Remote Ischemic Conditioning in Patients With Myocardial Infarction Treated With Primary Angioplasty

Impact on Left Ventricular Function Assessed by Comprehensive Echocardiography and Gated Single-Photon Emission CT

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

Methods and Results—Patients with a first STEMI were randomized to rIC (4 cycles of 5 minutes upper-limb ischemia) during transfer to primary percutaneous coronary intervention (pPCI) (n=123) versus pPCI alone (n=119). Ejection fraction (EF), LV volumes, (2D and 3D echocardiography and myocardial perfusion imaging), and speckle-tracking global longitudinal strain were compared between treatment groups. There was no significant difference in LV function at day 1 (EF-2D, 0.51±0.10 versus 0.49±0.10; P=0.22) and after 30 days (EF-2D, 0.54±0.08 versus 0.53±0.10) between the rIC and the pPCI-alone groups. 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 versus 0.46±0.09; P=0.05). In patients with anterior infarction (n=97), rIC preserved LV function on day 1 (EF-2D, 0.51±0.11 versus 0.46±0.11; P=0.03) and persistently after 30 days (EF-2D, 0.55±0.08 versus 0.50±0.11; P=0.04; EF-myocardial perfusion imaging, 0.55±0.10 versus 0.49±0.12; P=0.02). These patients had similar AAR, whereas rIC reduced infarct size from 16% to 7% of LV (P=0.01).

Conclusions—Although no significant overall effect was observed, rIC 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.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00435266.

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Key Words: scintigraphy ■ reperfusion injury ■ 2D echocardiography

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 to promptly 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 why a substantial number of patients with STEMI end up with low salvage, compromised LV function, and heart failure.4

Clinical Perspective on p 662

Local and remote ischemic conditioning (rIC) 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 rIC by repeated cycles of nonlethal 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 LV. Usually, conventional 2D and 3D echocardiographic imaging are used, yet recent data show 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 data sets 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 remodeling by comprehensive echocardiography and 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 rIC in STEMI trial was a single-center, 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 previously published in detail.6 In brief, patients were included from February 2007 to October 2008. Criteria for inclusion were as follows: (1) symptoms consistent with myocardial infarction lasting between 30 minutes and 12 hours, (2) ST-segment elevation of >0.1 mV in 2 or more contiguous leads, and (3) age ≥18 years. Patients were excluded from analysis on the basis of the following criteria: (1) previous coronary bypass surgery, (2) left bundle branch block, (3) treatment with fibrinolysis within the previous 30 days, (4) left main stenosis requiring coronary artery bypass surgery, (5) cardiogenic shock, and (6) previous myocardial infarction. During ambulance transfer, patients given a tentative diagnosis of STEMI were randomized to pPCI revascularization (pPCI alone [control group]) or pPCI revascularization plus remote conditioning (rIC+pPCI [intervention group]) through intermittent arm ischemia. Arm ischemia was obtained by 4 cycles of alternating 5-minute inflation and 5-minute deflation of an 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 complied 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 7; GE Healthcare; Horten, Norway) with a 3.5-MHz phased array transducer (M4S). The first echocardiography was performed at a median of 13 hours (Q1 to Q3; 8 hours to 18 hours) after pPCI. The observer was blinded to the treatment allocation. Patients were reexamined 24 hours and after 30 days. Examinations were made by 2 observers (K.M., N.H.A.). Data were stored digitally and analyzed off line by a single investigator (K.M.) blinded to clinical data, using dedicated software (EchoPac PC [software only] 7.0.0 [GE Healthcare; Milwaukee, Wis], including Tomtec 4D LV-Function [Tomtec Imaging Systems; Unterschleissheim, Germany]). Two-dimensional ejection fraction (EF) measurements were based on end-systolic and end-diastolic LV volumes, using the biplane method of discs.14 Volume data are averages of 3 measurements.

Full-volume 3D data sets were obtained using a 3.5-MHz matrix array transducer (3V). Optimal transducer position and angle was adjusted using the 3-plane imaging mode. When, in the respiratory cycle, optimal endocardium delineation was achieved, a full-volume electrocardiography-gated data set through 4 cardiac cycles was sampled during apnea. With use of the Tomtec 4D LV-Function software package, end-diastolic and end-systolic endocardial tracings were drawn manually in the 3 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. LV EF was calculated from end-diastolic and end-systolic estimates of these virtual LV-cavity casts.

