Postsystolic shortening is a strong predictor of recovery of systolic function in patients with non-ST-elevation myocardial infarction

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Aims Differentiation between necrotic and viable myocardium is difficult in the setting of acute myocardial infarction (MI). Post-systolic shortening (PSS) has been proposed as a marker of recovery after revascularization, but has not previously been assessed in patients with NSTEMI prior to revascularization. In this study, we aimed to examine the relation between PSS and improvement of contractile function after successful revascularization.

Methods and results Thirty-five patients with non-segment elevation MI and regional systolic dysfunction were examined immediately prior to revascularization, and at follow-up 9 ± 3 months after successful revascularization. Regional systolic function was assessed by speckle tracking echocardiography as regional strain, expressed as mean peak negative longitudinal strain in segments supplied by the culprit artery. Recovery of systolic function was assessed as the difference between regional strain at follow-up and baseline (ΔStrain). Post-systolic shortening was defined as shortening in diastole beyond minimum systolic length. By multivariate regression analysis, several other variables that may affect viability were also assessed. Post-systolic shortening was observed in 32 patients (91%), mean 2 1.9 ± 1.4%. Mean ΔStrain was −3.3 ± 2.9%. After adjustment for baseline systolic function, PSS (β = 0.77, P = 0.022), and angiographic severity were independent predictors of viability by multiple regression analysis. Interestingly, troponin T was not a significant predictor.

Conclusions Post-systolic shortening is associated with improved myocardial function after revascularization in patients with acute MI. It predicts long-term systolic function, and provides information on the potential benefit of the procedure.

Keywords Myocardial infarction • Echocardiography • Viability

Background

Acute myocardial infarction (MI) is often accompanied by impaired regional myocardial systolic function. Patients with non-ST-segment elevation myocardial infarction (NSTEMI) are recommended to undergo coronary angiography within 72 h after onset of chest pain.1 Within this timeframe, an observed impairment may be caused by several factors; ongoing ischaemia, stunning/hibernation, or irreversible necrosis. These factors often coincide, but the individual level of contribution may vary. In the early phase, viable and necrotic myocardium appears identical, and is characterized by impaired systolic function. Viable myocardium is likely to recover systolic function after revascularization, whereas necrotic myocardium is not. However, clinically it is often difficult to predict the impact of revascularization in terms of recovery of regional systolic function. Long-term systolic function is an important prognostic marker after MI. Information on recovery, and thereby prediction of long-term systolic function, may aid identification of patients at high risk of adverse events including heart failure.

Post-systolic shortening (PSS) is observed in both acute and chronic ischaemia, to a lesser degree also in normal myocardium,2 and has been proposed as a marker of recovery.3 It has been shown to predict recovery of systolic function in patients with...
ST segment elevation MI. Strain echocardiography is an accurate and validated measure of regional systolic left ventricular (LV) function. It is measured on a continuous linear scale, and is well suited for quantification of PSS as well as temporal changes in regional systolic function. The association between PSS assessed prior to revascularization and recovery of systolic function has not previously been investigated in patients with acute MI. If such an association exists, PSS may serve as a marker to predict the impact of the procedure in terms of recovery of systolic function. An estimate of recovery may also give information on long-term systolic function and probability of developing heart failure. The aim of this study was therefore to test whether PSS assessed prior to revascularization may predict recovery of systolic function after successful revascularization in NSTEMI patients with impaired regional myocardial systolic function at baseline.

Methods

Patients

This study was conducted prospectively in a single tertiary coronary care centre. Consecutive patients referred for coronary angiography with documented NSTEMI, defined according to current guidelines as ischaemic symptoms and elevated troponin levels, within 72 h were screened for enrolment. In this analysis, patients with one vessel clearly identified as culprit, with a significant stenosis (≥50% reduction in lumen diameter) on angiography who underwent successful complete revascularization by angioplasty or surgery and who at baseline had impaired systolic function in the region of the myocardium supplied by the culprit vessel were included. Patients with previous MI were excluded.

