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Post-Conditioning Reduces Infarct Size and Edema in Patients With ST-Segment Elevation Myocardial Infarction

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Objectives This study aimed to determine whether post-conditioning at the time of percutaneous coronary intervention could reduce reperfusion-induced myocardial edema in patients with acute ST-segment elevation myocardial infarction (STEMI).

Background Myocardial edema is a reperfusion injury with potentially severe consequences. Post-conditioning is a cardioprotective therapy that reduces infarct size after reperfusion, but no previous studies have analyzed the impact of this strategy on reperfusion-induced myocardial edema in humans.

Methods Fifty patients with STEMI were randomly assigned to either a control or post-conditioned group. Cardiac magnetic resonance imaging was performed within 48 to 72 h after admission. Myocardial edema was measured by T2-weighted sequences, and infarct size was determined by late gadolinium enhancement sequences and creatine kinase release.

Results The post-conditioned and control groups were similar with respect to ischemia time, the size of the area at risk, and the ejection fraction before percutaneous coronary intervention. As expected, post-conditioning was associated with smaller infarct size (13 ± 7 g/m^2 vs. 21 ± 14 g/m^2; $p = 0.01$) and creatine kinase peak serum level (median [interquartile range]: 1,695 [1,118 to 3,692] IU/l vs. 3,505 [2,307 to 4,929] IU/l; $p = 0.003$). At reperfusion, the extent of myocardial edema was significantly reduced in the post-conditioned group as compared with the control group (23 ± 16 g/m^2 vs. 34 ± 18 g/m^2; $p = 0.03$); the relative increase in T2W signal intensity was also significantly lower ($p = 0.02$). This protective effect was confirmed after adjustment for the size of the area at risk.

Conclusions This randomized study demonstrated that post-conditioning reduced infarct size and edema in patients with reperfused STEMI. (Post Cond No Reflow; NCT01208727) (J Am Coll Cardiol 2012;59:2175–81) © 2012 by the American College of Cardiology Foundation

Reperfusion therapy of jeopardized myocardium is the most effective method for reducing infarct size and improving the outcome in patients with ST-segment elevation myocardial infarction (STEMI). However, the restoration of coronary blood flow can paradoxically induce additional myocardial damage, making reperfusion therapy a "double-edged sword" (1). Reperfusion injury is a complex phenomenon mediated by several factors, including oxidative stress, intracellular calcium accumulation, rapid restoration of pH, and inflammation, and involves, at least partly, opening of the so-called mitochondrial permeability transition pore (2). Clinically identified features of this reperfusion injury may be reversible and transient, such as

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Abbreviations and Acronyms

ACS = abnormally contracting segments
CK = creatine kinase
CMR = cardiac magnetic resonance
LGE = late gadolinium enhancement
LV = left ventricle/ventricular
PCI = percutaneous coronary intervention
SI = signal intensity
STEMI = ST-segment elevation myocardial infarction
STIR = short tau inversion recovery
T2W = T2-weighted

arrhythmias or myocardial stunning, or irreversible, such as myocardial infarction or microvascular obstruction (1).

Myocardial edema begins during the ischemic phase but abruptly expands during the first minutes of reperfusion when the gradient between the hyperosmotic extravascular fluid and the normo-osmotic blood rapidly grows (1). By increasing the hydrostatic pressure within the interstitial space, this edema can contribute to capillary compression and aggravation of cell damage (3). Myocardial edema is thus a consequence, but through a vicious cycle, is also a mechanism of reperfusion injury (4). One may therefore question whether measuring myocardial edema might be interesting for estimation of reperfusion injury and evaluation of protective interventions.

Cardiac magnetic resonance (CMR) imaging is an appropriate method for measuring myocardial edema in vivo, which is depicted as the area of hypersignal on T2-weighted (T2W) images (5). Indeed, increases in the transverse component of the proton relaxation time (T2) and T2W signal intensity (SI) have been shown to correlate well with the water content in a model of ischemia reperfusion in dogs (6). This property has been used in various clinical settings, including the assessment of acute ischemic damage (5) and the quantification of myocardial salvage (7–9). However, to our knowledge, it has never been used to evaluate reperfusion injury per se.

