Strain Measurements During Adenosine Triphosphate Infusion Before and After Percutaneous Coronary Intervention

Motoko Hosaka, MD; Atsushi Takagi, MD; Tsutomu Takagi, MD;
Kyomi Ashihara, MD; Nobuhisa Hagiwara, MD

Background: In regional myocardial ischemia, contractile delay develops, which can be assessed by measuring time to peak strain (TPS) on tissue Doppler imaging. The aims of the present study were to clarify the usefulness of TPS measurements during adenosine triphosphate (ATP) stress in assessing myocardial ischemia and to evaluate whether prolongation of TPS disappears immediately after percutaneous coronary intervention (PCI) or not.

Methods and Results: A total of 26 patients underwent strain measurements before and after PCI. Corrected TPS for heart rate (TPSc) in target regions and in control regions were measured both at baseline and during ATP infusion. TPSc ratio was calculated as a ratio of TPSc during ATP stress to TPSc at baseline. TPSc in the target region significantly increased during ATP infusion before PCI, which was significantly longer than hyperemic TPSc in control regions. Accordingly, TPSc ratio in the target regions before PCI was significantly greater than that in control regions (1.22 ± 0.17 vs 0.96 ± 0.09 , respectively, $P < 0.0001$). Following PCI, the TPSc ratio in the target regions significantly decreased to 0.98 ± 0.05 ($P < 0.0001$). Receiver operating characteristic curve analysis provided a cut-off of 1.04 in TPSc ratio for detecting myocardial ischemia with a sensitivity of 93% and specificity of 93%.

Conclusions: TPS measurements during ATP stress differentiated target from control myocardium before PCI. The prolongation of TPSc disappeared immediately after PCI. (*Circ J* 2010; **74**: 1600–1608)

Key Words: Adenosine; Coronary artery disease; Tissue Doppler imaging

Tissue Doppler imaging (TDI)-derived strain measurements provide a quantitative assessment of left ventricular regional wall motion without the influence of cardiac tethering and translational artifacts.^{1,2}

Ischemic myocardium is known to present delayed onset and termination of shortening, which may be rarely provided visually. TDI is useful to detect this phenomenon as a prolongation of time to peak strain (TPS)³ or TPS rate.^{4,5} The prolongation of the isovolumic relaxation time has been known to precede systolic dysfunction during acute myocardial ischemia in animal models.^{3,6,7} In clinical studies, post-systolic shortening (PSS) was found in ischemic myocardium⁸ on TDI during dobutamine stress^{2,3,6,7,9–12} or during exercise stress.⁵

Adenosine triphosphate (ATP) is a strong vasodilator that dilates the coronary artery by activating A2 receptor after conversion into adenosine. ATP redistributes the coronary blood flow from ischemic region to non-ischemic region, from subendocardial myocardium to epicardial myocardium, resulting in coronary steal and regional myocardial ischemia.

The potential advantage of ATP over dipyridamole or

dobutamine is its extremely short half-life, less discomfort for the patients and more tolerability and safety as compared to dobutamine stress or exercise stress.^{13,14}

Previously we have reported that ATP stress provoked a transient delay of contraction assessed on TDI that was correlated with coronary flow reserve in left anterior descending artery (LAD) lesions.¹⁵ The clinical usefulness of ATP stress TDI, however, has not been validated in patients with right coronary artery (RCA) and/or left circumflex artery (LCX) lesions. Moreover, there has been no report on whether ATP-induced contractile delay in ischemic myocardium disappears after coronary revascularization or not.

The aims of the present study were therefore to (1) clarify the cut-off of TPSc ratio to detect myocardial ischemia among various regions including in LAD, RCA and LCX diseases; and (2) clarify whether ATP-induced prolongation of TPS disappears immediately after successful percutaneous coronary intervention (PCI) or not.