Intraobserver variability was assessed from readings on 25 randomly selected patients. The intraobserver repeatability analysis showed a mean absolute difference of 0.3% (95% CI, −0.2% to 0.7%) for GLS, −0.02 (95% CI, −0.04; 0.01) for Simpsons 2D EF, and −0.02 (−0.03 to 0.01) for 3D EF. Coefficients of repeatability (1.96 SD on differences) on a relative scale were 11% (95% CI, 8% to 15%) for GLS, 23% (95% CI, 18% to 32%) for 2D EF, and 9% (95% CI, 7% to 13%) for 3D EF.

Single-Photon Emission CT

In the main study, salvage index (the proportion of AAR salvaged by treatment) was the primary end point. Before pPCI, 99mTc-sestamibi was injected, and myocardial AAR was measured by MPI within 8 hours after pPCI. At the 30-day follow-up visit, patients received 700±10% MBq 99mTc-sestamibi IV after 15 minutes bed rest. Single-photon emission CT (SPECT) was performed after 1 hour using a high-resolution, parallel-hole collimator dual-headed rotating gamma camera (ADAC; Forte; Milpitas, Calif) with no scatter or attenuation correction. Images were gated at 8 frames per cardiac cycle. Accumulated radiation dose of the 2 MPI examinations were ~12 mSv, equaling 120 chest radiographs. This radiation dose corresponds to an estimated 0.1 absolute percent increase in lifetime risk of dying from a malignancy added to the background risk equaling 21%.15

Data were analyzed independently by 2 experienced nuclear cardiology readers. Images were analyzed with the commercially available automatic quantitative perfusion SPECT and quantitative gated SPECT programs (QPS and QGS) (Cedars-Sinai Medical Center; Los Angeles, Calif).17,18 In case of failure of the automatic algorithm, tools for masking extracardiac activity and defining the valve plane and the apex of the LV manually were used. Infarct size was calculated as the area of the LV containing counts lower than a mean normal limit for pixels, using a sex-specific MIBI MIBI rest database as reference. If the interreader difference in defect size exceeded 3%, a consensus reading was obtained from the 2 readers. Volumes of LV cavities at end systole and end diastole were assessed as described.19

Statistics

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

Continuous data conforming to a normal distribution are presented as mean±SD, nonnormal 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 χ² test or Fisher exact test when tabled numbers were <10. 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; College Station, Tex).

**Results**

Study Population and Patient Characteristics

Details on randomization, reason for exclusion after prehospital 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 and 42 pPCI alone) were excluded from analysis because they did not fulfill the study criteria. Nine patients (3 rIC+pPCI and 6 pPCI alone) had neither day-1 nor 1-month echocardiography. Thus, the study population comprised 242 patients (123 rIC+pPCI and 119 pPCI alone) completing the day-1, 30-day, or both echocardiography.

Baseline characteristics were similar except for hypertension (Table 1).

**Total Study Cohort**

Myocardial AARs were similar in treatment groups (rIC+pPCI, 26±14% of LV [n=81]; pPCI alone, 27±16% of LV [n=76]; P=0.9). Overall, LV function recovered significantly from day 1 (EF-2D, 0.50±0.10; GLS, −15.3±3.8%) to 1 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 1 month, an equal number of patients had a normal EF-2D (rIC+pPCI, 72 [70%] patients; pPCI alone, 73 [71%] patients; P=0.9). However, 3 (3%) patients in the rIC+pPCI group versus 13 (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% to 14%) in 108 patients versus 7% of LV (Q1 to Q3, 1% to 14%) in 110 patients (P=0.09) in the intervention and control groups, respectively.

**Impact of Remote Conditioning in Relation to Myocardium at Risk**

Myocardial AAR assessed by 99mTc-sestamibi MPI was available in 157 patients (rIC+pPCI, 81 patients; pPCI alone, 76 patients). AAR correlated weakly with LV function acutely and on follow-up (day-1 EF-2D, r²=0.11; day 1 GLS, r²=0.32; day-30 EF-2D, r²=0.18; day-30 GLS, r²=0.25; Table 1).