Ischemic post-conditioning (brief repeated periods of ischemia applied at the onset of reperfusion) is a cardioprotective strategy that has been proven to specifically attenuate lethal reperfusion injury in animal models and in patients with STEMI (10–12). Post-conditioning has been shown to reduce myocardial edema after reperfusion in experimental preparations (13). However, no previous studies have analyzed the impact of this protective intervention on post-reperfusion myocardial edema in patients with STEMI. The objective of the present study was to determine whether post-conditioning could reduce post-reperfusion myocardial edema, as assessed by CMR imaging, in patients with ongoing STEMI.

Methods

Study population. From May 2008 to October 2010, men and women of age ≥18 years who presented within 12 h after the onset of chest pain, who had ST-segment elevation of >0.1 mV in 2 contiguous leads, and for whom the clinical decision was made to treat with percutaneous coronary intervention (PCI) were considered for inclusion in the study. Patients were eligible whether they were undergoing primary PCI or rescue PCI. Occlusion of the culprit coronary artery (thrombolysis in myocardial infarction flow grade 0 to 1) at the time of admission was also a criterion for inclusion (14). Patients with cardiac arrest, ventricular fibrillation, cardiogenic shock, stent thrombosis, previous acute myocardial infarction, angina within 48 h before infarction, and contraindications to CMR imaging were not included in the study. Patients with occlusion of the left circumflex coronary artery were included only in the case of left circulation dominance. Patients with occlusion of the left main or with evidence of coronary collaterals (Rentrop grade ≥1) to the region at risk on initial coronary angiography (at the time of admission) were excluded (15). This study was approved by the Ethics Committee of Lyon, France (IRB 123406519). All patients gave written informed consent for participation.

Angiography and PCI. Left ventricular (LV) and coronary angiography was performed using standard techniques just before revascularization. The size of the area at risk was estimated for each patient by measuring the circumferential extent of abnormally contracting segments (ACS) according to the method of Feild et al. (16) and Lapeyre et al. (17), as performed in previous randomized trials (11,18). Briefly, the length of the end-diastolic ventricular endocardial perimeter (circumference) and the length of the ACS of the end-diastolic perimeter were determined by computerized planimetry (Image J 1.38× software). ACS were expressed as: ACS (%) = (abnormally contracting length of end-diastolic circumference/total end-diastolic circumference) × 100. Measurement of the ACS was performed in a blinded manner by an experienced investigator. Revascularization was performed with the use of direct stenting.

Experimental protocol. Patients were randomly allocated to either the control or the post-conditioned group. Coronary angiography was performed using standard techniques just before revascularization. Randomization was performed with the use of a computer-generated randomization sequence. Numbered sealed envelopes that contained the study group assignment were distributed to each catheterization laboratory and were opened after informed consent had been obtained. Revascularization was performed with the use of direct stenting as previously reported (11,12). In the control group, no additional intervention was performed during the first 8 min of reperfusion. In the post-conditioned group, within 1 min of reflow after direct stenting, the angioplasty balloon was reinflated 4 times for 1 min with low-pressure (4 to 6 atmospheres) inflations, each separated by 1 min of reflow. After the eighth minute of reperfusion, PCI was completed according to the physician's judgment with respect to patient status.