Received December 6, 2009; revised manuscript received April 9, 2010; accepted April 13, 2010; released online July 1, 2010 Time for primary review: 30 days

Cardiology, Tokyo Women's Medical University, Tokyo (M.H., A.T., K.A., N.H.); Takagi Cardiology Clinic, Kyoto (T.T.), Japan
Mailing address: Atsushi Takagi, MD, Cardiology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: mtakagi@hij.twmu.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-09-0972

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Figure 1. Strain image analysis. The region of interest was defined as at the middle segment of the left ventricular wall. Peak strain (PS) and time to peak strain (TPS) were measured. TPS was obtained from the top of the R wave to peak systolic strain. TPS was corrected for the heart rate using the Bazett formula. TPSc ratio was calculated as the ratio of TPSc at adenosine triphosphate (ATP) stress to TPSc at baseline. $TPSc = TPS / \sqrt{RR}$; $TPSc\ ratio = TPSc\ (during\ ATP\ infusion) / TPSc\ (baseline)$. *R-top.

Methods

Study Patients

A total of 26 patients were enrolled who were referred for PCI including 13 patients with stable angina pectoris and 13 patients with unstable angina pectoris. Patients with unstable angina were included after medical stabilization.

All patients underwent successful PCI without complication. Patients with atrial fibrillation, branch bundle block, ventricular hypertrophy with diastolic wall thickness >12 mm, cardiomyopathy, valvular heart disease, decompensated congestive heart failure, bronchial asthma, hemodialysis, and anemia were excluded. PCI to the region of previous myocardial infarction was also excluded. All patients gave informed consent before examination.

Coronary Angiography and PCI

In all patients with stable angina, myocardial ischemia was proven on exercise stress electrocardiogram or myocardial perfusion scintigraphy. Among patients with unstable angina, myocardial ischemia was proven on electrocardiogram during chest pain in 4 patients, on myocardial perfusion imaging in 4 patients and by ST-T changes after exercise in 4 patients. In 1 patient, coronary flow reserve obtained by trans-thoracic Doppler echocardiography was assessed. Quantitative coronary angiography was done using CMSTM (MEDIS, Leiden, The Netherlands). Successful endpoint of PCI was defined as %diameter stenosis $<35\%$ with Thrombolysis In Myocardial

Infarction (TIMI) 3 flow. If serum level of cardiac enzyme was elevated, the patient was excluded from further analysis.

Data Acquisition

Echocardiography was performed on the day before PCI and the next day after PCI with Vivid 7TM (GE Health Care, Milwaukee, WI, USA). All patients had no wall motion abnormality at rest on visual assessment of the target regions before PCI.

Visual assessments of regional left ventricular wall motion were performed independently of the strain analysis. Each of the 16 apical segments at baseline and during ATP infusion were assessed according to a visual scoring system in which 1=normal, 2=hypokinesis, 3=akinesis, 4=dyskinesis, and 5=aneurysmal. Wall motion score index (WMSI) was calculated by dividing the sum of all scores by the number of interpreted segments.¹⁶

The operator carefully aligned the myocardial wall parallel to the ultrasound beam in TDI. TDI at a high frame rate >100 fps was obtained using a 1.7/3.4-MHz harmonics transducer at baseline and during iv ATP infusion at a speed of $0.14\ mg \cdot kg^{-1} \cdot min^{-1}$ for 2 min. Images were obtained from the standard apical 2- and 4-chamber views, and digital cine-loops of 3 cardiac cycles in sinus rhythm were stored.

TDI and Strain Analysis

Tissue Doppler data were analyzed offline with commercially available software (EchoPacTM, GE Vingmed Ultrasound,

Table. Patient Characteristics and Clinical Results

No. patients	26
Age (years), mean $\pm$ SD	65.3 $\pm$ 10.2
M/F	21/5
Previous history of old MI, n (%)	3 (11)
Coronary risk factors, n (%)	
Hypertension	19 (73)
Hyperlipidemia	20 (80)
Diabetes mellitus	13 (50)
Smoking	13 (50)
Clinical status, n (%)	
Stable angina pectoris	13 (50)
Unstable angina pectoris	13 (50)
Diseased vessel, n (%)	
1 vessel disease	24 (92)
2 vessel disease	2 (8)
No. lesions	28
Target vessel, n (%)	
Left anterior descending	19 (68)
Right	6 (21)
Left circumflex	3 (11)
Baseline TIMI grade flow, n (%)	
TIMI $\leq$ 2	8 (29)
TIMI 3	20 (71)
Stent implanted, n (%)	26 (93)
Diameter stenosis (%), mean $\pm$ SD	71.1 $\pm$ 13.9

MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

Horten, Norway). Longitudinal strain was calculated from tissue Doppler velocity data by defining the region of interest (ROI) with 6 mm length below the endocardium, which was semi-automatically tracked for the whole cardiac cycle. The operator readjusted the location of the sampling volume manually to maintain the same area of tissue despite its motion in every frame. For LAD lesion, sample volumes were placed in the middle septum on apical 4-chamber view or middle anterior wall on apical 2-chamber view. The smaller volume in these 2 views was accepted. For RCA lesion, sample volumes were placed in the middle of the inferior wall. For LCX lesion, the ROI was defined as in the middle of the lateral wall.

