Long-Term Benefit of Postconditioning

Hélène Thibault, MD; Christophe Piot, MD, PhD; Patrick Staat, MD; Laurence Bontemps, MD; Catherine Sportouch, MD; Gilles Rioufol, MD, PhD; Thien Tri Cung, MD; Eric Bonnefoy, MD, PhD; Denis Angoulvant, MD; Jean-François Aupetit, MD, PhD; Gérard Finet, MD, PhD; Xavier André-Fouët, MD; Jean Christophe Macia, MD; Franck Raczka, MD; Rolland Rossi, MD; Rolland Itti, MD, PhD; Gilbert Kirkorian, MD, PhD; Geneviève Derumeaux, MD, PhD; Michel Ovize, MD, PhD

Background—We previously demonstrated that ischemic postconditioning decreases creatine kinase release, a surrogate marker for infarct size, in patients with acute myocardial infarction. Our objective was to determine whether ischemic postconditioning could afford (1) a persistent infarct size limitation and (2) an improved recovery of myocardial contractile function several months after infarction.

Methods and Results—Patients presenting within 6 hours of the onset of chest pain, with suspicion for a first ST-segment–elevation myocardial infarction, and for whom the clinical decision was made to treat with percutaneous coronary intervention, were eligible for enrollment. After reperfusion by direct stenting, 38 patients were randomly assigned to a control (no intervention; n=21) or postconditioned group (repeated inflation and deflation of the angioplasty balloon; n=17). Infarct size was assessed both by cardiac enzyme release during early reperfusion and by ^{201}thallium single photon emission computed tomography at 6 months after acute myocardial infarction. At 1 year, global and regional contractile function was evaluated by echocardiography. At 6 months after acute myocardial infarction, single photon emission computed tomography rest-redistribution index (a surrogate for infarct size) averaged 11.8±10.3% versus 19.5±13.3% in the postconditioned versus control group (P=0.04), in agreement with the significant reduction in creatine kinase and troponin I release observed in the postconditioned versus control group (−40% and −47%, respectively). At 1 year, the postconditioned group exhibited a 7% increase in left ventricular ejection fraction compared with control (P=0.04).

Conclusions—Postconditioning affords persistent infarct size reduction and improves long-term functional recovery in patients with acute myocardial infarction. **(*Circulation*. 2008;117:1037-1044.)**

Key Words: infarction ■ ischemia ■ myocardial infarction ■ postconditioning ■ reperfusion

Acute myocardial infarction (AMI) is a frequent and disabling disease, with nearly 1.5 million new cases each year in the United States.[1] Heart failure is a common outcome of AMI, with a mortality rate >50% at 5 years.[2] Studies have demonstrated that infarct size is a major determinant of prognosis after AMI.[3,4] Interventions aimed at reducing infarct size may therefore be of major clinical interest to improve the prognosis of AMI patients.

Clinical Perspective p 1044

Opening of the occluded coronary artery is the first treatment of AMI, and there is evidence that reperfusion improves long-term outcome.[5,6] However, experimental and clinical reports indicate that reperfusion has deleterious effects, including myocardial stunning, ventricular arrhythmias, and no reflow.[7] Although the existence of lethal reperfusion injury has been much debated,[8] Zhao et al[9] recently demonstrated in the dog model that repetition of brief episodes of ischemia immediately at the onset of reperfusion after a prolonged ischemic insult can dramatically reduce infarct size. This phenomenon (termed postconditioning), which clearly identifies reperfusion necrosis, has since been reported in several animal species.[10–15] Our group was the first to demonstrate that this protection also applies to the human heart.[16] In a "proof-of-concept" study, we showed that 4 episodes of 1-minute inflation/1-minute deflation of the angioplasty balloon immediately after a direct stenting of the occluded culprit coronary artery was able to reduce total creatine kinase (CK) release during reperfusion, an estimate of infarct size, by 36% in AMI patients.[16]

Received July 24, 2007; accepted December 24, 2007.

From the Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France (H.T., P.S., L.B., G.R., E.B., D.A., G.F., X.A.-F., R.R., R.I., G.K., G.D., M.O.); Hôpital Arnaud de Villeneuve, Montpellier, France (C.P., C.S., T.T.C., J.C.M., F.R.); Hôpital Saint Luc–Saint Joseph, Lyon, France (J.A.); and INSERM U886, Lyon, France (H.T., G.R., D.A., G.F., G.D., M.O.).

