Assessment of ischemia reperfusion injury after PCI for ST-elevation myocardial infarction using speckle tracking echocardiography

Jing Ping Sun MD, FACC, FAHA¹*, Yi Liang MD¹*, Fen Zhang MD¹, Liangjie Xu MD¹, Xinxin Chen MS¹, Wei Yuan, MD, PhD¹, Robert C. Bahler MD, FACC²# Jinchuan Yan MD, PhD¹#

¹ Affiliated Hospital of Jiangsu University, Zhenjiang, China
² Case Western Reserve University School of Medicine, Cleveland, OH, USA
*Co-first author
#Co-corresponding author

Corresponding authors:
Jinchuan Yan, MD, PhD
Professor of Medicine,
Director, Department of Cardiology
Affiliated Hospital of Jiangsu University, Zhenjiang, China
Tel: 86-0511-85026551 Email: yanjinchuan@hotmail.com

Robert C. Bahler MD, FACC
Emeritus Professor of Medicine, Case Western Reserve University School of Medicine at
MetroHealth Medical Center, Cleveland, OH, USA
Tel:1-216-292-5529 Fax 1216778-2739 Email: rbahler@metrohealth.org

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Keywords: Primary PCI, Reperfusion injury, Speckle tracking imaging
Abstract

Background: Ischemia reperfusion injury (IRI) frequently follows successful PCI for STEMI. Echocardiographic assessment of global longitudinal strain post-STEMI has been shown to be predictive of infarct size and prognosis. Multi-layer speckle tracking echocardiography (STE) detects dysfunction in different myocardial layers and could provide further functional data following PCI.

Objectives: We describe the changes in layer-specific myocardial function over the first 24 hours after successful PCI for ST-elevation myocardial infarction (STEMI).

Methods: Patients (n=120) with STEMI and no prior myocardial infarction underwent echocardiography pre-PCI; immediately, 3 and 24 hours post-PCI. A reduction of endo-myocardial strain immediately post-PCI as compared to the pre-PCI value was considered IRI.

Results: All patients had elevated biomarkers of infarction and uncomplicated clinical courses after PCI. Pre-PCI all patients had reduced global longitudinal strain. Patients with IRI had a further reduction in longitudinal endo-myocardial strain in the infarction region immediately post-PCI. At 3 hours strain began to improve and continued to improve at 24 hours. This pattern was seen in each of the ischemic territories of anterior descending, circumflex and right coronary arteries. All patients without IRI had improvement in longitudinal endo-myocardial strain following PCI. The longitudinal endo-myocardial changes were more evident than those of full thickness longitudinal strain. The incidence of IRI was directly related to total ischemia time.

Conclusions: Longitudinal endo-myocardial strain is a sensitive indicator of IRI. Evidence of early recovery from IRI was seen at 3 hours post-PCI. Speckle tracking echocardiography is a sensitive method to describe focal alterations in myocardial function.

Trial registration: ChiCTR-DDD-17012790
Condensed abstract

Ischemia reperfusion injury (IRI) following successful PCI for STEMI is common. Multiple modalities can quantitate injury/infarction but sequential functional changes after PCI are unknown. Layer specific speckle tracking echocardiography (STE) can quantitate dysfunction in the endo-myocardial region. In 120 STEMI patients, this strain was reduced prior to PCI and declined further immediately after PCI in 51%, indicating IRI. Strain improved modestly at 3 hrs and more at 24 hrs. Immediate improvement in strain occurred in patients without IRI. The incidence of IRI was directly related to total ischemia time. Sequential changes in myocardial function can be quantitated by STE.