Echocardiography

Echocardiographic examinations were performed with a Vivid 7 scanner (GE Vingmed, Horten, Norway), using a phased array transducer. The mean frame rate was 69 ± 12 frames/s. The patients were examined immediately prior to coronary angiography, and at a follow-up visit scheduled 9 months later. Three consecutive cycles in three apical planes (four-chamber, two-chamber, and long axis) were obtained by conventional two-dimensional grayscale echocardiography, using second harmonic imaging. Loops were digitally stored and later analysed off-line using Echo-Pac version 7.0.0. (GE Vingmed). Left ventricular volumes were calculated by the modified Simpson rule, and the left ventricular ejection fraction (LVEF) was calculated. All examinations were performed by one operator. All analysis were performed off-line, and blinded to patient identity and other data.

Strain and post-systolic shortening analyses

Longitudinal strain was measured by speckle tracking echocardiography, in a 16 segments LV model. Segmental myocardial systolic function was assessed as peak negative systolic strain, which represents maximum systolic longitudinal shortening. As demonstrated in Figure 1, PSS was defined as the segmental shortening in diastole beyond minimum systolic segment length, as percentage of end-diastolic segment length; i.e. peak negative strain in diastole minus peak negative strain in systole. If minimum segment length was within systole, PSS was set to zero. Hence, PSS can only take negative values. Duration of systole was defined as apical long-axis view as the time from peak R in the ECG to the first frame where the aortic valve was closed. Based on a standardized model of myocardial perfusion territories, regional strain and PSS were calculated as the average values of segments belonging to each perfusion territory in the left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA), respectively. Values from the perfusion territory in which the culprit vessel was located, the ‘culprit territory’, were then used for further analyses.

Assessment of recovery

Recovery of systolic function after revascularization is only meaningful to discuss in patients with impaired systolic function prior to revascularization. As many NSTEMI patients have small infarctions and normal or near normal systolic function at baseline, we included only patients with at least one segment within the culprit territory with hypo- or akinesia (by visual assessment). Recovery of systolic function was calculated as ΔStrain, the difference between strain values in the culprit territory at follow-up and at baseline (Strain\text{follow-up} − Strain\text{baseline}). Negative values indicate improved function.

Coronary angiography and revascularization

Coronary angiography was performed by standard (judkins) technique, using digital image acquisition and storage. All analyses were performed off-line by a single experienced invasive cardiologist, blinded to the results of the other imaging studies. In patients with single vessel disease, the diseased vessel was identified as culprit. In multi vessel disease, the culprit vessel was identified by a combination of angiographic and electrocardiographic criteria. Culprit vessel patency was assessed as a dichotomous variable; (patent = 0, occluded = 1) by visual assessment of coronary flow. Percutaneous coronary intervention (PCI) was performed at the discretion of the operator. Patients with three vessel disease, left main stenosis or coronary lesions not amenable to PCI were typically referred for surgical revascularization. Successful complete revascularization was defined as either post-procedural TIMI 3 flow in all epicardial vessels, or bypass surgery.

Statistical analyses

Variables are presented as mean ± SD. Changes from baseline to follow-up were analysed with paired samples Student’s t-test. Linear regression analysis was used to identify predictors of recovery. We defined recovery as the absolute improvement from baseline (ΔStrain). With this definition, the level of impairment at baseline is an important confounder. This implies that patients with a large
impairment at baseline have a larger potential of recovery compared with patients with only minimal impairment. All analysis was therefore performed after adjustment for baseline systolic function, by entering baseline systolic function as a fixed covariate in the regression analyses.

In addition to PSS, we considered time to PCI, mode of revascularization (surgical or percutaneous), levels of troponin T (TnT), changes in loading parameters, single vs. multi vessel disease and patency of the culprit lesion as potential predictors of changes in systolic function after revascularization. Parameters that, after adjustment for baseline systolic function, were significant predictors of ΔStrain with a P-value < 0.1 were then entered into a multiple regression model. All statistical analyses were performed on SPSS v. 13 (SPSS, Inc., Chicago, IL, USA).

