Remote Ischemic Conditioning in Myocardial Infarct Patients Treated with Primary Angioplasty: Impact on Left Ventricular Function Assessed by Comprehensive Echocardiography and Gated SPECT

Running Title: Munk et al: Remote Conditioning of the Heart in STEMI

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Abstract

Background—We have found that remote ischemic conditioning (rIC), adjunctive to primary angioplasty, increases myocardial salvage in ST-elevation myocardial infarction (STEMI) patients with extensive myocardial area at risk (AAR). The present substudy aimed to evaluate the short term effects of rIC on LV function.

Methods and Results—Patients with a first STEMI were randomized to rIC (four cycles of five minutes upper limb ischemia) during transfer to primary PCI (pPCI) (n=123) vs. pPCI alone (n=119). Ejection Fraction (EF), LV volumes, (2D- and 3D echocardiography, and MPI), and speckle tracking global longitudinal strain (GLS) were compared between treatment groups. There was no significant difference in LV function at day one (EF-2D 0.51±0.10 vs. 0.49±0.10, p=0.22) and after 30 days (EF-2D 0.54±0.08 vs. 0.53±0.10) between the rIC and the pPCI alone group. In patients with extensive AAR (>35 % of LV, n=53), EF after 30 days was higher after rIC than after pPCI alone (EF-2D: 0.51±0.07 vs. 0.46±0.09, p=0.05. In patients with anterior infarction, n=97, rIC preserved LV function on day one (EF-2D: 0.51±0.11 vs. 0.46±0.11, p=0.03) and persistently after 30 days (EF-2D:0.55±0.08 vs. 0.50±0.11, p=0.04; EF-MPI: 0.55±0.10 vs. 0.49±0.12, p=0.02) These patient had similar AAR, while rIC reduced infarct size from 16 % to 7 % of LV, p=0.01

Conclusions—Although no significant overall effect was observed, remote ischemic conditioning seemed to result in modest improvement in LV function in high risk patients prone to develop large myocardial infarcts. These results need to be confirmed in larger trials.


Key Words: scintigraphy; reperfusion injury; strain; 2D speckle tracking
Introduction

In ST-segment elevation myocardial infarction (STEMI), extensive necrosis and poor left ventricular (LV) function predicts an impaired prognosis\(^1,2\). To salvage myocardium at risk the cornerstone of therapy is promptly to restore culprit vessel flow preferably by primary percutaneous coronary intervention (pPCI)\(^3\). However, abrupt restoration of blood flow may itself cause detrimental myocardial reperfusion injury, which possibly explains that a substantial number of patients with STEMI end up with low salvage, compromised LV function, and heart failure\(^4\).

Local- and remote ischemic conditioning are potent activators of innate protection against ischemia-reperfusion injury. The underlying mechanisms behind these cardioprotective strategies are not fully clarified. Common pathways involve modification of mitochondrial function by opening ATP-sensitive potassium channels and closing mitochondrial permeability transition pores\(^5\). Recently, we demonstrated that remote ischemic conditioning (rIC) by repeated cycles of non-lethal upper limb ischemia applied during ambulance transfer in patients with evolving STEMI increased myocardial salvage\(^6\). The benefit was most pronounced in patients with extensive myocardium at risk. It is of major clinical importance to assess the effects of rIC on the function of the left ventricle. Usually, conventional 2D, and 3D echocardiographic imaging are used. Yet, recent data have reported that global strain in the long axis plane assessed by speckle tracking deformation imaging may be superior to conventional echocardiography in estimating LV function and infarct size\(^7-10\). Conventional and speckle tracking derived indices are retrieved from the same echocardiographic datasets and are not independent. Therefore, as a supplementary independent method, LV function was assessed by myocardial perfusion imaging (MPI) in addition to echocardiography.
Thus, the aim of the present substudy was to evaluate the effect of rIC on LV function and remodelling by comprehensive echocardiography and myocardial perfusion imaging (MPI) within 24 hours after pPCI, and after 30 days follow up. The effect of rIC was analyzed in relation to the size of the myocardial area at risk (AAR), infarct location, and target vessel patency.
Methods