The top of the R wave was chosen as the time point of end diastole (**Figure 1**). Peak strain (PS) was expressed in percent and was negative in myocardial shortening. PS was defined to be the lowest strain over an RR interval. The time delay from the R- to PS was also measured as TPS, which was corrected for the heart rate using the Bazett formula as TPSc:¹⁷

$$\text{TPSc} = \text{TPS} / \sqrt{\text{RR}}$$

PS and TPSc was measured both in target and control regions at baseline and during ATP infusion. Measurements were averaged for 3 cardiac cycles.

To assess the prolongation of TPSc caused by ATP infusion, TPSc ratio was calculated as the ratio of TPSc at ATP stress to TPSc at baseline (**Figure 1**):

$$\text{TPSc ratio} = \text{TPSc (during ATP infusion)} / \text{TPSc (baseline)}$$

Echocardiography was analyzed by 1 experienced investigator who was blinded to the results of coronary angiography.

Statistical Analysis

Continuous variables are expressed as mean ± SD. Statistical analysis was done using StatView 5.0™ (SAS Institute, Cary, NC, USA). Differences between baseline and ATP infusion data were analyzed on Wilcoxon signed rank test. Comparisons of continuous variables between target regions and control regions were analyzed on Mann–Whitney U-test. P<0.05 was considered statistically significant. Sensitivity and specificity for TPSc, TPSc ratio and PS as a predictor of significant coronary stenosis were calculated on receiver operating characteristic (ROC) curves, which were used to designate cut-offs.

Feasibility of TPS and Inter–Intra-Observer Variability

We previously reported the reproducibility of PS measurement.¹⁵ TPS measurement was expressed as 95% limits of agreement between the first and second measurements for a single experienced investigator who was unaware of the patients' data. Intraobserver variability was 1.1±2.8% for PS and -1.6±14.8 ms for TPS. There were no significant differences found between first and second TPS measurements.¹⁵

Results

Patient Characteristics and Procedure

The patient characteristics and clinical results are given in

Table. Coronary angiography demonstrated a total of 28 lesions, 19 in LAD, 6 in RCA and 3 in LCX. TIMI flow grade was <2 in 8 lesions and TIMI 3 in 20 lesions. On QCA, mean %diameter stenosis was 71.1±13.9.

Visual Wall Motion Assessment

There were no significant differences in WMSI between baseline and ATP infusion before PCI (1.02±0.74 vs 1.02±0.76, respectively, P=0.65), and after PCI (1.01±0.03 vs 1.01±0.02, respectively, P=0.33). During ATP infusion heart rate increased from 59.9±10.7 to 66.6±11.7 beats/min (P=0.03). There were no side-effects of ATP stress.

PS

As in **Figure 2**, there were no significant differences in PS between baseline and ATP infusion within target regions (-21.2±5.4% vs -22.7±6.3%, respectively, P=0.18) and within control regions (-18.8±5.4% vs -17.7±6.9%, respectively, P=0.91) even before PCI. After PCI there were also no significant differences in PS between baseline and ATP infusion within the target region (-23.7±7.6% vs -23.6±8.5, respectively, P=0.88) and in control regions (-18.7±6.4% vs -20.0±6.6, respectively, P=0.16). Comparing PS between target and control regions before PCI, PS measurements in target regions were also equivalent to those in control regions both at baseline and during ATP infusion.

Figure 4. Difference of corrected time to peak strain for heart rate (TPSc) ratio between the target and control regions before and after percutaneous coronary intervention (PCI). The TPSc ratio in the target region was significantly greater than that in the control region. After successful intervention, TPSc ratio in the target region became equivalent to that in the control region.