Results

Patients

One hundred and twenty-four consecutive patients with NSTEMI were examined by echocardiography prior to coronary angiography. Identification of one culprit vessel was possible in 105 (85%) patients, of whom, 88 (84%) underwent successful complete revascularization. Of these, impaired regional systolic function was found in 16 patients (46%). Multi vessel disease was found in 26 patients (74%). Percutaneous coronary intervention was performed in 25 patients (71%) median 2 (range 1–3) days after hospital admission, whereas 10 patients (29%) underwent bypass surgery median 8 (range 3–53) days after hospitalization, (P < 0.001 vs. PCI patients). The mean number of diseased vessel in PCI patients was 1.7 ± 0.7 vs. 2.7 ± 0.5 in patients who underwent surgery (P = 0.001). TIMI 3 flow in all epicardial vessels was achieved in all PCI patients. All surgically treated patients received a left mammaria graft, and the mean number of distal anastomoses was 3.6 ± 1.1. Between revascularization and follow-up, one patient developed reinfection with minimal enzyme release (TnT 180 ng/L). A new PCI was performed in the same vessel as was initially treated.

Table 1  Patient characteristics, risk factors, and baseline medical treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 35</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>56.3 ± 9.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 ± 3.4</td>
</tr>
<tr>
<td>Risk factors (%)</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>30 (86)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (9)</td>
</tr>
<tr>
<td>History of CAD</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TnT ng/L (mean ± SD)</td>
<td>1550 ± 1149</td>
</tr>
<tr>
<td>Medication (%)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>35 (100)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>35 (100)</td>
</tr>
<tr>
<td>LMWH</td>
<td>35 (100)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>27 (77)</td>
</tr>
<tr>
<td>Statin</td>
<td>32 (91)</td>
</tr>
<tr>
<td>ACE-inhibitor or ARB</td>
<td>7 (20)</td>
</tr>
</tbody>
</table>

Data, including medication, are recorded at tertiary care centre, and presented as mean ± SD or n (%); BMI, body mass index; CAD, coronary artery disease; TnT, troponin T; LMWH, low-molecular weight heparin; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GpIIbIIa, glycoprotein IIb/IIIa.

Angiographic findings and revascularization

The distribution of culprit vessel was: LAD, n = 10 (29%), LCx: n = 9 (26%); RCA, n = 16 (46%). An occluded culprit lesion was found in 16 patients (46%). Multi vessel disease was found in 26 patients (74%). Percutaneous coronary intervention was performed in 25 patients (71%) median 2 (range 1–3) days after hospital admission, whereas 10 patients (29%) underwent bypass surgery median 8 (range 3–53) days after hospitalization, (P < 0.001 vs. PCI patients). The mean number of diseased vessel in PCI patients was 1.7 ± 0.7 vs. 2.7 ± 0.5 in patients who underwent surgery (P = 0.001). TIMI 3 flow in all epicardial vessels was achieved in all PCI patients. All surgically treated patients received a left mammaria graft, and the mean number of distal anastomoses was 3.6 ± 1.1. Between revascularization and follow-up, one patient developed reinfection with minimal enzyme release (TnT 180 ng/L). A new PCI was performed in the same vessel as was initially treated.

Haemodynamic parameters and left ventricular ejection fraction

Between baseline and follow-up, we observed no change in systolic blood pressure (144 ± 26 vs. 141 ± 20 mmHg, P = 0.56), no change in end-diastolic volume (117 ± 27 vs. 116 ± 26 mL, P = 0.92), and no change in the heart rate (64 ± 9 min⁻¹ vs. 62 ± 9 min⁻¹, P = 0.38). The left ventricular ejection fraction increased from 51 ± 7 to 60 ± 10% (P < 0.001).