Study population

The remote ischemic conditioning in STEMI trial (Clinicaltrials.gov, NCT00435266) was a single-centre randomized controlled trial that compared prehospital treatment with cycles of upper limb ischemia as adjunctive to pPCI with standard pPCI in patients with acute STEMI. Patient inclusion, randomization, and intervention have been outlined in details 6. In brief, patients were included from February 2007 until October 2008. Criteria for inclusion were: 1) symptoms consistent with myocardial infarction lasting between 30 minutes and 12 hours; 2) S-T segment elevation of more than 0.1 mV in two or more contiguous leads, and 3) age over 18 years. Patients were excluded from analysis on the following criteria: 1) previous coronary bypass surgery; 2) left bundle branch block; 3) treatment with fibrinolysis within previous 30 days; 4) left main stenosis requiring coronary bypass surgery; 5) cardiogenic shock, and 6) previous myocardial infarction. During ambulance transfer, patients with a tentative diagnosis of STEMI were randomized to primary percutaneous coronary revascularization (pPCI alone; control group), or primary percutaneous coronary revascularization plus remote conditioning (rIC+pPCI; intervention group) through intermittent arm ischemia. Arm ischemia was obtained by four cycles of alternating 5-min inflation and 5-min deflation of a upper-arm blood-pressure cuff to 200 mm Hg or 25 mm Hg above systolic blood pressure in case this was >175 mm Hg. Before coronary intervention patients received treatment with aspirin 300 mg, clopidogrel 600 mg, and unfractionated heparin 10.000 IU. Abciximab was given when not contraindicated.

The study protocol complies with the Declaration of Helsinki, and was approved by the local ethics committee. All participants gave informed consent.
Echocardiography

We used a commercially available ultrasound system (Vivid seven, GE Healthcare Horten, Norway) with a 3.5 MHz phased array transducer (M4S). The first echocardiography was performed at median 13 [8; 18] hours after primary PCI. The observer was blinded to the treatment allocation. Patients were re-examined after 30 days. Examinations were made by two observers (K.M, N.H.A). Data were stored digitally and analyzed offline by a single investigator (K.M), blinded to clinical data, using dedicated software (Echopach PC SW-Only, 7.0.0, GE Healthcare, Milwaukee, Wisconsin, USA. including Tomtec 4D LV-Function, Unterschleissheim, Germany). Two dimensional EF measurements were based on end-systolic/diastolic LV volumes, using the biplane method of discs. Volume data are averages of three measurements.

Systolic strain was obtained from frame-by-frame tracking of speckle patterns throughout the left sided myocardium in standard 2D cine-loops, with frame rates between 50-90 1/s. Timing of systole was determined from aortic valve opening/closure. The speckle area of interest was manually adjusted for optimal tracking results. Segments with unacceptably low tracking quality, due to poor image acquisition or artifacts, were excluded. Global longitudinal systolic strain (GLS) was calculated by the software as the average longitudinal systolic strain of 17 myocardial segments at the time in systole when the value peaked. The software allowed calculation of GLS only when tracking quality was adequate in at least 5 of 6 segments in each apical view.

Full volume three dimensional datasets were obtained using a 3.5 MHz matrix array transducer (3V). Optimal transducer position and angle was adjusted using the three-plane imaging mode. When, in the respiratory cycle, optimal endocardium delineation was achieved, a full volume ECG-gated dataset through four cardiac cycles was sampled during
apnea. Using the software package (Tomtec 4D LV-Function, Unterschleissheim, Germany) end-diastolic and end-systolic endocardial tracings were drawn manually in the three apical standard image planes. The software then tracked the surface in each frame throughout the cardiac cycle. The surface delineation was adjusted manually as needed. Left ventricular ejection fraction was calculated from end-diastolic and end-systolic estimates of these virtual LV-cavity casts.