![Figure 1. Study population. CABG indicates coronary artery bypass graft.](http://circimaging.ahajournals.org/)

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P0.0001 for all). Depending on the magnitude of the AAR, patients were divided into groups by tertiles as follows: AAR ≤18% of LV (rIC+pPCI AAR, 11.6% [n=27]; pPCI-alone AAR, 9.6% [n=27]; P=0.15), AAR 19% to 34% of LV (rIC+pPCI AAR, 26.4% [n=26]; pPCI-alone AAR, 29.4% [n=24]; P=0.02), and AAR ≥35% of LV (rIC+pPCI AAR, 42.5% [n=28]; pPCI-alone AAR, 44.6% [n=24]; P=0.17). In those with extensive AAR ≥35% of LV, rIC+pPCI patients had higher EF-2D after 1 month than those treated conventionally (rIC+pPCI, 0.51±0.07 [n=23]; pPCI alone, 0.46±0.09 [n=20]; P=0.046). There was a significant difference in infarct size between these patients groups (rIC+pPCI, 15% of LV; Q1 to Q3, 10% to 25% [n=24]; pPCI alone, 24% of LV; Q1 to Q3, 18% to 29% [n=24]; P=0.045). No differences were seen in the lower- and middle-tertile groups. In the upper-, middle-, and lower-AAR-tertile groups, 1-month GLS was −15.8±2.6% versus −13.5±3.2% (P=0.01), −17.0±2.8% versus −19.0±3.7% (P=0.06), and −18.3±3.0% versus −19.1±3.0% (P=0.87) in the rIC+pPCI and pPCI-alone groups, respectively.

Impact of Remote Conditioning in Relation to Infarct Location

Ninety-seven patients (rIC+pPCI, 47 patients; pPCI alone, 50 patients) had a culprit lesion within the left anterior descending (LAD) coronary artery territory. There was no difference in AAR between treatment groups in patients with culprit lesions in LAD (rIC+pPCI AAR, 34±11% [n=31]; pPCI alone AAR, 33±17% [n=33]; P=0.8) or in those with culprit lesions outside-LAD vascular bed (rIC+pPCI AAR, 22±13% [n=50]; pPCI alone AAR, 22±13% [n=42]; P=0.9). In patients with LAD-related STEMI, EF-2D on day 1 was 0.51±0.11 in rIC+pPCI patients versus 0.46±0.11 in pPCI-alone patients (P=0.03). GLS and LV volumes did not differ. After 1 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 versus pPCI-alone groups (Figure 2, Table 3).

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 (n=42) developed smaller infarcts of 7% of LV (Q1 to Q3, 1% to 16%) versus 16% of LV (Q1 to Q3, 4% to 25%) in the control group (n=44) (P=0.01). For patients with STEMI due to culprit vessels located outside the LAD territory, no difference was observed between treatment groups with regard to EF (2D, 3D, gated SPECT), GLS, and LV volumes on day 1 and after 1 month.

Impact of Remote Conditioning in Relation to Preprocedural Vessel Patency

One hundred thirty-seven patients had occluded culprit vessels (thrombolysis in myocardial infarction [TIMI] flow grade 0 to 1) on arrival at the catheterization laboratory. In the total population, EF-2D on day 1 was 0.49±0.10 in patients with occluded vessels versus 0.51±0.11 in patients with patent vessels (P=0.08) on arrival. Corresponding values for GLS were
Moreover, in the subset of patients with LAD infarct, those with extensive AAR, 34% to 24% (Table 3). The results of the present study demonstrate that patients with extensive AAR >35% of LV gain substantial benefit from rIC in terms of a persistent preservation of LV function. Moreover, in the subset of patients with LAD infarct, those treated with rIC+pPCI had preserved LV myocardial performance acutely and persistently after 1 month, and MPI demonstrated significantly decreased LV volumes, indicating less adverse remodeling after rIC. The findings were consistent by 2 independent imaging modalities. Besides patients with large AAR, patients with anterior infarction constituted an additional high-risk population.6,21,22 Hence, rIC as an 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 (EF-2D day 30, 0.54±0.09). The majority (69%) of patients 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 prehospital 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 myocardial infarction-reperfusion studies in unselected STEMI populations have shown neutral results on LV function.23,24 Even a large-scale metaanalysis (14 355 patients) that compared thrombolytic reperfusion therapy with conservative treatment failed to demonstrate more than a tendency toward LV improvement.25 Conversely, in small-sized studies with fewer than 100 selected patients with STEMI caused by LAD or right coronary artery occlusion, improvement of LV function has been demonstrated by modification of reperfusion with nicorandil26 or postconditioning.27