Regional myocardial systolic function, viability, and post-systolic shortening

A significant correlation between baseline systolic function and ΔStrain was found (r = 0.58, P < 0.001), confirming the confounding effect, and the necessity to adjust for systolic function at baseline in further analyses. At baseline, strain values in culprit territories were impaired compared with non-culprit territories, (regional systolic strain = −12.3 ± 3.2% vs. −16.1 ± 2.5%, P < 0.001). This difference was smaller but still significant at follow-up (−15.6 ± 2.8% vs. −16.8 ± 2.6%, P = 0.01). Patients with at least one akinetic segment within the culprit territory (n = 21, 60%) demonstrated more PSS (−2.2 ± 1.6 vs. −1.3 ± 1.1%, P = 0.05), and further impaired systolic function (systolic strain −11.6 ± 3.1 vs. −13.6 ± 3.0%, P = 0.06), compared with patients with merely hypokinetic segments. Systolic function improved in 30 patients (86%). Mean ΔStrain was −3.3 ± 2.9%. Mean ΔStrain from baseline to follow-up was larger in culprit territory compared with non-culprit territories (−3.3 ± 2.9 vs. −0.7 ± 2.3%, P < 0.001). Strain values in remote myocardium remained unchanged (−16.1 ± 2.5 vs. −16.8 ± 2.6%, P = 0.10). All segments within the individual culprit territories had negative strain values, indicating that dyskinetic segments were not present in our population. Post-systolic shortening was observed in culprit territory of 32 patients (91%); with a range from −0.2 to −5.1%. Mean PSS was −1.9 ± 1.4% at baseline, and −1.0 ± 0.8% at follow-up (P < 0.001), with unchanged prevalence. Changes in PSS also correlated to ΔStrain (r = −0.61, P < 0.001, Figure 2. All measures of PSS and systolic function
were virtually identical in patients with single vs. multi vessel disease, both in culprit area and in remote myocardium. At baseline, PSS was significantly correlated to regional systolic strain. \( r = 0.60, P < 0.001 \). Thus, more severely impaired baseline function is associated with increased levels of PSS.

**Independent predictors of recovery of systolic function**

The main findings in this study are demonstrated in Tables 2 and 3. Post-systolic shortening and patency of the culprit vessel were both predictors of \( \Delta \text{Strain} \) in univariate analyses (Table 2), after adjustment for baseline function. In multivariate analyses, PSS and culprit vessel patency both remained significant independent predictors of \( \Delta \text{Strain} \) (Table 3), PSS being the strongest predictor (standardized \( \beta = 0.38, P = 0.02 \)). The unadjusted \( \beta \) of PSS is 0.77. This implies that a 1% increase in PSS on average is associated with a 0.77% increase in \( \Delta \text{Strain} \). Adjusted \( R^2 \) for the entire model was 0.48. Typical strain curves from a patient with substantial PSS at baseline and complete recovery of systolic function at follow-up are demonstrated in Figure 3. Changes in the LV volumes or the heart rate were not found to be confounders. We also examined changes in use of medications as possible confounders, and did not find such effects.

**Discussion**

Our study demonstrates that in NSTEMI patients with impaired regional systolic function, PSS can predict recovery of systolic function after revascularization. This finding has two major implications. Importantly, it confirms the finding in previous studies that PSS is associated with recovery of systolic function and as such, viable myocardium. Furthermore, this association is extended to a population where assessment of potential for recovery is crucial, namely patients with acute MI and high-grade coronary artery stenosis or persistent occlusions assessed before revascularization. Differentiation between viable and necrotic myocardium is clinically valuable. Unfortunately, information about potential recovery is not often available in this clinical setting. Assessment of PSS by strain echocardiography is non-invasive, easily obtained and may provide useful information.