Intra-observer variability was assessed from readings on 25 randomly selected patients. The intra observer repeatability analysis showed mean differences of 0.3 per cent points, 95 % CI (-0.2; 0.7) for Global longitudinal systolic strain; -2 per cent points, 95 % CI (-4; 1) for Simpson’s 2D EF; and -2 per cent points for, 95 % CI (-3; -1), 3D EF. Coefficients of repeatability (1.96 SD on differences) on a relative scale were 11 %, 95 % CI (8; 15) for Global longitudinal strain, 23 %, 95 % CI (18; 32) for 2D-EF, and 9 %, 95 % CI (7; 13) per cent for 3D-EF.

Single photon emission computed tomography (99mTc-sestamibi-SPECT)

In the main study, salvage index (the proportion of area at risk salvaged by treatment) was the primary endpoint. Prior to pPCI, 99mTc-sestamibi was injected, and myocardial area at risk (AAR) was measured by MPI within 8 hours after pPCI. At the 30-day follow up visit patients received 700±10% MBq 99mTc-sestamibi intravenously after 15 min. bed rest. SPECT was performed after one hour using a high-resolution, parallel-hole collimator dual-headed rotating gamma camera (ADAC, Forte, Milpitas, CA, USA) with no scatter or attenuation correction. Images were gated at 8 frames per cardiac cycle. Accumulated radiation dose of the two MPI examinations were ≈12 mSv, equalling 120 chest x-rays. This corresponds to an estimated 0.1 absolute % increase in lifetime risk of dying from a malignancy added to the background risk equalling 21 %.
Data were analysed independently by two experienced nuclear cardiology readers. Images were analysed with the commercially available automatic quantitative perfusion SPECT and quantitative gated SPECT program (QPS and QGS) (Cedars-Sinai Medical Center). In case of failure of the automatic algorithm, tools for masking extra cardiac activity and/or defining the valve plane and the apex of the left ventricle manually were used. Infarct size was calculated as the area of the left ventricle containing counts lower than a mean normal limit for pixels using a sex specific MIBI MIBI rest database as reference. If the inter-reader difference in defect size exceeded 3 %, a consensus reading was obtained from the two readers. Volumes of left ventricular cavities at end systole and end-diastole were assessed as described.

Statistics
The sample size was given by the main study. However, in planning this echocardiographic study we made considerations whether GLS could be achieved in an adequate number to reach acceptable statistical power. An absolute difference in GLS of 2 per cent (~absolute difference in EF of 0.05) between treatment groups was regarded as a clinical relevant improvement. Based on a mean GLS: -14.6±4.6 per cent in STEMI patients, with a risk of type 1 error (α=0.05) we estimated that a power (1- β) of 0.80 requires 85, and a power of 0.90 requires 110 participants in each group.

Continuous data conforming to a normal distribution are presented as mean ± standard deviation (SD), non-normal continuous data are presented as median including first (Q1) and third (Q3) quartiles, and categorical data are presented as absolute values with percentages. Histograms and Q-Q-plots were used to check continuous values for normality. Comparison of continuous variables between treatment groups was done by unpaired t test and by Mann-Whitney U test in variables that were not normally distributed. Categorical data were
compared using chi^2 test or Fisher’s exact test when tabled numbers were below ten. Reproducibility and agreement between echocardiographic and SPECT volume data were compared by the Bland-Altman method \(^{20}\). We used a standard statistical software package (STATA/IC 10.1, StataCorp LP, Texas, College Station, USA).
Results

Study population and patient characteristics

Details on randomization, reason for exclusion after pre-hospital randomization, and completeness of data are outlined in Figure 1. Of 333 patients enrolled during transfer to pPCI, 166 were assigned to rIC+pPCI and 167 to pPCI alone. Eighty two (40 rIC+pPCI; 42 pPCI alone) were excluded from analysis since they did not fulfill the study criteria. Nine patients (three rIC+pPCI; six pPCI alone) did neither have day one or one month echocardiography. Thus, the study population comprises 242 patients (123 rIC+pPCI; 119 pPCI alone) completing the day one and/or the 30 day echocardiography. Baseline characteristics were similar except from hypertension (Table 1).