Abbreviations

DES = drug eluting stent

IRI = ischemia reperfusion injury

CMR = cardiac magnetic resonance imaging

LAD = left anterior descending coronary artery

LCX = left circumflex coronary artery

LV = left ventricle

LVEF = left ventricular ejection fraction

RCA = right coronary artery

STE = speckle tracking echocardiography
INTRODUCTION

Myocardial ischemia-reperfusion injury (IRI) was described decades ago as a phenomenon where myocardial function worsened in the ischemic area following reperfusion of the occluded artery. This phenomenon occurs frequently in patients undergoing PCI for STEMI and has been associated with worse outcomes (1-3). Despite the reduction in benefits as a consequence of IRI, the early and successful myocardial reperfusion with either thrombolytic agents or primary percutaneous coronary intervention (PCI) has proven the most effective strategy to reduce infarct size and improve clinical outcomes (3). Numerous efforts to identify therapies that could lessen IRI have failed to be clearly beneficial with the possible exceptions of metoprolol (4) and post conditioning after PCI (5, 6). Recognition of IRI in humans has utilized multiple modalities including the ECG, bio-markers of myocardial damage and most imaging modalities; in the last decade, cardiac magnetic resonance imaging (CMR) has become the dominant technique for assessment of myocardial injury (7-9). Serial observations of IRI have been limited due to both the logistics of performing multiple CMR studies, as well as the subjective aspect of assessing segmental wall motion abnormalities with both CMR and echocardiography. Myocardial strain analyses by both CMR and speckle tracking echocardiography (STE) have afforded a more accurate quantitation of changes in focal left ventricular (LV) function (9-10). However, only STE would be suitable for serial observations of focal myocardial dysfunction in humans following STEMI and reperfusion. Consequently, our knowledge of the short-term evolution of myocardial function with IRI is quite limited. Our study aims were 1) to describe the serial changes in focal myocardial function seen with successful reperfusion of the occluded infarct related coronary artery in patients with acute ST-elevation myocardial infarction (STEMI) and 2) to demonstrate the
utility of STE to provide serial and quantitative assessment of myocardial function within ischemic segments of the LV myocardium.

METHODS

Study population

This was a prospective study of 120 patients with STEMI (convenience sample) undergoing percutaneous coronary intervention (PCI). The studies were registered in Chinese Clinical Trial Registry (ChiCTR-DDD-17012790) and completed from July 20, 2017 to July 16, 2018 in the Affiliated Hospital of Jiangsu University, Zhenjiang, China. Inclusion criteria included acute STEMI of less than 12 hours, symptoms lasting less than 24 hours and the need for urgent PCI. Exclusion criteria were acute heart failure, cardiogenic shock, bundle branch block, atrial fibrillation, frequent premature beats, third degree atrioventricular block, severe malignant arrhythmia, poor image quality and patients or families not agreeing to participate. The study protocol was approved by the Institutional Review Board of Affiliated Hospital of Jiangsu University. Each patient signed the consent.

Clinical Data

The ECG, blood pressure, and blood sample for biomarkers were obtained at patient arrival. The onset of symptoms to balloon time was recorded as well as symptoms during the PCI procedure.

Echocardiographic and imaging analysis

Imaging was performed with Vivid E 9 (General Electric, Milwaukee, WI, USA). A complete echocardiographic study, using standard views and with care taken to avoid foreshortening,
was performed at patient arrival to the catheterization laboratory, immediately post PCI, and at 3 and 24 hours after the PCI procedure.

All images were recorded for 3 cardiac cycles. Mitral inflow velocities were obtained from the apical window using pulsed wave Doppler with the sample volume placed at the center of the leaflet tips. Pulmonary venous flow was obtained from one of the pulmonary veins, guided by color Doppler. Tissue Doppler velocities in early diastole (e’) were recorded from both the septal and lateral sides of the mitral annulus. Tricuspid regurgitation velocities were recorded by continuous wave Doppler from multiple windows.

Measurements were performed using computerized off-line analysis stations. LV volumes, LVEF, and left atrial maximal volumes were measured using the bi-plane method and the modified Simpson’s rule. Mitral annulus tissue Doppler velocities, the velocity of tricuspid regurgitation, Doppler parameters of mitral and pulmonary vein flow were measured according to the American Society of Echocardiography (ASE) recommendations (11). All routine two-D and Doppler parameters were evaluated according to ASE recommendations (12). Strain parameters were analyzed using a new EchoPAC workstation with myocardial layer-specific software (BT13 software version 113.1.X, GE Healthcare, Milwaukee, WI) and with automatic function imaging (AFI). The software uses STE to quantitate strain and allows selection of a specific myocardial region for both full thickness longitudinal strain analysis (myocardial longitudinal strain analysis) as well as analysis of strain from a specific myocardial layer. The spatial deformation (strain) of each layer can be divided into longitudinal and circumferential components.