Clinical trial registration information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00419198.

Correspondence to Professor Michel Ovize, Hôpital L. Pradel, Hospices Civils de Lyon, 59, Bd Pinel, 69394 Lyon Cedex 03, France. E-mail ovize@sante.univ-lyon1.fr

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.107.729780**

Although that study was very encouraging, widespread use of postconditioning as an adjunct treatment targeting reperfusion injury in AMI patients requires demonstration of a persistent clinical benefit. To address this issue, we enrolled 38 patients with ongoing AMI in a prospective randomized controlled trial. After several months of follow-up, we assessed whether postconditioning had (1) afforded a sustained infarct size reduction (^{201}thallium single photon emission computed tomography [SPECT]) and (2) improved myocardial contractile function (echocardiography).

Methods

The study was performed according to the Declaration of Helsinki (revised version of Somerset West, Republic of South Africa, 1996) and according to the European Guidelines of Good Clinical Practice (version 11, July 1990) and French laws.

Study Population

Eligibility Criteria for Participants

This study population is fully different from that reported in the initial trial by Staat et al.[16] Male and female patients, aged >18 years, presenting within 6 hours of the onset of chest pain, who had ST-segment elevation >0.1 mV in 2 contiguous leads, and for whom the clinical decision was made to treat with percutaneous coronary intervention (PCI), were eligible for enrollment. The culprit coronary artery had to be either the left anterior descending artery or right coronary artery and to be occluded at the time of admission (Thrombolysis in Myocardial Infarction [TIMI] flow grade 0).[17]

Patients with cardiac arrest, cardiogenic shock, previous AMI, preinfarction angina within 48 hours (ie, potential benefit of protection by preconditioning), or evidence of coronary collaterals (Rentrop grade ≥1) to the risk region, as assessed by coronary angiography at admission, were not included.[18]

The study protocol was approved by the promotor of the study (Hospices Civils de Lyon) and the Ethics Committee of our institution. All subjects gave written informed consent before inclusion into the study.

Data Collection

Data from all 3 centers were collected by the principal investigator clinical research assistants at the Louis Pradel Cardiology Hospital, Lyon, France.

Interventions

Coronary angiography was performed by a standard technique. Acute biplane left ventricular (LV) angiography (30° right anterior oblique), performed just before coronary angioplasty, was used to measure the circumferential extent of the abnormally contracting segments, an estimate of the area at risk, as described previously.[16,19] The length of the abnormally contracting segments was determined by computerized planimetry and expressed as a percentage of the LV circumference. Coronary angioplasty was performed according to the direct stenting technique. After the tip of the guidewire had been positioned downstream of the culprit lesion, the balloon was inflated for ≈20 seconds at 12 to 16 bars for a proper implantation of the coronary stent. In the control group, no additional intervention was performed during the first 8 minutes of reperfusion. In the postconditioned group, within 1 minute of reflow after the direct stenting, the angioplasty balloon was reinflated 4 times for 1 minute, with low-pressure (4 to 6 atm) inflations, each separated by 1 minute of reflow.[16] After minute 8 of reperfusion, the PCI procedure was completed according to the physician's judgment with respect to patient status. The postconditioning protocol was feasible and safe in all patients allocated to this group.

Objectives

The primary objective of this study was to determine whether postconditioning might afford a persistent infarct size reduction, as assessed by SPECT imaging at 6 months after infarction. The secondary objective was to determine whether postconditioning might improve myocardial contractile function, as evaluated by echocardiography at 1 year.

Main Outcomes

All analyses, including that of SPECT imaging and echocardiography data, were performed by independent observers unaware of the treatment group. The PCI cardiologist in charge of the PCI procedure was not involved in any of the data analyses.