Figure 5. A 71-year-old man had 90% stenosis in his left anterior descending artery, which was treated successfully by coronary stent implantation. Baseline corrected time to peak strain for heart rate (TPSc) was 297 ms in the target region before percutaneous coronary intervention (PCI). It was prolonged to 430 ms by adenosine triphosphate (ATP) infusion, resulting in a TPSc ratio of 1.44. After PCI the baseline TPSc was 313 ms. Because ATP did not prolong TPSc, the resulting TPSc ratio was 0.99. *R-top.

TPSc

TPSc before PCI at baseline in target regions was similar to that in control regions (332 ± 42.7 ms vs 340.0 ± 53.7 ms, respectively, $P=0.66$; **Figure 3**). ATP, however, induced significant prolongation of TPSc only in target regions (from 332 ± 42.7 ms to 404.1 ± 58.6 ms, respectively, $P<0.0001$), while ATP infusion significantly shortened TPSc in control regions (from 340.0 ± 53.7 ms to 327.4 ± 64.1 ms, respectively, $P=0.03$). As a result, TPSc during ATP infusion was significantly longer in target regions before PCI. After PCI, there was no difference in TPSc at baseline between target regions and control regions (331 ± 55.1 ms vs 344.8 ± 52.4 ms, respectively, $P=0.16$). In both target and control regions, however, ATP significantly shortened TPSc (331.6 ± 55.1 ms vs 324.5 ± 58.0 ms, respectively, $P=0.01$; 344.8 ± 52.4 ms vs 315.8 ± 48.3 ms, respectively, $P=0.0002$) after successful PCI.

TPSc Ratio

TPSc ratio was significantly greater in target regions than in control regions before PCI (1.22 ± 0.17 vs 0.96 ± 0.09 , respectively, $P<0.0001$; **Figure 4**). Immediately after PCI, the TPSc ratio both in target and control regions was <1.0 , but there was still a significant difference in TPSc ratio between target and control regions (0.98 ± 0.05 vs 0.92 ± 0.10 , respectively, $P=0.005$). The change of TPSc ratio after PCI was statistically significant in target regions. There was no significant difference in TPSc ratio of target region before PCI between patients with unstable angina and with stable angina (1.17 ± 0.11 vs 1.26 ± 0.20 , $P=0.169$, respectively). To assess the impact of change in heart rate on TPSc ratio, we analyzed the correlation between change in heart rate and TPSc ratio, but no significant correlation was found ($P=0.21$).

Figure 5 shows a representative case. A 71-year-old man had 90% stenosis in his LAD, which was treated successfully by coronary stent implantation. Baseline TPSc was 297 ms in the target region before PCI. It was prolonged to 430 ms by ATP infusion, resulting in a TPSc ratio of 1.44. After PCI, baseline TPSc was 313 ms. The resulting TPSc ratio was 0.99 in the target region.

Figure 6 shows the correlation between coronary artery severity and TPSc ratio in the target region before PCI. There was no significant correlation between % diameter stenosis

Figure 6. Correlation between coronary severity and corrected time to peak strain for heart rate (TPSc) ratio in the target region before percutaneous coronary intervention (PCI).

and TPSc ratio.

ROC analysis to assess cut-off for myocardial ischemia showed that TPSc ratio was the strongest predictor (with an area under the ROC curve of 0.97), among TPSc ratio, TPSc and PS. A cut-off of 1.04 had a sensitivity of 93% and specificity of 93% to assess regional myocardial ischemia (**Figure 7**).

Discussion

In recent years, pharmacological stress testing has evolved as an alternative to physical exercise for inducing myocardial ischemia. The diagnostic endpoint for detecting myocardial ischemia has been transient worsening of regional motion during stress in visual assessment. Adenosine and dipyridamole induced ischemia mainly due to blood flow maldistribution with reduction in subendocardial flow in ischemic myocardium. Dobutamine increases myocardial oxygen consumption and induced wall motion abnormalities in the presence of significant coronary stenosis.^{18,19} The sensitivity and specificity of visual assessment to detect myocardial ischemia,

Figure 7. Receiver operating characteristic (ROC) curves of corrected time to peak strain (TPSc) ratio, corrected time to peak strain (TPSc) during adenosine triphosphate (ATP) stress and peak strain (PS) for detecting significant coronary artery disease. AUC, area under the curve. ROC analysis produced a cut-off of 1.04 in TPSc ratio for detecting myocardial ischemia with a sensitivity of 93% and specificity of 93%.

however, depends on experience and is subjective. Recent developments of TDI allow us to precisely and quantitatively assess the regional wall motion. Ischemic myocardium shows delayed onset and termination of systolic shortening or systolic asynchrony that can be observed as the delayed contraction in the ejection phase or tardokinesis or PSS.