**Cardiac catheterization**
Each PCI was performed according to standard procedures by interventional cardiologists using a 6- or 7-French guiding catheter. The PCI wire was chosen according to the lesion and vessel characteristic. Compliant or non-compliant balloon was used according to the degree of calcification. Patients received a drug eluting stent (DES) such as paclitaxel-eluting stent/sirolimus-eluting stent/zotarolimus-eluting stent based on the lesion characteristics. The stent was inflated at 6 to 12 atm according to the nominal pressure. The non-compliant balloon was generally used after implantation of DES. The success of angiography was defined as a residual stenosis of less than 20% with no less than TIMI 3 grade flow after stent implantation. During the procedure, an anticoagulant (e.g., heparin) was administered per protocol (100 units/kg, ACT>250 sec). Glycoprotein IIb/IIIa inhibitors were used at the operator’s discretion.

Of the 120 patients 111 received drug-eluting stent(s), 8 were treated by PCI without stents, and one case was treated with thrombus aspiration only.

**Statistical analysis**

Baseline characteristics are presented as mean ± SD for continuous variables or numbers (percentage) for categorical variables. Reperfusion injury was defined as decreases in longitudinal endo-myocardial strain immediately post PCI. Data from the 12 patients with multiple coronary artery occlusions were excluded from the analyses. The initial comparison of the strain parameters at different time-points was performed using repeated measures ANOVA. When the means for the 4 time-points of observation differed, *a priori* contrasts were analyzed for 1) baseline and immediately post PCI and 2) baseline and 24 hours post PCI. To determine the incidence of reperfusion injury in patients with different myocardial
ischemia times, the study group was divided into tertile based on the time from onset of symptoms to balloon time and the tertiles and times were compared using one way ANOVA (SPSS (25.0 / August 8, 2017, IBM).

RESULTS

Baseline characteristics of study subjects

None of the 120 patients developed new symptoms or new arrhythmias during PCI. All patients had sinus rhythm and were hemodynamically stable. No deaths occurred in this selected population. The baseline characteristics of patients with and without IRI are shown in Table 1. Angina pectoris was present in 26 patients prior to STEMI. Biomarkers (CK-MB, MYO, TNI, and BNP) were elevated in all of cases.

The results of full thickness and layer myocardial strain in patient with STEMI

The pre-PCI echocardiographic imaging found that the average longitudinal strain, as estimated by the automatic function imaging (AFI), was significantly lower in the perfusion territories of the left descending coronary artery (LAD) in 47 cases; the left circumflex artery (LCX) in 19 cases; the right coronary artery (RCA) in 42 cases and in the territories of multiple coronary arteries in 12 cases. Full thickness segmental strain by AFI detected abnormal reductions in strain in all patients. The AFI localization of ischemia/injury and the coronary angiographic evidence of major obstructions were concordant in all patients. Reperfusion was successful in all patients.

Typical alterations in longitudinal strain, as can be seen in STEMI, are shown in Figure 1. By definition IRI was present when segmental systolic function worsened immediately after PCI.
The amplitude of longitudinal endo-myocardial strain in the STEMI region decreased immediately post PCI in all patients with IRI; in contrast, those without IRI had a progressive improvement of strain amplitude following PCI (Figure 2). The amplitude of strain in those with IRI began to improve by 3 hours after PCI and showed continued improvement at 24 hours.

Within each ischemic territory (LAD, LCX, RCA) the amplitude of endo-myocardial longitudinal strain was significantly reduced immediately post PCI in 29 (62%), 11 (58%) and 19 (45%) patients respectively (i.e. IRI), whereas the endo-myocardial longitudinal strain improved immediately post PCI in 18 (38%), 8 (42%) and 23 (55%) cases respectively (Table 2). Although these same trends were seen in patients with IRI of the LCX territory, they did not reach significance due to the small sample size (Table 2). The directional changes in full thickness myocardial longitudinal strain within the ischemia territory were similar to those of the endo-myocardium longitudinal strain but less significant. Left ventricular twist was improved after PCI in patients with and without IRI but not significantly. In general, endo-myocardial circumferential strain did not show clear trends except improvement occurred in patients with LAD occlusions and without IRI.