SPECT Imaging at 6 Months After Infarction

At 6 months after AMI, patients underwent SPECT imaging to estimate infarct size. After intravenous injection at rest of a nominal activity of 110 to 120 MBq of ^{201}thallium, a first SPECT acquisition was performed 10 to 15 minutes after injection with the use of a General Electric DSTi small field of view, double-head, rotating gamma camera. Four hours later, after tracer redistribution without reinjection, a second SPECT was acquired in the same conditions. Tracer uptake was quantified with the use of MyoQuant (Vision, General Electric) software.[20,21] From the observed myocardial perfusion defect, we measured (1) the area of impaired perfusion, termed defect size (expressed as a percentage of the entire LV), and (2) the mean ^{201}thallium uptake (expressed as a percentage of the perfusion in nonischemic regions) within the area of abnormal perfusion. From this, we calculated a perfusion defect index, which takes into account both the size (defect size) and the severity (percent reduction of ^{201}thallium uptake) of the myocardial perfusion deficit, with the following equation: perfusion defect index=(1−thallium uptake)×defect size. We used this rest-redistribution perfusion defect index as an estimate of infarct size.

Echocardiography at 1 Year After Infarction

Patients were scanned in the left supine position from an apical window with the use of Vivid 7 systems (GE-Vingmed, Milwaukee, Wis). LV volumes and LV ejection fraction were measured by biplane Simpson's rules.[22] To evaluate regional systolic function, the LV was divided according to the 16-segment model, as recommended by the American Society of Echocardiography.[22] For each segment, wall motion was scored from 1 (normal) to 4 (dyskinetic), and the wall motion score index was derived. Longitudinal strain rate was calculated from color tissue Doppler velocity data (calculation distance, 8 mm) with the use of dedicated software (Echopac, GE). We measured peak systolic strain rate during ejection time. Values were obtained by averaging 3 consecutive cardiac cycles and were expressed in seconds^{-1} (strain rate). These values are negative in shortening and positive in lengthening myocardium.

Early Estimation of Infarct Size by Release of Cardiac Enzymes

Blood samples were taken at admission and repeatedly during day 1 to 3. Area under the curve (arbitrary units) values of serum CK release and troponin I (TnI) (Beckman Kit, expressed in IU/L) were measured in each patient by computerized planimetry (Image J 1.29x).

Sample Size

Thirty-eight patients were enrolled prospectively into this multicenter, randomized, open-label, controlled protocol (Figure 1). Calculation of sample size was performed according to our primary objective, ie, assessment of infarct size by SPECT imaging at 6 months. Referring to the database of the Nuclear Medicine Department of our institution, with the bilateral hypothesis of a 35% reduction of infarct size (as previously reported in the Staat study), for $\alpha=0.05$ and $\beta=0.20$, we calculated that the sample size should be n=38.[16]

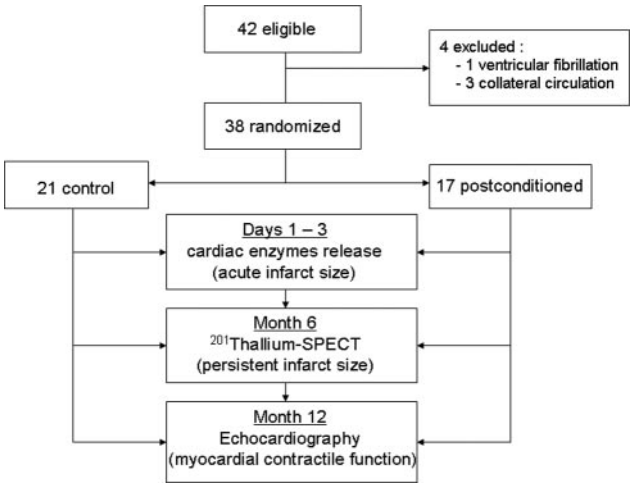

Figure 1. Flow diagram.

Treatment Allocation

Randomization envelopes containing the study group (control or postconditioned) had been prepared in advance by the promotor of the study (Hospices Civils de Lyon), following a preestablished randomization list and a computer-generated randomization sequence. Numbered sealed envelopes were placed in the catheterization laboratory for the study investigators. After evaluating whether a patient was eligible for the study, the PCI cardiologist informed the patient of the protocol. In case the patient had given informed consent, the PCI cardiologist asked the catheterization laboratory nurse to open a randomization envelope, and the protocol was applied accordingly.