Many reports have shown that myocardial ischemia causes both delayed onset and delayed termination of systolic shortening in animal models.^{2-4,6,7,9} In clinical studies, PSS has been demonstrated in ischemic regions during dobutamine stress echocardiography¹⁰⁻¹² or during exercise stress echocardiography on TDI.⁵ PSS was also described as a transient phenomenon during balloon inflation during PCI.²⁰⁻²² Little has been reported, however, on quantitative analysis of PSS during stress.^{15,23}

In the present study we have demonstrated that PSS developed in ischemic myocardium during ATP stress, which was represented by prolongation of TPSc. Moreover, this TPSc prolongation immediately disappeared after successful revascularization. Our methods appeared to be useful at the bedside to differentiate ischemic from non-ischemic myocardium using a quantitative cut-off.

Contractility vs Timing

Thambyrajah et al have assessed peak systolic strain rate during exercise stress before and after PCI.⁵ They found a significant prolongation of time to peak systolic strain rate at peak stress in ischemic regions before PCI, while there were no statistically significant differences in the other parameters of strain amplitude or strain rate amplitude.

In the present study there were no significant differences of WMSI between target and control regions at baseline before and after PCI. During ATP infusion, visual assessment could not detect wall motion abnormality. Strain amplitude also showed no significant difference between baseline and hyperemia both within target regions and control regions. Interestingly, myocardium without ischemia showed shortening of TPSc while ischemic myocardium showed prolongation of TPSc during ATP infusion. As a result, the difference in TPSc ratio between target and control regions was enhanced by ATP infusion. After successful PCI, TPSc shortened significantly during ATP infusion both in target and control regions compared with baseline. The mechanism for this is unknown, but by the agreement of the Thambyrajah et al report and the present one it can be said that assessment of the contractile phase is better to for assessing myocardial ischemia than assessment of the strength of contraction.⁵ In the present study ATP might have only caused subtle dyssynchrony in the ischemic myocardium but could not change the strength of contractility. In the Voigt et al study strain analysis showed that strain amplitude of ischemic regions remained almost constant because of increased or newly occurred PSS during dobutamine stress.¹⁰ The fact that we defined the ROI as at the subendocardium might have contributed to increase the sensitivity in the detection of this subtle change during ATP infusion. Strain measurement seemed to be superior to visual analysis in assessing tardokinesis, which is subject to noise, and angle artifacts.² Another issue is variability in measurements. In our previous study, better agreement between the first and second measurements was observed in TPSc measurements than in PS.¹⁵

TPSc vs TPSc Ratio

The present results suggested that prolongation of TPSc is a useful index to detect ischemic myocardium. The range of

TPSc varied, however, among the regions. It is known that PSS can be seen in 100% of the ischemic but also in 47% of the non-ischemic segments at peak stress with dobutamine.^{10,23} Moreover, in the clinical setting, the value of TPSc can be affected by the presence or absence of left ventricular hypertrophy, left bundle block or cardiac afterload. Therefore, as in the previous study, we analyzed the TPSc ratio instead of TPSc to separate ischemic from non-ischemic prolongation.¹⁵

Immediate Disappearance of ATP-Induced TPSc Prolongation After PCI

Delayed recovery of myocardial contraction in spite of normal perfusion after transient severe ischemia has been recognized as myocardial stunning. Ishii et al. reported that delayed relaxation or delayed contraction is observed in patients with vasospastic angina for several weeks after attack of spasm on color kinesis.^{24,25} The ischemic memory in myocardial contraction is thought to remain for hours or days or weeks.^{5,26,27} This ischemic memory is explained by the delay of metabolic stunning even after blood flow restoration.²⁸

In contrast, in the present study ATP-induced TPSc prolongation disappeared immediately after successful revascularization. One explanation is the very short duration of the action of ATP. We injected ATP iv only for 2 min. The duration of ATP action might be too short to cause ischemic memory. Phase analysis might be another reason to explain the immediate disappearance of TPSc prolongation.