Total study cohort

Myocardial area at risk were similar in treatment groups (rIC+pPCI: 26±14 % of LV, n=81 vs. pPCI alone: 27±16 % of LV, n=76, p=0.9). Overall, left ventricular function recovered significantly from day one (EF-2D: 0.50±0.10; GLS:-15.3±3.8 %) to one month (EF-2D: 0.53±0.10, p=0.0001; GLS: -16.9±3.4 %, p<0.0001). No significant differences were observed between treatment groups overall (Table 2). After one month, an equal number of patients had a normal EF-2D≥0.50, n=72 (70 %) in the rIC+pPCI vs. n=73 (71 %) in the pPCI alone (p=0.9). However, three (3 %) in the rIC+pPCI group vs. 13 patients (13 %) in the pPCI alone group had an EF-2D ≤ 0.40 (p=0.01). Final infarct size was 4 % of LV (Q1 to Q3 1-14), n=108 vs. 7 % of LV (Q1 to Q3 1-14), n=110, p=0.09, in the intervention and control group, respectively.
Impact of remote conditioning in relation to myocardium at risk (area at risk)

Myocardial area at risk (AAR) assessed by $^{99m}$Tc-sestamibi MPI was available in 157 patients (rIC+pPCI (n=81)/pPCI alone (n=76)). AAR correlated weakly with LV function acutely and on follow up (day one EF-2D: $r^2=0.11$; day one GLS: $r^2=0.32$, day 30 EF-2D: $r^2=0.18$; day 30 GLS: $r^2=0.25$ (p<0.0001 for all). Dependent on the magnitude of the AAR patients were divided into groups by tertiles: AAR≤18 % of LV (rIC+pPCI: AAR 11±6 %, n= 27 vs. pPCI alone: AAR 9±6%, n=27 p=0.15), AAR 19 to 34 % of LV (rIC+pPCI: AAR 26±4 n=26, vs. pPCI alone: AAR 29±4 %, n=24, p=0.02), and AAR≥35 % of LV (rIC+pPCI: AAR 42±5 %, n=28 vs. pPCI alone: AAR 44±6 %, n=25, p=0.17). In those with extensive AAR>35 % of LV, rIC+pPCI patients had higher EF-2D after one month than those treated conventionally (rIC+pPCI: 0.51±0.07, n=23 vs. pPCI alone: 0.46±0.09, n=20 p=0.046). There was significant difference between infarct size in these patients (rIC+pPCI: 15 % of LV, (Q1 to Q3 10-25), n=24 vs. pPCI alone: 24 % of LV (Q1 to Q318-29), n=24, p=0.045. No differences were seen in the low- and mid-tertile groups. In the upper, middle, and lower AAR-tertile, one-month GLS was -15.8±2.6 vs. -13.5±3.2 %, (p=0.01), -17.0±2.8 vs. -19.0±3.7 %, (p=0.06), -18.9±3.0 vs. -19.1±3.0 %, (p=0.87), in the rIC+pPCI and pPCI alone groups, respectively.

Impact of infarct location (LAD vs. non-LAD)

Ninety seven patients (rIC+pPCI: 47; pPCI-alone: 50) had a culprit lesion within the left anterior descendent coronary artery territory (LAD). There was no difference in AAR between treatment groups in patients with culprit in LAD (rIC+pPCI: AAR 34±11%, n=31 vs. pPCI alone: AAR 33±17%, n=33, p=0.8) or in those with culprit outside LADs vascular bed (rIC+pPCI: AAR=22±13%, n=50 vs. pPCI alone: AAR = 22±13%, n=42 p=0.9). In patients with LAD-related STEMI, EF-2D on day one was 0.51±0.11 in rIC+pPCI patients
vs. 0.46±0.11 in patients treated with pPCI alone (p=0.03). GLS and LV volumes did not differ. After one month, patients with LAD-related STEMI persistently had a higher EF (2D echocardiography and gated SPECT), and a borderline higher GLS (more negative) in the rIC+pPCI vs. pPCI alone group (Table 3, Figure 2). Besides better LV function, smaller LV volumes (reaching statistical significance by gated SPECT) were observed with rIC, indicating less adverse remodeling (Table 3). Furthermore, rIC+pPCI treated patients developed smaller infarcts 7 % of LV (Q1 to Q3: 1 to 16), n=42 vs. 16 % of LV (Q1 to Q3 4 to 25), n=44 in the control group, p=0.01. For patients with STEMI due to culprit vessels located outside LAD’s territory, no difference was observed between treatment groups with regard to EF (2D, 3D, gated SPECT), GLS and LV-volumes on day one and after one month.