Myocardial edema and infarct size. All CMR imaging studies were performed on a 1.5-T MAGNETOM Avanto total imaging matrix system (Siemens Healthcare, Erlan-

gen, Germany) 48 to 72 h after admission with vectocardiogram monitoring and a phased-array cardiac receiver coil. The standard acute myocardial infarction protocol complied with the recommendations of the Society for Cardiac Magnetic Resonance (19). LV volumes and mass measurements were taken from the balanced steady-state free precession cine sequences with dedicated software (Argus, Siemens Medical Solutions, Malvern, Pennsylvania). T2W imaging was based on breath-hold T2W–short tau inversion recovery (T2W-STIR) sequences (matrix 118 × 256, voxel size 2.3 × 1.3 × 7 mm, flip angle 90/180°, effective echo time 47 ms, bandwidth 235 Hz/pixel) that covered the whole LV. The extent of myocardial edema was quantified using VPT software (Siemens Corporate Research, Erlangen, Germany), as previously reported (20). After manual tracing of the epicardial and endocardial contours, the T2W hyperintense area was quantified on the T2W images using semiautomatic detection with the full width at half-maximum approach (21). If present, a central core of hypointense signal within the area of increased SI (hemorrhagic infarction) was included in the T2W-CMR hypersignal area. Increased SI from the blood pool adjacent to the endocardium due to slow flow was excluded. For each slice level, T2W images were matched with cine-MR images for the same corresponding time trigger to provide anatomic landmarks and differentiate between slow flowing blood and increased myocardial intensities. The myocardial edema area and the total LV slice area were quantified in each short-axis slice. Eventually, the extent of myocardial edema was expressed as the indexed mass of the myocardial edema (in grams of tissue) according to the following formula: Σ (hyperenhanced area [cm^2] × slice thickness [cm] × myocardial-specific density [1.05 g/cm^3]/body surface area [m^2]). Regions of interest of the same size were manually drawn within the hypersignal area (excluding the central core of the hyposignal) and the remote myocardium of the median LV slice to measure the mean T2W SI peak value from the distribution scatter. Then, the percent signal enhancement between the myocardial edema area and remote myocardium was calculated as follows: $\%SE = (SI_E - SI_R)/SI_R$ (6,22).

Infarct size was assessed by 2 different techniques: 1) the peak of serum creatine kinase (CK) release determined from blood samples obtained at admission and repeatedly over the next 3 days (every 4 h on day 1 and every 6 h on days 2 and 3); and 2) the area of late gadolinium enhancement (LGE) on the CMR images. LGE was evaluated 10 min after the injection of gadolinium (0.2 mmol/kg at 3 ml/s; DOTAREM, Guerbet, France) with the use of a 3-dimensional inversion-recovery gradient-echo sequence. The images were analyzed in the same T2W-CMR–matched short-axis slices by delineation of the areas of LGE using semiautomatic detection with the full width at half-maximum approach (9,23). The area of LGE was expressed as the indexed mass of the infarcted myocardium. In cases of a dark subendocardial zone in the area of the hyperenhancement (microvascular obstruction), the zone was included in the infarct area.

All CMR images were analyzed by 2 senior investigators blinded to the study arm and any other clinical or imaging data. Consensus between the 2 observers was used for subsequent analysis. For all of these analyses, manual adjustments were performed when the computer algorithm was considered to be obviously wrong.

Statistical analysis. The target sample size was calculated to assess the effect of post-conditioning on the myocardial edema measured by CMR imaging. The expected effect was a 30% reduction in the extent of edema (comparable to the infarct size reduction observed in our previous studies), with a statistical power of 80% and a probability of a type I error of 0.05 with a 2-sided test (11,12).

Continuous data were reported as mean ± SD or median and interquartile range (IQR) for values without normal distribution. Categorical data were reported as frequencies and percentages. The data were analyzed according to the intention-to-treat principle. The Fisher exact test was used to compare categorical data. Either the unpaired Student *t* test or the Mann-Whitney test was used to compare continuous variables between the 2 independent groups. Simple linear regression analysis was used to assess the correlation between continuous variables. We performed an analysis of covariance to compare the treatment effect on infarct size, serum CK release, and myocardial edema after adjustment on the size of the area at risk. An analysis was also performed to adjust the effect of treatment on myocardial edema for the effect on the infarct size.