Finally, we do not know whether this TPSc prolongation represents myocardial ischemia or merely demonstrates ATP-induced PSS as an inducible phenomenon. In our previous report we found a correspondence between ATP-induced TPSc delay with coronary flow reserve. In the present study, however, we did not measure coronary flow reserve. Moreover, we failed to show a correlation between % diameter stenosis of target vessel and TPSc ratio. There were collateral circulation developments especially in patients with unstable angina. Therefore, % diameter stenosis of the target vessel did not always represent the deterioration of coronary flow in the target regions. But immediate disappearance of TPSc prolongation during ATP stress in target regions after successful PCI suggested that this phenomenon induced by ATP represents regional myocardial ischemia.

Sensitivity and Specificity

To assess the clinical usefulness, it is important to compare the sensitivity and specificity against former studies. Recent AHA/ACC guidelines state that dobutamine stress has substantially higher sensitivity than vasodilator stress for detecting coronary heart disease. Picano et al, however, found a similar accuracy between dobutamine and dipyridamole of 84% and 87%, respectively, after analyzing 5 papers.²⁹ The sensitivity was found to be 86% in dobutamine, and 85% in dipyridamole stress, while specificity was 86% and 89%, respectively.

It has been reported that ATP stress induces more subtle myocardial dysfunction compared with dobutamine stress.^{30,31} In the present study visual assessment and PS amplitude were not able to show significant differences during ATP stress between ischemic and non-ischemic myocardium. TPSc ratio with a cut-off of 1.04, however, had a sensitivity of 93% and specificity of 93% to detect myocardial ischemia. The cut-off of 1.04 was different from that in our former study. There might be several explanations. In the previous study we used a cut-off ≥ 1.1 , which corresponded to coronary flow reserve

<2.0. Coronary flow reserve could be affected by microvascular disease or hypertrophy. Another difference between the former and the present study was the coronary severity. In the present study mean % diameter stenosis was $71.1 \pm 13.9\%$, which is greater than that in our previous study. This might affect the cut-off.

Study Limitations

The study subjects consisted of a limited number of heterogeneous patients including those with stable and unstable angina pectoris. Therefore, the conclusions reached should be interpreted with caution due to the underpowered nature of the study. Because the severity of coronary artery disease might increase the sensitivity, the cut-off criteria for detecting regional myocardial ischemia could be different if the different types of patients were enrolled. Because the present study consequently included patients mainly with single vessel disease, the results should be carefully adapted in patients with multi-vessel diseases.

A larger number of patients with multi-vessel coronary artery disease is warranted.

We used strain measurements for assessing regional myocardial ischemia. Recent studies suggest that strain rate measurement may be sensitive for inotropy. Strain rate profiles, however, tend to be more sensitive for the noise. TPSc analysis using strain measurement ensured better robustness of the results.

Despite several limitations, the present results have demonstrated the clinical utility of ATP stress in assessing myocardial ischemia. A different response to ATP infusion between target and control myocardium; TPSc prolongation in target regions and TPSc shortening in control regions, demonstrated strong clinical significance. ATP is less expensive in Japan, causes less discomfort to patients and is more tolerable compared to dobutamine or exercise stress echocardiography. Sicari et al. have said that side-effects preclude the achievement of maximal pharmacological stress in <10% of patients with dobutamine and in <5% of patients with dipyridamole stress.¹⁹ The present results, which demonstrate without any incidences of adverse side-effects are important in clinical use. Because of the prognostic importance of silent myocardial ischemia, which could be followed by catastrophic cardiac events such as heart attack or sudden death,³² our methods could also be useful for the screening of silent myocardial ischemia among patients with high coronary risk.

Conclusions

TPS measurements during ATP stress differentiated target from control myocardium at cut-off in TPSc ratio of 1.04, with a sensitivity of 93% and specificity of 93% to detect myocardial ischemia. The prolongation of TPSc during ATP infusion disappeared immediately after PCI. ATP stress strain analysis appeared to be useful to detect coronary diseases in a clinical setting.