Impact of pre-procedural vessel patency

One hundred and thirty seven patients had occluded culprit vessel (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0-1) on arrival at the catheterization laboratory. In the total population, EF-2D on day one was 0.49±0.10 in patients with occluded vessels vs. 0.51±0.11 (p=0.08) in patients with patent vessels on arrival. Corresponding values for GLS were –14.2±3.6 vs. -16.0±4.3 %, (p<0.002). On day 30, EF-2D was 0.51±0.08 vs. 0.56±0.09 (p=0.0001) and GLS -16.5±3.1 vs.-17.9±3.8 % (p=0.01) in patients with occluded and patent vessels, respectively. There was no difference in AAR between rIC+pPCI 34±11 % of LV, n=45 vs. pPCI alone 34±13 % of LV, n=45, and no difference was found in infarct size (rIC+pPCI: 9 % of LV (Q1 to Q3 3-18), n=59 vs. pPCI alone: 13 % of LV (Q1 to Q34-24), n=65, p=0.11. On day 30, rIC did not significantly affect LV function either in patients with patent target vessel or in patients with occluded target vessel on arrival (Table 3).

Comparison of ejection fraction and volumes by gated SPECT and echocardiography.
SPECT yielded higher volume estimates than echocardiography. Volume over-/underestimation were of the same relative size for systolic and diastolic volumes, so there was no significant bias between EF estimates by SPECT and echocardiography (2D ejection fraction vs. SPECT (bias: 0, 95 % CI (-0.02 to 0.01), lower limit of agreement: -0.15, upper limit of agreement: 0.15); 3D echocardiography vs. SPECT (bias: 0.01, 95 % CI (-0.01 to 0.02), lower limit of agreement: -0.14, upper limit of agreement: 0.16).

**Method feasibility**

The quality of the obtained echocardiographic recordings did not allow complete assessment of all indices in every patient. The patients completing each examination along with the number of patients with each index available are outlined in Table 2. From these numbers the feasibility was calculated for EF-2D: 0.94 and 0.95; EF-3D: 0.77 and 0.81; and GLS 0.84 and 0.88 on day one and day 30, respectively.
Discussion

The results of the present study demonstrate that patients with extensive AAR>35% of LV gain substantial benefit from remote ischemic conditioning in terms of a persistent preservation of LV function. Moreover, in the subset of LAD-infarct patients, those treated with rIC+pPCI had preserved LV myocardial performance acutely and persistently after one month and MPI demonstrated significantly decreased LV volumes indicating less adverse remodeling after rIC. The findings were consistent by two independent imaging modalities. Besides patients with large AAR, patients with anterior infarction constitute an additional “high risk” population. Hence, remote ischemic conditioning as adjunctive to pPCI is of potential clinical benefit, particularly in high risk patients.

Overall, the present study population had a well preserved residual LV function (mean EF-2D day 30: 0.54±0.09). The majority of patients (69 %) had an EF-2D≥0.50 and only 8 % experienced a critically low EF-2D≤0.40 after 30 days reflecting best medical practice with respect to pre-hospital diagnostics and rapid hospital admission, optimal revascularization techniques, and most advantageous medical therapy. This encouraging outcome challenges the possibility to demonstrate an overall benefit on LV function by a strategy aiming to attenuate reperfusion injury. Previous clinical MI-reperfusion studies in unselected STEMI-populations have shown neutral results on LV function. Even a large scale meta-analysis (14.355 patients) that compared thrombolytic reperfusion therapy with conservative treatment, failed to demonstrate more than a tendency towards LV improvement. Conversely, in small sized studies with less than 100 selected patients with STEMI caused by LAD or RCA occlusion, improvement of LV function have been demonstrated by modification of reperfusion with Nicorandil or post-conditioning.
In addition to assessment of LV function by traditional EF measurement, we studied the longitudinal systolic function by two dimensional speckle tracking strain imaging. Longitudinal systolic function was affected similarly after STEMI in our study compared with previous investigations\textsuperscript{14, 28}. Consistent with traditional LV measurements, in patients with extensive myocardium at risk, GLS increased by rIC, and in those with LAD-STEMI conditioned patients had borderline significantly higher GLS. Speckle tracking strain has been validated in phantoms and in vivo\textsuperscript{29-31}. GLS by speckle tracking correlates with infarct size\textsuperscript{8-10}, and has been proposed to be more precise than 2D EF in quantifying LV function\textsuperscript{7}. Encouraged by these results, we expected that GLS would also more precisely than traditional measures of LV function reflect the underlying pathology of the ischemic myocardium. However, when comparing the value of indices of LV function as markers of the final infarct size, we have found GLS and EF-2D equally precise (regression of echocardiographic indices on infarct size and comparison of the model residuals reveals that GLS and EF yield equally precise infarct size estimates (data not shown)).