This statistical analysis was conducted using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, Illinois). All tests were 2-sided. A p value of < 0.05 was considered statistically significant.

Results

Study population. Seventy-six patients were considered to be eligible for the present study. Of these, 14 were not included for the following reasons: previous myocardial infarction in the same territory (n = 4), Thrombolysis In Myocardial Infarction flow grade of >1 at admission (n = 3), or evidence of coronary collaterals to the area at risk on admission coronary angiography (n = 7). Twelve additional patients were excluded because CMR imaging could not be performed or was not interpretable. Data are thus presented for 50 patients (25 in the control group and 25 in the post-conditioned group). Baseline characteristics of the study population are presented in Table 1, and no significant differences in these characteristics were observed between the 2 groups. No significant differences were observed in LV volumes, ejection fraction, or mass between the groups (Table 2).

As expected, the infarct size, as measured by myocardial LGE extent, in the post-conditioned group was 38% less than that in the control group, averaging 13 ± 7 g/m^2 versus 21 ± 14 g/m^2, respectively (p = 0.01) (Fig. 1A). The infarct size reduction by post-conditioning was also confirmed

Table 1 Baseline Characteristics of the Study Population

	Control Group (n = 25)	Post-Conditioned Group (n = 25)	p Value
Age, yrs	57 ± 12	57 ± 13	0.88
Male/female	18/7	19/6	0.78
BMI, kg/m^2	26 ± 4	26 ± 4	1.0
Hypertension	12 (48)	10 (40)	0.78
Smoking	16 (64)	17 (68)	1.0
Dyslipidemia	12 (48)	9 (36)	0.57
Diabetes	4 (14)	5 (20)	1.0
Angiographic findings			
Infarct-related artery			0.33
LAD	14 (56)	14 (56)	
RCA	9 (36)	11 (44)	
Cx	2 (8)	0 (0)	
Area at risk, % LV	36 ± 12	39 ± 14	0.41
PCI			
Duration of ischemia, min	215 ± 20	289 ± 31	0.08
Post-PCI TIMI flow grade	2.9 ± 0.3	2.9 ± 0.6	0.94
Treatment before PCI			
Intravenous nitrates	7 (28)	6 (24)	1.0
Morphine	13 (52)	19 (76)	0.14
Thrombolytic agents	4 (16)	3 (12)	1.0
Treatment at time of PCI			
Heparin	25 (100)	25 (100)	1.0
Aspirin and/or clopidogrel	25 (100)	25 (100)	1.0
Glycoprotein IIb/IIIa inhibitor	18 (72)	19 (76)	1.0

Values are mean ± SD, n/n, or n (%).

BMI = body mass index; Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; LV = left ventricle; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

when the size of the area at risk was taken into account (p = 0.0005 by covariance analysis). Finally, the peak for serum CK release was significantly lower in the post-conditioned group versus that in the control patients (median [IQR]: 1,695 [1,118 to 3,692] UI/l vs. 3,505 [2,307 to 4,929] UI/l; p = 0.003) (Fig. 1B) for all sizes of the area at risk (p = 0.02 by covariance analysis). Similar infarct size reduction was obtained when the area under the curve of CK release was considered (not shown).

Myocardial edema and post-conditioning. The mean area at risk size as measured by ACS was comparable for the post-conditioned and control groups (39 ± 14% vs. 36 ± 14% of LV circumference; p = 0.41).

The mean extent of myocardial edema in the post-conditioned group was 32% less than that in the control group, averaging 23 ± 16 g/m^2 versus 34 ± 18 g/m^2, respectively (p = 0.03) (Fig. 2A). In the control group, there was a significant correlation between the extent of edema and size of the area at risk (p = 0.0001). Importantly, the regression line for the post-conditioned group had a smaller slope than the regression line for the control group, indicating that for any given size of area at risk, the extent of myocardial edema was smaller in the post-conditioned patients. This difference in the slope was significant by analysis of covariance (p = 0.006) (Fig. 2B). Moreover, the normalized T2W signal difference between the edema area and remote area was significantly lower in the post-conditioned group than in the controls (median [IQR]: 58% [58% to 169%] vs. 82% [62% to 115%]; p = 0.02).