References

1. Takayama M, Norris RM, Brown MA, Armiger LC, Rivers JT, White HD. Postsystolic shortening of acutely ischemic canine myocardium predicts early and late recovery of function after coronary artery reperfusion. *Circulation* 1988; **78**: 994–1007.
2. Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography: Validation of a new method to quantify regional myocardial function. *Circulation* 2000; **102**: 1158–1164.
3. Jamal F, Kukulski T, Strotmann J, Szilard M, D'Hooge J, Bijns B, et al. Quantification of the spectrum of changes in regional myocardial function during acute ischemia in closed chest pigs: An ultrasonic strain rate and strain study. *J Am Soc Echocardiogr* 2001; **14**: 874–884.
4. Yip G, Khandheria B, Belohlavek M, Pislaru C, Seward J, Bailey K, et al. Strain echocardiography tracks dobutamine-induced decrease in regional myocardial perfusion in nonocclusive coronary stenosis. *J Am Coll Cardiol* 2004; **44**: 1664–1671.
5. Thambyrajah J, Vijayalakshmi K, Graham RJ, Turley AJ, de Belder MA, Stewart MJ. Strain rate imaging pre- and post-percutaneous coronary intervention: A potential role in the objective detection of ischaemia in exercise stress echocardiography. *Eur J Echocardiogr* 2008; **9**: 646–654.
6. Pislaru C, Belohlavek M, Bae RY, Abraham TP, Greenleaf JF, Seward JB. Regional asynchrony during acute myocardial ischemia quantified by ultrasound strain rate imaging. *J Am Coll Cardiol* 2001; **37**: 1141–1148.
7. Pislaru C, Anagnostopoulos PC, Seward JB, Greenleaf JF, Belohlavek M. Higher myocardial strain rates during isovolumic relaxation phase than during ejection characterize acutely ischemic myocardium. *J Am Coll Cardiol* 2002; **40**: 1487–1494.
8. Onishi T, Uematsu M, Nanto S, Morozumi T, Watanabe T, Awata M, et al. Detection of diastolic abnormality by dyssynchrony imaging: Correlation with coronary artery disease in patients presenting with visibly normal wall motion. *Circ J* 2009; **73**: 125–131.
9. Skulstad H, Urheim S, Edvardsen T, Andersen K, Lyseggen E, Vartdal T, et al. Grading of myocardial dysfunction by tissue Doppler echocardiography: A comparison between velocity, displacement, and strain imaging in acute ischemia. *J Am Coll Cardiol* 2006; **47**: 1672–1682.
10. Voigt JU, Lindenmeier G, Exner B, Regenfus M, Werner D, Reulbach U, et al. Incidence and characteristics of segmental post-systolic longitudinal shortening in normal, acutely ischemic, and scarred myocardium. *J Am Soc Echocardiogr* 2003; **16**: 415–423.
11. Voigt JU, Nixdorf U, Bogdan R, Exner B, Schmiedehausen K, Platsch G, et al. Comparison of deformation imaging and velocity imaging for detecting regional inducible ischaemia during dobutamine stress echocardiography. *Eur Heart J* 2004; **25**: 1517–1525.
12. Citro R, Galderisi M. Myocardial postsystolic motion in ischemic and not ischemic myocardium: The clinical value of tissue Doppler. *Echocardiography* 2005; **22**: 525–532.
13. Anthonopoulos LP, Bonou MS, Kardaras FG, Sioras EP, Kardara DN, Sideris AM, et al. Stress echocardiography in elderly patients with coronary artery disease: Applicability, safety and prognostic value of dobutamine and adenosine echocardiography in elderly patients. *J Am Coll Cardiol* 1996; **28**: 52–59.
14. Qu HY, Yao GH, Sun WY, Chen L, Li XN, Zhang PF, et al. Assessment of ischemic myocardium by strain-rate imaging during adenosine stress echocardiography. *Int J Cardiovasc Imaging* 2007; **23**: 725–732.
15. Takagi T, Takagi A, Hozumi T, Yoshikawa J. Detection of significant stenotic lesions in the left anterior descending coronary artery using adenosine triphosphate stress strain imaging: Comparison with coronary flow velocity reserve measurement using transthoracic Doppler echocardiography. *J Am Soc Echocardiogr* 2006; **19**: 1001–1011.
16. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; **2**: 358–367.
17. Arad M, Abboud S, Radai MM, Adunsky A. Effect of ischemic stroke on the dynamic beat-to-beat QT-RR relationship. *Pacing Clin Electrophysiol* 2001; **24**: 323–328.
18. Pingitore A, Picano E, Colosso MQ, Reisenhofer B, Gigli G, Lucarini AR, et al. The atropine factor in pharmacologic stress echocardiography: Echo Persantine (EPIC) and Echo Dobutamine International Cooperative (EDIC) Study Groups. *J Am Coll Cardiol* 1996; **27**: 1164–1170.
19. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, et al. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr* 2008; **9**: 415–437.
20. Jamal F, Kukulski T, D'Hooge J, De Scheerder I, Sutherland G. Abnormal postsystolic thickening in acutely ischemic myocardium during coronary angioplasty: A velocity, strain, and strain rate doppler myocardial imaging study. *J Am Soc Echocardiogr* 1999; **12**: 994–996.