Although echocardiographic recordings were obtained under optimal conditions with the patients carefully positioned on a dedicated ultrasound table, both speckle tracking and real-time 3D echocardiography were hampered by a limited feasibility. The consequent loss of data, may explain the loss of statistical power by GLS and 3D-EF compared to 2D LV measurements in the subset of patients with LAD-STEMI.

Thus, the precision-merits of GLS and 3D-EF as markers of LV function as confirmed from lower coefficients of repeatability in this study may be lost by a reduced feasibility.

\textit{Limitations}

Our main results were found in subgroups, increasing the likelihood that these effects have arisen by change as a result of multiple testing. One should therefore be careful in the
interpretation, and the corresponding p values should be taken with caution. From a statistical viewpoint, a significance level of p < 0.05 is a liberal threshold that may have inflated type I error in this setting. However, it must be emphasized that the subgroups consisted of high risk patients prone to develop large infarcts, in which it is plausible that treatment effects, if any, should be most pronounced and therefore easier to detect.

Data on LV function prior to randomization were not available due to the unpredictable nature of STEMI. Therefore, we cannot rule out that a difference in LV function might have existed before the index infarction. Theoretically, this could have influenced our results.

**Conclusion**

Although data on LV function obtained from the whole study cohort revealed no significant differences, remote ischemic conditioning during transfer to primary angioplasty modestly improved LV function and remodelling in patients at risk of large myocardial infarcts. Future large-scale studies are needed to confirm these findings and to clarify whether this effect can be translated into improved clinical outcome.
Acknowledgements

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Disclosures

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Table 1. Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>rIC + pPCI (n = 123)</th>
<th>pPCI-alone (n = 119)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>62±11</td>
<td>62±11</td>
<td>0.77</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26±4</td>
<td>26±4</td>
<td>0.43</td>
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<tr>
<td>Female sex</td>
<td>28 (23%)</td>
<td>26 (22%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Present Smoker</td>
<td>69 (56%)</td>
<td>67 (57%)</td>
<td>0.92</td>
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<tr>
<td>Hypertension</td>
<td>47 (38%)</td>
<td>29 (24%)</td>
<td>0.020*</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>18 (15%)</td>
<td>21 (18%)</td>
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<tr>
<td>Diabetes</td>
<td>11 (9%)</td>
<td>10 (8%)</td>
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</tr>
<tr>
<td>Infarct-related coronary artery</td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>LAD</td>
<td>47 (38%)</td>
<td>50 (42%)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>20 (16%)</td>
<td>15 (13%)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>56 (46%)</td>
<td>54 (45%)</td>
<td></td>
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<tr>
<td>Occluded vessel on arrival (TIMI 0-1)</td>
<td>67 (58%)</td>
<td>70 (61%)</td>
<td>0.57</td>
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<tr>
<td>Symptom to balloon time, min</td>
<td>190 [134;304]</td>
<td>185 [129;299]</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Categorical data presented as absolute values (percentage), normally distributed data as means ± standard deviations, non-normal continuous data as median including first and third quartile in brackets.