To our knowledge, PSS has not previously been studied in patients with acute MI prior to revascularization. Previous clinical studies have been on either chronic MI or on STEMI patients after reperfusion. As demonstrated in this study, there are large variations in the ability to recover contractile function after revascularization. Prediction of recovery of systolic function provides an estimate of long-term systolic function and thereby probability of developing heart failure and later adverse events. In addition, such prediction performed before the procedure may prove useful; as it indicates potential benefit from the intervention.

**Methodology**

Our study is strengthened by the use of speckle tracking strain for assessment of PSS and systolic function. Compared with Doppler
strain, this modality is angle independent and less susceptible to signal noise. Importantly, strain echocardiography enables quantification of myocardial systolic function and PSS on a linear scale, and not as dichotomous phenomena which may lead to loss of information. As both variables are linear, cut-off values to predict recovery was not used, but a predicted recovery can be assessed using β-values from the regression analysis. Another strength of our study is the inclusion of and comparison to other variables that may affect changes in systolic function. Interestingly, PSS remains the strongest predictor of such changes, even after adjustment for other factors including patency of the infarct-related artery and levels of TnT. In this study, recovery of systolic function was the primary endpoint. As such, it serves as a marker of viable myocardium. Previously, several definitions of viability have been used. Still, the crude ability to recover systolic function is important, as it relates to long-term systolic function and thereby risk of adverse events.

Since no change was observed in the systolic blood pressure, heart rate or end-diastolic volume, the improved systolic function is not likely to have been caused by remodelling or altered loading conditions. Significant changes in systolic function were also observed only within the culprit territory, whereas function in remote myocardium remained unchanged. One very interesting finding in our study is that levels of TnT, which are related to the amount of myocardial necrosis, were not associated with reduced viability. This indicates that even patients with a large amount of necrosis may benefit from revascularization, even when this is performed several days after hospital admission.

**Figure 3** Example of strain curves from the apical long-axis view, from a patient with an occluded LCx at baseline. Substantial post-systolic shortening is observed in the basal- and mid-inferolateral segments (yellow and cyan traces. After successful revascularization, normal systolic function is observed in the same segments at follow-up.

**Previous studies**

Post-systolic shortening and its relation to ischaemia and recovery has previously been studied in both experimental and clinical settings. Post-systolic shortening is related to the degree of flow reduction, and correlates inversely to parameters of systolic function in the ischaemic area. The latter is in keeping with our findings. Post-systolic shortening is also observed, albeit less frequently and with a smaller amplitude, in normal myocardium. In the acute ischaemic setting, Brown et al. found a close correlation between PSS and recovery of systolic function after reperfusion in an experimental study on animals. These findings were confirmed clinically by Hosokawa et al., who demonstrated that in patients with reperfused anterior MI, PSS is a marker of recovery. In chronic ischaemic heart disease, PSS is shown to predict viability by PET or stress echocardiography. These findings have been questioned by others, who state that PSS is a non-specific phenomenon related to ischaemia and impaired systolic function.

In a recent study by Mollema et al., speckle tracking strain was found to highly useful for the combined assessment of final infarct and viability in patients with recent MI. Hanekom et al. used strain echocardiography to predict recovery after revascularization in patients with MI. They found little predictive power of parameters obtained at rest, but low-dose dobutamine strain and the strain rate were predictors of recovery. In our study, rest parameters have good predictive power. This seeming discrepancy may be due to several factors. Perhaps most important, we studied patients 1–3 days after MI, while Hanekom et al., studied...
patients >6 weeks after MI. This may indicate that PSS should be interpreted differently in the acute and chronic phases. Interestingly, while they found no difference in PSS in segments that did and those that did not recover at rest, a four-fold larger PSS at low-dose dobutamine was observed in segments that recovered, compared with those that did not.