In addition to assessment of LV function by traditional EF measurement, we studied the longitudinal systolic function by 2D speckle-tracking strain imaging. Longitudinal systolic function was affected similarly after STEMI in our study compared with previous investigations.14,28 Consistent with the results from the traditional LV measurements, GLS significantly higher. Speckle-tracking strain has been validated in phantoms and in vivo.29–31 GLS by speckle tracking correlates with infarct size8–10 and has been proposed to be

### Table 3. LV After 30 Days in Patients With Culprit Lesions in LAD and Patients With Occluded Target Vessels on Arrival to the Catheterization Laboratory

<table>
<thead>
<tr>
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<th>LAD-STEMI</th>
<th>(TIMI Flow Grade 0–1) on Arrivial</th>
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<tbody>
<tr>
<td></td>
<td>rIC+pPCI (n=42)</td>
<td>pPCI Alone (n=42)</td>
</tr>
<tr>
<td><strong>GLS, %</strong></td>
<td>−16.3±3.0 (n=38)</td>
<td>−14.8±3.6 (n=36)</td>
</tr>
<tr>
<td><strong>2D EF</strong></td>
<td>0.55±0.08 (n=40)</td>
<td>0.50±0.11 (n=39)</td>
</tr>
<tr>
<td>Diastolic volume, cm³</td>
<td>86±28</td>
<td>93±29</td>
</tr>
<tr>
<td>Systolic volume, cm³</td>
<td>40±18</td>
<td>48±27</td>
</tr>
<tr>
<td><strong>3D EF</strong></td>
<td>0.55±0.09 (n=35)</td>
<td>0.51±0.09 (n=33)</td>
</tr>
<tr>
<td>Diastolic volume, cm³</td>
<td>99±27</td>
<td>108±29</td>
</tr>
<tr>
<td>Systolic volume, cm³</td>
<td>46±18</td>
<td>53±24</td>
</tr>
<tr>
<td><strong>SPECT EF</strong></td>
<td>0.55±0.10 (n=38)</td>
<td>0.49±0.12 (n=40)</td>
</tr>
<tr>
<td>Diastolic volume, cm³</td>
<td>118±38</td>
<td>140±55</td>
</tr>
<tr>
<td>Systolic volume, cm³</td>
<td>56±28</td>
<td>76±52</td>
</tr>
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</table>

Data are presented as mean±SD; n indicates number of patients for whom echocardiography was performed.

*p<0.05, rIC vs pPCI; **p<0.01, rIC vs pPCI.
more precise than 2D EF in quantifying LV function. Encouraged by these results, we expected that GLS also would reflect more precisely than traditional measures of LV function 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 to be equally precise. (Regression of echocardiographic indices on infarct size and comparison of the model residuals revealed that GLS and EF yielded 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.

Limitations
Our main results were found in subgroups, increasing the likelihood that these effects have arisen by chance as a result of multiple testing. One therefore should be careful in the interpretation, and the corresponding P values should be taken with caution. From a statistical viewpoint, a significant 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 before randomization were not available because of the unpredictable nature of STEMI. Therefore, we cannot rule out that a difference in LV function might have existed before the index infarction. Theoretically, such difference could have influenced our results.

Conclusion
Although data on LV function obtained from the whole study cohort revealed no significant differences, rIC during transfer to primary angioplasty modestly improved LV function and remodeling 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.

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Disclosures
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References
Survivors of myocardial infarction with compromised left ventricular (LV) function are prone to experience adverse events, such as ventricular arrhythmia, heart failure, and death. A major target for primary coronary revascularization in patients with ST-segment elevation myocardial infarction is to diminish post-myocardial infarction LV dysfunction. Previously, we have found adjunctive treatment by remote ischemic conditioning (ie, the application of intermittent peripheral limb ischemia during transport of patients to invasive treatment) to increase myocardial salvage. In the present study, we evaluated whether remote ischemic conditioning mediated a clinically relevant improvement of LV function using 2 independent methods: echocardiography and myocardial perfusion imaging. In the total cohort, there was no significant effect, but in patients at a high risk of developing a large infarction (ie, patients with large myocardial area at risk and those with left anterior descending occlusion), remote conditioning improved LV ejection fraction and remodeling. Before wide clinical implementation of this low-cost and simple cardioprotective modality, trials confirming our findings as well as data on hard clinical outcomes are needed.
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