The effect of post-conditioning on myocardial edema was dependent on the infarct size (p = 0.35 after correction for the infarct size). Indeed, in both groups, we found a statistically significant correlation between infarct size and extent of myocardial edema, indicating that infarct size was a major determinant of edema. As shown in Figure 3, the larger the infarct, the larger the edema.

Discussion

In the present study, we found that the extent of myocardial edema after reperfusion therapy in patients with STEMI can be attenuated by angioplasty post-conditioning.

Impact of post-conditioning on myocardial edema. In the dog model, Zhao et al. (10) demonstrated that ischemic post-conditioning significantly reduced myocardial edema, as assessed by the ex vivo measurement of water content in a tissue sample of the area at risk. Other reports in rat or mouse models confirmed that ischemic post-conditioning could reduce edema in other organs, including the skeletal muscle and brain (24,25). Our study is the first to show that ischemic post-conditioning could attenuate myocardial edema in the clinical setting of STEMI. The mechanism of the reduction of myocardial edema by post-conditioning is unclear. Our data strongly suggest that it is most likely related to the infarct size–reducing effect because we found a good correlation between infarct size and myocardial edema together with a comparable impact of post-conditioning on infarct size and myocardial edema. Reduction of cell death with subsequent reduced release of water content into the extracellular space probably contributed to the limiting of edema by post-conditioning. The negative modulation of coronary perfusion pressure would potentially reduce the Starling forces, favoring the movement of intravascular water toward the interstitial space. Eventually, the limiting of both the inflammation process and the generation of reactive oxygen species by post-conditioning, as reported in experimental models, might prevent endothelial injury and subsequent increase in capillary permeability (1).

T2W-CMR for the assessment of reperfusion injury. T2W-CMR is a water-sensitive modality that offers a unique means for assessment of myocardial edema in vivo

Table 2 LV Volumes and Mass According to the Reperfusion Strategy

	Control Group (n = 25)	Post-Conditioned Group (n = 25)	p Value
LVEDV, ml/m^2	79 ± 17	73 ± 23	0.07
LVESV, ml/m^2	40 ± 15	35 ± 11	0.24
LVEF, %	50 ± 12	52 ± 8	0.66
LV mass, g/m^2	74 ± 15	73 ± 12	0.69

Values are mean ± SD.

LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

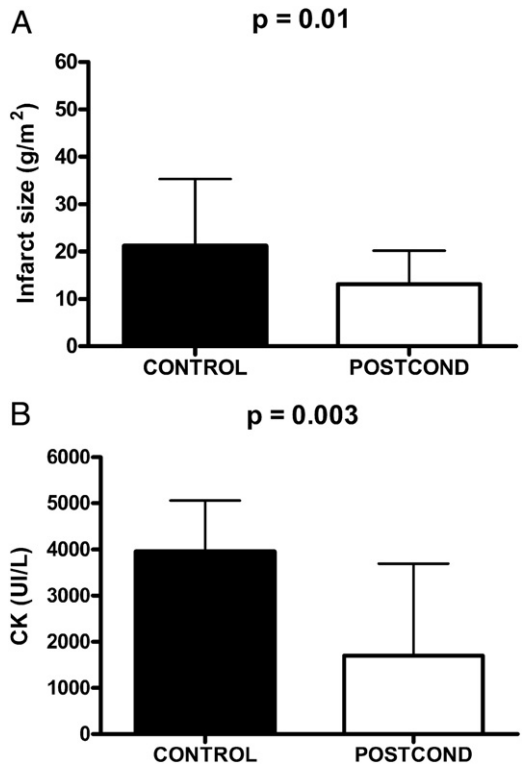

Figure 1 Infarct Size and Post-Conditioning

(A) The indexed mass of infarction was significantly reduced in the post-conditioned (POSTCOND) group compared with the control group (mean ± SD). **(B)** The peak for serum creatine kinase (CK) release was also significantly reduced in the post-conditioned patients (median and 75th percentile).