Baseline function as a confounder
As expected, we found recovery to be associated with the level of impairment at baseline, and therefore performed regression analyses after adjustment for baseline function. Failure to make this adjustment may erroneously identify factors to be predictors of recovery, simply through being associated with the level of baseline impairment. Indeed, PSS is associated with the level of impairment at baseline. However, PSS remains significant after adjustment for baseline function, confirming it to be an independent predictor of recovery. Clinically, our findings indicate that increased recovery after revascularization can be expected in patients with large amounts of PSS compared with patients with smaller amounts, given the same level of impairment at baseline. Similarly, increased recovery can be expected in patients with a patent IRA, compared with a patient with persistent occlusion. In our study, the predictive power of PSS was slightly stronger compared with vessel patency.

Mechanisms of post-systolic shortening
Whether PSS represents actively contracting myocardium or a passive elastic phenomenon has been debated. In a comprehensive experimental study, Skulstad et al., demonstrated that in akinetic or hypokinetic myocardium, PSS represents active contraction, and therefore, potentially, viable myocardium. In dyskinetic myocardial segments, PSS was found to be a non-specific marker of severe ischaemia. These findings may imply that PSS should be interpreted differently based on residual myocardial systolic function. In our study, all segments within the culprit territory demonstrated systolic contraction, expressed by negative systolic strain values. Our findings thus support the experimental data, and confirm the association between PSS and viability in myocardium with residual contractile function.

Limitations
We studied a limited number of patients, who are not representative of the entire NSTEMI population. While described in detail, the selection of patients remains a limitation. Importantly, only patients with certain impaired systolic function at baseline were studied. This is reflected in the high prevalence of severe angiographic findings. This selection was necessary since patients with impaired systolic function are the only ones with potential for significant improvement, and in whom the question of recovery of systolic function is even relevant. The clinical condition these patients represent, however, is not rare. Even though several factors that may affect recovery were assessed, unmeasured confounders may have influenced our results. The definition of successful revascularization is common and pragmatic, but does not account for differences in revascularization on the micro vascular level, or events occurring during surgery. Vessel patency on follow-up is also unknown. Use of a standardized model for myocardial perfusion territories may be inaccurate, as vessel anatomy is variable. In addition, all patients in our study underwent successful complete revascularization, which is not always the case in a clinical setting.

Conclusion
Post-systolic shortening assessed prior to revascularization is a strong independent predictor of recovery of systolic function in patients who undergo successful revascularization after NSTEMI. Strain echocardiography is well suited for assessment of PSS. It is widely available, rapidly obtainable and non-invasive. By providing an estimate of recovery, it also provides an estimate of long-term systolic function. In patients in whom there is doubt concerning the potential effect of revascularization, assessment of PSS may prove useful to predict the potential benefit from the procedure in terms of LV systolic function, and also by predicting recovery give clue on long-term systolic function.

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References


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**IMAGE FOCUS**

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An incidentally found unusual quadricuspid pulmonary valve with transthoracic echocardiography

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A 76-year-old female was admitted to the hospital with progressive dyspnoea. There was marked cardiomegaly and diffuse pulmonary oedema on chest X-ray and pitting oedema. On admission, transthoracic echocardiography revealed large amount of pericardial effusion with haemodynamic compromise (early diastolic right ventricular collapse, early systolic right atrial inversion, respiratory variation of mitral E wave, and plethora of inferior vena cava) and moderate pulmonary regurgitation (Figure 1B) with dilated main pulmonary artery (Figure 1A). Additionally, echocardiography revealed an unusual quadricuspid pulmonary valve in the parasternal long-axis view (Figure 1C–F). The pulmonary valve has unusual four even-sized cusps, with poor coaptation and pulmonary regurgitation. Pericardial fluid cytology revealed malignant lymphoma, diffuse large B cell type.

Quadricuspid pulmonary valve is a rare congenital anomaly and occasionally combined with pulmonary regurgitation. Diagnosis of a quadricuspid pulmonary valve by transthoracic two-dimensional echocardiography is very difficult due to the anatomical disposition of the valve. Because of its rare association with significant clinical complications or symptoms, quadricuspid pulmonary valve has been diagnosed almost exclusively after death.