strain parameters

In the risk segment, the absolute value of peak systolic strain significantly decreased during occlusion compared with baseline and the decrease persisted until 10 min after reperfusion. ESI, PSI, and MDI significantly increased during occlusion and the increase persisted until 20 min after reperfusion for both ESI and PSI, and even at 30 min after reperfusion for MDI. * indicates $p < 0.05$ versus baseline. Abbreviations as in Figure 1.

Figure 4: Receiver operating characteristic curve analysis

Receiver operating characteristic curves of area strain parameters for the diagnosis of ischemic memory at 10 and 20 min after reperfusion. Areas under curve (AUCs) for ESI and PSI were significantly or tended to be higher than that of peak systolic strain. The AUC for MDI was significantly higher than that for ESI or PSI alone except ESI at 20 min after reperfusion. *$p < 0.05$ versus line of no information (AUC = 0.5), †$p < 0.05$ versus peak systolic strain, ‡$p < 0.05$ versus ESI, §$p < 0.05$ versus PSI. Abbreviations as in Figure 1.

Figure 5: Spatial extent of abnormal area strains

(A) Representative area strain curves in midventricular and basal segments. The absolute values of peak systolic strain decreased and large ESL and PSS occurred in inferior and inferolateral segments during occlusion. Peak systolic strain recovered to the baseline level after reperfusion, whereas ESL and PSS widely persisted in these segments for more than 20 min after reperfusion. (B) In the same dog, six segments with abnormal peak systolic strains during occlusion were defined as the risk segments. Abnormal segments in peak systolic strain rapidly decreased after reperfusion. However, abnormal segments in MDI and "ESI and/or PSI" persisted within the risk segments even at 30 min after reperfusion. Abbreviations as in Figure 1.

Figure 6: Percentages of abnormal segments within the risk segments and percentages of normal segments within the non-risk segments

The percentage of the abnormal segments for ESI or PSI was significantly larger than that for peak systolic strain at 20 min after reperfusion. Although the percentage of abnormal segments for MDI was almost the same as that for ESI or PSI in all risk segments, that for MDI tended to be larger than that for ESI or PSI in the apical and midventricular segments (68 segments). "ESI and/or PSI" demonstrated the largest percentage of abnormal segments in all strain parameters although the difference was not statistically significant. In each parameter, the percentage of normal segments was approximately 90% or above. *$p < 0.05$ versus peak systolic strain. Abbreviations as in Figure 1.

Table 1 Coronary flow and hemodynamics

			Reperfusion		
	Baseline	Occlusion	10 min	20 min	30 min
LCx flow (mL/min)	13±5	0±0*	14±7	13±6	12±6
Heart rate (bpm)	129±14	130±13	128±14	126±14	126±14
LVSP (mmHg)	111±16	101±15	110±17	110±17	109±17
LVEDP (mmHg)	5±2	7±2*	5±2	5±2	5±3
dP/dt_{max} (mmHg/s)	2226±441	1922±436	2049±404	2037±400	2034±425
dP/dt_{min} (mmHg/s)	–2010±462	–1568±521*	–1930±470	–1948±494	–1921±477
Tau (ms)	41±7	48±14*	43±7	43±7	42±8

*$p < 0.05$ versus baseline. dP/dt_{max} = maximum time derivatives of left ventricular pressure; dP/dt_{min} = minimum time derivatives of left ventricular pressure; LCx = left circumflex coronary artery; LV = left ventricular; LVEDP = LV end-diastolic pressure; LVSP = LV systolic pressure.

Table 2 Odds ratio of area strain parameters for the diagnosis of ischemic memory after reperfusion by multiple logistic regression analysis

	Reperfusion 10 min		Reperfusion 20 min	
	OR (95% CI)	p	OR (95% CI)	p
Peak systolic strain	0.93 (0.78-1.10)	0.381	0.88 (0.74-1.04)	0.127
ESI	1.94 (1.05-3.58)	0.033	2.33 (1.29-4.21)	0.005
PSI	1.36 (1.11-1.67)	0.003	1.31 (1.08-1.58)	0.006

95% CI = 95% confidence interval; OR = odds ratio. Other abbreviations as in Figure 1.

Table 3 Inter-observer and intra-observer variabilities by intraclass correlation coefficients

	Inter-observer	95% CI	intra-observer	95% CI
Peak systolic strain	0.957	0.845-0.989	0.954	0.836-0.988
ESI	0.996	0.986-0.999	0.974	0.907-0.994
PSI	0.949	0.809-0.987	0.961	0.859-0.990
MDI	0.986	0.945-0.996	0.962	0.865-0.990

Abbreviations as in Figure 1 and Table 2.