without using radiation or contrast agents. Higgins et al. (26) were the first to show an increase in T2 relaxation time in a model of myocardial ischemia in the dog. Garcia-Dorado et al. (6) used T2W-CMR to analyze myocardial edema in a pig model of ischemia-reperfusion. They demonstrated that T2 relaxation time and T2W SI correlated well with tissue water content and were both higher in reperfused myocardium than in nonreperfused and remote myocardium (6). We showed here, for the first time in patients with STEMI, that both the extent of the hypersignal on T2W images and the relative increase in T2W SI were significantly smaller in post-conditioned patients than in controls.

Several clinical investigations previously used CMR to evaluate the impact of cardioprotection strategies, but they mostly focused on infarct size reduction and did not specifically analyze myocardial edema (18,27). The present study raises a new interesting question: Is myocardial edema a representative marker for reperfusion injury? This premise is supported by the good correlation between the extent of edema and infarct size and the comparable attenuation of both features by ischemic post-conditioning. Using edema as a marker of reperfusion injury may have several advantages, including early estimation after reflow and good sensitivity to protective interventions as shown here with post-conditioning. Additional studies will be required to determine whether edema, as assessed by T2W-CMR, might be a prognostic marker. This would be indirectly supported by recent clinical study reports that patients without STEMI with myocardial edema at T2W-CMR had a higher risk of cardiovascular events within 6 months after acute coronary syndrome compared with those without edema (28). This concept of edema as a marker of reperfusion injury should be integrated in the global pathogenesis of the ischemia-reperfusion phenomenon and take into consideration the complex and evolving related issues (29). Beyond infarction, myocardial stunning, myocardial hemorrhage, inflammation, and microvascular obstruction might influence myocardial edema as a marker of reperfusion injury (29). Alternatively, CMR studies have suggested that the extent of myocardial edema is maximal and stable over the first week after infarction, which would make it and more

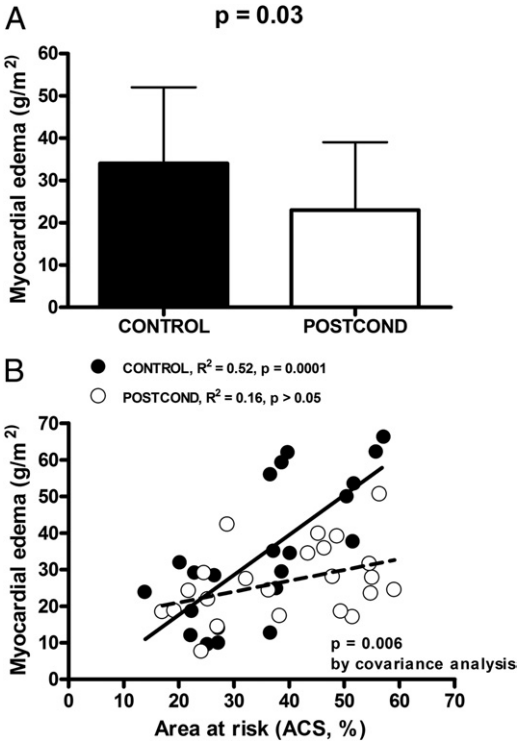

Figure 2 Effect of Post-Conditioning on Reperfusion-Induced Myocardial Edema

(A) The indexed mass of myocardial edema was significantly reduced in the post-conditioned (POSTCOND) group compared with the control group. **(B)** The indexed mass of myocardial edema was expressed as a function of the circumferential extent of abnormally contracting segments (ACS) to give an estimate of the area at risk. In the control group, there was a significant correlation between the area at risk and myocardial edema. This correlation was significantly weaker in the post-conditioned group than in the controls. The regression line for the post-conditioned group had a smaller slope than that for the control group, indicating that for a given size of area at risk, the extent of myocardial edema was smaller in the post-conditioned patients than in the control group.