**Changes in parameters of conventional echocardiography in patients with and without IRI**

Most of the routine parameters of 2D and Doppler echocardiography were not altered after PCI, but the septal e’ decreased significantly from baseline in patients with IRI (6.5 ±1.8 to 4.3±1.2 cm/s, p=<0.0001) as well as those without IRI (6.5±1.5 to 4.3±1.5 cm/s, p=0.002). There were few significant differences between the 2 groups apart from a higher velocity of pulmonary vein A wave reversal, a greater left atrial volume, and greater end-diastolic and
end-systolic volumes in those with IRI. LVEF improved from 55±9 to 58±10% in patients with IRI and from 57±7 to 60±7% in patients without IRI. The difference in the time from onset of symptom to balloon time was strikingly longer in those with IRI (Table 1) resulting in the incidence of IRI being markedly higher in the tertile with the longest time from symptom onset to reperfusion (total ischemia time) (Figure 3).

**DISCUSSION**

We observed in a very selected population of patients with STEMI that 1) IRI can become evident immediately following reperfusion, 2) the incidence of IRI is directly related to the duration of the preceding ischemia and 3) some recovery of function from IRI can begin as soon as 3 hours following reperfusion. The study provides the first serial description of focal LV function in STEMI over the first 24 hours after successful PCI, and highlights the value of echocardiographic STE in identifying layer specific changes in function.

Prior imaging studies following STEMI and successful reperfusion have mostly selected a single point of time after reperfusion. Although the time-point for imaging after PCI or thrombolysis has varied, both CMR and echocardiography have provided prognostic information that was related to the extent of myocardial injury and the precision of these estimates has been enhanced by strain measurements (13). Prior echocardiographic STE investigations of STEMI have focused on global longitudinal and circumferential strain and their ability to assess prognosis (14-16) and their ability to identify the extent of myocardial injury as compared to single photon emission CT (15) or to cardiac peak troponin T (17).

Multi-layer STE has been available the past few years and has allowed analysis of endomyocardial, mid-myocardial and epicardial function in different diseases (18–20). We have
applied this technology to serial observations of patients with STEMI and observed that endo-myocardial longitudinal strain measurements may be more reflective of IRI as compared to either global longitudinal strain or ischemia segmental myocardial longitudinal strain, an observation consistent with the known distribution of acute myocardial ischemia with its initial impact on the sub-endocardial region (21).

We defined IRI as a further decrease, as compared to baseline imaging, in longitudinal endo-myocardial strain immediately following PCI. Since there are no prior imaging studies immediately after PCI, our definition cannot be compared to prior studies. The closest analogy to our observing a prompt improvement in longitudinal endo-myocardial function in patients without IRI is the prompt resolution of ST elevation that is seen in some patients shortly after successful reperfusion for STEMI. Until now the ECG provided the best initial assessment of the presence or absence of important IRI (22). The absence of a further reduction in strain post PCI does not negate the possibility that IRI occurred; it only infers that IRI was not sufficient to prevent some functional recovery. Microvascular obstruction as seen by CMR is a clear indicator of injury but does not segregate whether the injury was from the initial ischemia versus that from IRI (24). Additional studies comparing the strain data to the ECG data are warranted.

Our observation that the extent of IRI was directly to the total ischemia time is not surprising and is consistent with the observations of other investigators (17, 23, 25), giving emphasis to the importance of achieving reperfusion as promptly as possible.

Strengths of this study include an investigation confined to one institution with its associated uniformity of treatment, and the repeated measures of myocardial function over a pre-
specified time-period. Study limitations include the selected population of patients with STEMI, assessment of myocardial function only within the first 24 hours after PCI, plus the uncertainty of how both pre-conditioning and collateral circulation may have influenced the development and clinical course of IRI. Our study is only descriptive of the phenomenon of IRI in myocardial function and does not address the cellular mechanisms. Future investigations should extend our observations to include the relationship between patients with and without IRI immediately post PCI and their long-term outcomes.

Clinical perspectives: What is next? Ischemia reperfusion injury (IRI) can be detected by strain measurements using multi-layer speckle tracking echocardiography and is seen in half of patients immediately after successful PCI for STEMI. Does recognition of early IRI influence long-term outcomes? Does the appearance of early IRI parallel a delayed resolution of ST elevation?

What is new? Detection of IRI immediately after successful PCI for STEMI has not been previously described. The subsequent clinical course over the following 24 hours was not known.

What is known? The phenomenon of myocardial IRI has been recognized in experimental animals and man for decades and is thought to contribute significantly to the extent of myocardial injury that follows prolonged ischemia and reperfusion.

Sources of Funding

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**Conflict of interest:** None declared.

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Figure legends:

Figure 1. Title: Bull's eye display of the changes in peak longitudinal strain.