TIMI: Thrombolysis in Myocardial Infarction flow grade; rIC+pPCI: remote ischemic conditioning group; pPCI alone: patients treated conventionally (control group); LAD: left anterior descendent coronary artery; LCX: left circumflex coronary artery; RCA: Right coronary artery.

*p value<0.05, rIC+pPCI vs. pPCI alone
Table 2. Total study population, indices of LV function.

<table>
<thead>
<tr>
<th></th>
<th>rIC+pPCI</th>
<th>pPCI alone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day one</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Echocardiography (n:117/121)</strong> *</td>
<td></td>
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<tr>
<td>Global systolic strain (%) (n: 100/100)</td>
<td>-15.2±3.8</td>
<td>-14.8±4.2</td>
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<tr>
<td>2D ejection fraction, (n:111/112)</td>
<td>0.51±0.10</td>
<td>0.49±0.10</td>
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<tr>
<td>diastolic volume (cm³)</td>
<td>81±23</td>
<td>80±22</td>
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<td>systolic volume (cm³)</td>
<td>41±18</td>
<td>41±17</td>
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<tr>
<td>3D ejection fraction (n: 90/93)</td>
<td>0.49±0.09</td>
<td>0.48±0.09</td>
<td>0.32</td>
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<td>diastolic volume (cm³)</td>
<td>91±24</td>
<td>90±21</td>
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<tr>
<td>systolic volume (cm³)</td>
<td>46±17</td>
<td>47±16</td>
<td>0.87</td>
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<tr>
<td>SPECT ejection fraction (n: 53/53)</td>
<td>49±12</td>
<td>4.9±13</td>
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<td>diastolic volume (cm³)</td>
<td>110±41</td>
<td>113±45</td>
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</tr>
<tr>
<td>systolic volume (cm³)</td>
<td>59±29</td>
<td>64±37</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Day 30</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Echocardiography (n: 109/107)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global systolic strain (%), (n:96/94)</td>
<td>-17.2±3.0</td>
<td>-16.9±3.9</td>
<td>0.61</td>
</tr>
<tr>
<td>2D ejection fraction, (n: 103/103)</td>
<td>54±0.08</td>
<td>0.53±0.10</td>
<td>0.42</td>
</tr>
<tr>
<td>diastolic volume (cm³)</td>
<td>85±26</td>
<td>86±26</td>
<td>0.90</td>
</tr>
<tr>
<td>systolic volume (cm³)</td>
<td>40±17</td>
<td>42±22</td>
<td>0.58</td>
</tr>
<tr>
<td>3D ejection fraction, (n:88/86)</td>
<td>0.54±0.08</td>
<td>0.52±0.09</td>
<td>0.13</td>
</tr>
<tr>
<td>diastolic volume (cm³)</td>
<td>97±26</td>
<td>98±26</td>
<td>0.76</td>
</tr>
<tr>
<td>systolic volume (cm³)</td>
<td>45±17</td>
<td>48±22</td>
<td>0.29</td>
</tr>
<tr>
<td>SPECT ejection fraction (n: 101/96)</td>
<td>0.54±0.11</td>
<td>0.53±0.11</td>
<td>0.63</td>
</tr>
<tr>
<td>diastolic volume (cm³)</td>
<td>116±36</td>
<td>124±46</td>
<td>0.14</td>
</tr>
<tr>
<td>systolic volume (cm³)</td>
<td>56±28</td>
<td>62±41</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation.

* n:x/y denotes the number of patients completing imaging in rIC+PCI/pPCI alone at day one and day 30 after STEMI.

Abbreviations as in table 1.
Table 3. Left ventricular function after 30 days in patients with culprit lesion in LAD, and patients with occluded target vessel on arrival to the catheterization laboratory.