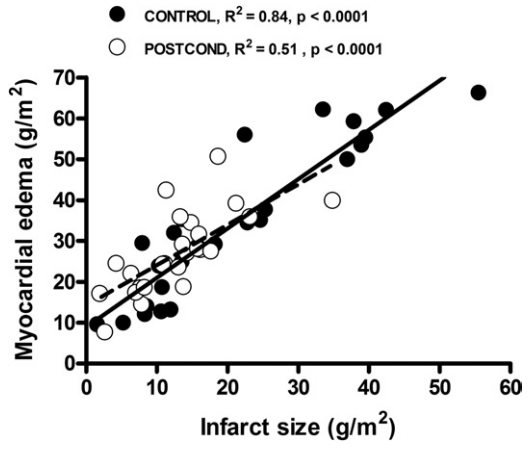

Figure 3 Myocardial Edema as a Function of Infarct Size

In both groups, we found a statistically significant correlation between infarct size and extent of myocardial edema, indicating that infarct size was a major determinant of edema. POSTCOND = post-conditioning.

generally, the area with reversible damage surrounding the infarct zone a clinically accessible surrogate endpoint for evaluation of the effect of a cardioprotective strategy such as post-conditioning (7).

Myocardial edema reduction and assessment of the area at risk. An accurate assessment of the size of the area at risk is crucial for evaluation of protective interventions and precise estimation of the myocardial salvage index, which has been demonstrated to be a strong predictor of mortality and morbidity in reperfused patients with STEMI (8). In the present study, similar to previous reports from our group (11,12,18), we used LV angiography to measure the size of the area at risk during ischemia (i.e., before reflow). Therefore, the area at risk size could not be influenced by any treatment (e.g., post-conditioning) initiated after reflow. Accumulating evidence indicates that T2W-CMR can quantify the area at risk through edema imaging in animals and humans with acute myocardial infarction (21). In fact, T2W-CMR can image the water accumulation within the myocardium subjected to acute ischemia and reperfusion up to 2 weeks after the event and can be viewed as a reperfusion-based estimate of the area at risk (7,30). The impact of therapeutic interventions performed at the time of (or after) reperfusion on reperfusion-based area at risk assessment has not been considered so far. The demonstration that post-conditioning was able to reduce myocardial edema poses a new question about the assessment of the area at risk by edema-based imaging techniques in infarct size reduction trials. As previously suggested (31), one can speculate that such a technique might underestimate the area at risk in the treated group, but not in the control group, and could therefore artificially increase the infarct size/area at risk ratio (or decrease myocardial salvage) in the former, further leading to either missing or underestimating the protective effect.

Study limitations. The "black blood" T2W-STIR sequences are subject to known limitations, including surface coil intensity variations, bright signal from stagnant blood that potentially can interfere with elevated T2 in the subendocardium, motion artifacts, and subjective interpretations of the images. Alternative methods have been proposed recently to image myocardial edema after reperfusion (32,33). The "bright blood" T2W–steady-state free precession sequences take advantage of improved coil sensitivity normalization and faster imaging. So far, T2W-STIR sequences are the only edema imaging sequences ever to be validated against pathology (21) and to have their prognostic value established in patients with reperfused acute myocardial infarction (8,28,34,35). In the future, T2 mapping techniques will probably solve most of the remaining issues (36).

Conclusions

This randomized controlled trial demonstrated that angioplasty post-conditioning decreased myocardial edema in patients with STEMI. This beneficial impact was likely related to the infarct size–reducing effect. Additional studies will be required to determine whether myocardial edema may be considered to be a new marker of myocardial reperfusion injury.

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