Legend: Imaging before PCI (A) in a patient with an acute inferior wall myocardial infarction showed reduced peak longitudinal strain in the inferior wall. Immediately after PCI (B) there was a further reduction of strain indicating reperfusion injury. Further improvement in strain occurred at 24 hours (C). Panel B illustrates the value of peak longitudinal strain to identify reperfusion injury.

Figure 2. Title: Longitudinal endo-myocardial strain in all patients with ST-elevation myocardial infarction.

Legend: Imaging prior to PCI showed reduced strain which declined further in patients with reperfusion injury. At 3 hours post PCI the strain began to improve in patients with ischemia reperfusion injury. Further improvement was evident at 24 hours. Patients without reperfusion injury showed continuous improvement of strain after PCI. After = immediately after PCI, base = just prior to PCI.
Figure 3. Title: Incidence of ischemia reperfusion injury as related to total ischemia time.

Legend: Reperfusion injury increased markedly as total ischemia time increased.
Table 1. Baseline clinical and echocardiographic characteristics of patients with and without ischemia-reperfusion injury.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reperfusion injury</th>
<th>No reperfusion injury</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>61±12</td>
<td>61±12</td>
<td>0.94</td>
</tr>
<tr>
<td>Male, (%)</td>
<td>29 (88)</td>
<td>12 (80)</td>
<td>0.05</td>
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<tr>
<td>Heart rate, beat/minute</td>
<td>77±19</td>
<td>79±15</td>
<td>0.54</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>130±21</td>
<td>24±20</td>
<td>0.17</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>78±13</td>
<td>75±13</td>
<td>0.33</td>
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<tr>
<td>Symptom to balloon time, min</td>
<td>479±304</td>
<td>59±146</td>
<td>&lt;0.0001</td>
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<tr>
<td>Relative wall thickness</td>
<td>0.46±0.09</td>
<td>0.45±0.07</td>
<td>0.45</td>
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<tr>
<td>CK-MB, IU/L</td>
<td>55±115</td>
<td>38±32</td>
<td>0.38</td>
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<tr>
<td>Myoglobin, ng/ml</td>
<td>287±187</td>
<td>296±174</td>
<td>0.83</td>
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<tr>
<td>TNI, ng/ml</td>
<td>13±11</td>
<td>11±10</td>
<td>0.36</td>
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<td>BNP, pg/ml</td>
<td>270±425</td>
<td>259±146</td>
<td>0.57</td>
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<tr>
<td><strong>Echocardiographic data</strong></td>
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<tr>
<td>LV diastole dimension, mm</td>
<td>46±5</td>
<td>44±7</td>
<td>0.03</td>
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<td>LV mass index, gm/m²</td>
<td>99±26</td>
<td>92±23</td>
<td>0.16</td>
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<tr>
<td>LV end-diastole volume, ml</td>
<td>84±22</td>
<td>78±18</td>
<td>0.16</td>
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<tr>
<td>LV end-systole volume, ml</td>
<td>39±16</td>
<td>34±11</td>
<td>0.03</td>
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<td>LV ejection fraction, %</td>
<td>55±9</td>
<td>57±7</td>
<td>0.20</td>
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<td>Left atrium volume index, ml/m²</td>
<td>27±7</td>
<td>23±6</td>
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<tr>
<td>Pulmonary vein atrial reversal velocity, cm/s</td>
<td>34±8</td>
<td>31±6</td>
<td>0.03</td>
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</tbody>
</table>
Table 2. Strain (%) at different time points with acute myocardial infarction and reperfusion.

<table>
<thead>
<tr>
<th>Ischemic region</th>
<th>Reperfusion injury</th>
<th>Strain measurements</th>
<th>Strain measurements</th>
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<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>LAD</td>
<td>n = 29</td>
<td>n = 18</td>
<td>n = 29</td>
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<tr>
<td>LCX</td>
<td>n = 11</td>
<td>n = 8</td>
<td>n = 11</td>
<td>n = 8</td>
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<td></td>
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<tr>
<td>RCA</td>
<td>n = 19</td>
<td>n = 23</td>
<td>n = 19</td>
<td>n = 23</td>
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*=baseline vs after PCI, Δ=baseline vs 24 hrs post; p<0.05. LAD = left anterior descending artery territory, LCX = left circumflex artery territory, RCA = right coronary artery territory.