21. Kukulski T, Jamal F, D'Hooge J, Bijmens B, De Scheerder I, Sutherland GR. Acute changes in systolic and diastolic events during clinical coronary angioplasty: A comparison of regional velocity, strain rate, and strain measurement. *J Am Soc Echocardiogr* 2002; **15**: 1–12.
22. Kukulski T, Jamal F, Herbots L, D'Hooge J, Bijmens B, Hatle L, et al. Identification of acutely ischemic myocardium using ultrasonic strain measurements: A clinical study in patients undergoing coronary angioplasty. *J Am Coll Cardiol* 2003; **41**: 810–819.
23. Zhu H, Hozumi T, Takemoto Y, Takagi Y, Negishi K, Abo K, et al. Estimation of myocardial ischemia by diastolic strain analysis in exercise stress echocardiography: Comparison with exercise thallium-201 single photon emission computed tomography. *J Cardiol* 2006; **47**: 165–172 (in Japanese).
24. Ishii K, Miwa K, Makita T, Okuda N. Prolonged postischemic regional left ventricular delayed relaxation or diastolic asynchrony detected by color kinesis following coronary vasospasm. *Am J Cardiol* 2003; **91**: 1366–1369.
25. Miwa K, Ishii K, Makita T, Okuda N. Diagnosis of multivessel coronary vasospasm by detecting postischemic regional left ventricular delayed relaxation on echocardiography using color kinesis. *Circ J* 2004; **68**: 483–487.
26. Ambrosio G, Betocchi S, Pace L, Losi MA, Perrone-Filardi P, Soricelli A, et al. Prolonged impairment of regional contractile function after resolution of exercise-induced angina: Evidence of myocardial stunning in patients with coronary artery disease. *Circulation* 1996; **94**: 2455–2464.
27. Ishii K, Miwa K, Sakurai T, Kataoka K, Imai M, Kintaka A, et al. Detection of postischemic regional left ventricular delayed outward wall motion or diastolic stunning after exercise-induced ischemia in patients with stable effort angina by using color kinesis. *J Am Soc Echocardiogr* 2008; **21**: 309–314.
28. Dilsizian V, Bateman TM, Bergmann SR, Des Prez R, Magram MY, Goodbody AE, et al. Metabolic imaging with beta-methyl-p-[(123)I]-iodophenyl-pentadecanoic acid identifies ischemic memory after demand ischemia. *Circulation* 2005; **112**: 2169–2174.
29. Picano E, Molinaro S, Pasanisi E. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: A meta-analysis. *Cardiovasc Ultrasound* 2008; **6**: 30.
30. Djordjevic-Dikic AD, Ostojic MC, Beleslin BD, Stepanovic J, Petrasinovic Z, Babic R, et al. High dose adenosine stress echocardiography for noninvasive detection of coronary artery disease. *J Am Coll Cardiol* 1996; **28**: 1689–1695.
31. Marwick TH. Adenosine echocardiography in the diagnosis of coronary artery disease. *Eur Heart J* 1997; **18**(Suppl D): D31–D36.
32. Gutterman DD. Silent myocardial ischemia. *Circ J* 2009; **73**: 785–797.