<table>
<thead>
<tr>
<th></th>
<th>LAD-STEMI</th>
<th>(TIMI flow grade 0-1) on arrival</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rIC+pPCI</td>
<td>pPCI-alone</td>
<td>P value</td>
<td>rIC+pPCI</td>
</tr>
<tr>
<td>n: echocardiography performed</td>
<td>(n=42)</td>
<td>(n=42)</td>
<td></td>
<td>(n=61)</td>
</tr>
<tr>
<td>Global systolic strain (%)</td>
<td>-16.3±3.0, n=38</td>
<td>-14.8±3.6, n=36</td>
<td>0.065</td>
<td>-16.5±2.6, n=57</td>
</tr>
<tr>
<td>2D ejection fraction</td>
<td>0.55±0.08, n=40</td>
<td>0.50±0.11, n=39</td>
<td>0.037*</td>
<td>0.51±0.07, n=50</td>
</tr>
<tr>
<td>diastolic volume (cm³)</td>
<td>86±28</td>
<td>93±29</td>
<td>0.29</td>
<td>91±25</td>
</tr>
<tr>
<td>systolic volume (cm³)</td>
<td>40±18</td>
<td>48±27</td>
<td>0.12</td>
<td>45±17</td>
</tr>
<tr>
<td>3D ejection fraction</td>
<td>0.55±0.09, n=35</td>
<td>0.51±0.09, n=33</td>
<td>0.16</td>
<td>0.52±0.08, n=52</td>
</tr>
<tr>
<td>diastolic volume (cm³)</td>
<td>99±27</td>
<td>108±29</td>
<td>0.23</td>
<td>102±25</td>
</tr>
<tr>
<td>systolic volume (cm³)</td>
<td>46±18</td>
<td>53±24</td>
<td>0.16</td>
<td>49±16</td>
</tr>
<tr>
<td>SPECT ejection fraction</td>
<td>0.55±0.10, n=38</td>
<td>0.49±0.12, n=40</td>
<td>0.024*</td>
<td>0.50±0.10, n=53</td>
</tr>
<tr>
<td>Diastolic volume (cm³)</td>
<td>118±38</td>
<td>140±55</td>
<td>0.045*</td>
<td>128±32</td>
</tr>
<tr>
<td>Systolic volume (cm³)</td>
<td>56±28</td>
<td>76±52</td>
<td>0.038*</td>
<td>66±27</td>
</tr>
</tbody>
</table>

Data are expressed as means with standard deviation.
Abbreviations as in table 1
*p value<0.05, rIC+pPCI vs. pPCI alone
Figure Legends

Figure 1: Study population. CABG=Coronary by-pass grafting.

Figure 2: Thirty day ejection fraction by biplane method (first column), global longitudinal strain (second column) and ejection fraction by gated SPECT (third column) in patients with a STEMI confined to LAD, with respect to treatment allocation. Black lines indicate mean values in each treatment group.
Pre-hospital Randomization (n=333)

Not meeting study criteria (n=40)
- 15 STEMI not confirmed
- 1 previous CABG
- 3 symptom duration > 12 h
- 21 previous myocardial infarction

rIC+pPCI (n=166)

pPCI alone (n=167)

Lost to day one echocardiography (n=5)
- 3 very early transfer to local hospital
- 1 dead
- 1 aortic counter pulsation therapy

rIC+pPCI (n=126)

pPCI alone (n=125)

Lost to day one echocardiography (n=8)
- 3 very early transfer to local hospital
- 2 acute CABG
- 1 acute surgery for tamponade
- 1 dead
- 1 aortic counter pulsation therapy

Lost to echocardiographic follow up (n=17)
- 9 did not wish/failed to show up
- 3 dead
- 5 echo not performed

rIC+pPCI
- Echo completed day one (n=121)
- Echo completed day 30 (n=109)
- Echo completed day one and/or day 30 (n=123)

pPCI alone
- Echo completed day one (n=117)
- Echo completed day 30 (n=107)
- Echo completed day one/and or day 30 (n=119)
Remote Ischemic Conditioning in Myocardial Infarct Patients Treated with Primary Angioplasty: Impact on Left Ventricular Function Assessed by Comprehensive Echocardiography and Gated SPECT
Kim Munk, Niels Holmark Andersen, Michael Rahbek Schmidt, Soren Steen Nielsen, Christian Juhl Terkelsen, Erik Sloth, Hans Erik Bøtker, Torsten Toftegaard Nielsen and Steen Hvitfeldt Poulsen

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