Statistical Analysis

Comparison between continuous variables (area under the curve of serum CK or TnI release, time of ischemia, abnormally contracting segments, echocardiography LV ejection fraction, wall motion score index, and strain rate or SPECT rest-redistribution index) was performed with the use of an unequal variance Student *t* test. Categorical variables were examined with a Fisher exact test. To compare the treatment effect on infarct size after adjustment on the size of the area at risk, we performed an ANCOVA (Statview). Data are presented as mean±SD.

The authors declare that they had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Participant Flow

Forty-two patients, aged 56±18 years, were considered eligible to participate in the study between January 2005 and February 2007 (Figure 1). Among those 42 patients, 4 were excluded: 1 because of ventricular fibrillation before coronary angioplasty and 3 because of evidence of coronary collateral circulation to the area at risk. Results are presented for 38 patients and analyzed according to the intention-to-treat analysis principle. This population represents ≈25% of all ST-segment–elevation myocardial infarction (MI) patients admitted to our institution with a need of emergency revascularization by PCI. All patients received the study treatment as determined by the randomization procedure, without any crossover.

Baseline Data

None of the patients had had previous MI. No patient reported any episodes of chest pain within 48 hours before hospital admission (angina pectoris before AMI might have preconditioned the heart). At admission, heart rate and blood pressure, blood glucose levels, and ECG signs of ischemia were comparable between groups (Table 1). Parameters of LV and coronary artery disease were similar between the 2 groups (Table 1). At discharge, both groups had similar treatment except for a trend ($P=0.07$) toward a larger use of diuretics in the control group (Table 1).

Angioplasty Procedure

Angioplasty allowed a reperfusion TIMI flow grade >2 in all but 1 patient in each group. Stenting was performed in all cases without any adverse event. In the postconditioned group, repeated balloon inflations were performed safely.

Infarct Size

Cardiac Enzyme Release

The intention-to-treat analysis indicated that the area under the curve of serum CK release averaged 226 843±92 644 and 378 770±194 777 in the postconditioned versus control group, respectively (40% reduction in infarct size; $P=0.008$) (Table 2). For TnI release, the reduction averaged 47% ($P=0.001$). In the control group, there was a fair correlation between serum CK release and abnormally contracting segments, with CK=14 872×abnormally contracting segments−206 475 ($r^2=0.66$) ($r^2=0.75$ for TnI) (ANCOVA: $F_{1,35}=13\ 755$; $P<0.001$).

SPECT Imaging

SPECT imaging was performed at 5.2±2.4 months after AMI (Figure 2). None of the patients had displayed any clinical evidence of acute coronary syndrome since AMI. Area at risk (abnormally contracting segments at initial LV angiography) was similar between the 2 groups, averaging 3±13% and 40±8% in control and postconditioned groups, respectively. The perfusion defect index on redistribution SPECT, an estimate of infarct size, was significantly reduced in the postconditioned versus control group, averaging 11.8±10.3% versus 19.5±13.3%, respectively, which represents a 39% reduction ($P=0.04$) (Table 2).

Functional Recovery at 1 Year After AMI

Echocardiography was performed at 11.4±3.6 months after AMI. On the day of the echocardiography, heart rate and systolic and diastolic pressure were comparable between the 2 groups, averaging 64±12 bpm, 129±12 mm Hg, and 76±12 mm Hg in the postconditioned group versus 63±13 bpm, 121±16 mm Hg, and 68±13 mm Hg in the control group, respectively (P=NS). LV ejection fraction was significantly improved in the postconditioned versus the control group ($P=0.04$) (Table 2). Wall motion score index was significantly reduced in the postconditioned versus the control group ($P=0.02$). Although in the nonischemic region, peak systolic strain rate was similar between the 2 groups, it was significantly increased in the area at risk in the postconditioned versus control group ($P<0.001$) (Table 2).

Discussion

This randomized, controlled, single-blinded trial addressed whether ischemic postconditioning might afford persistent

Table 1. Baseline Characteristics

	Control Group (n=21)	Postconditioned Group (n=17)	P
Age, y	56±13	56±12	0.97
Male sex, %	78	76	0.64
Body mass index, kg/m^2	26±5	27±4	0.47
Hypertension, %	35	29	0.54
Smokers, %	65	65	0.63
Dyslipidemia, %	49	52	0.37
Diabetes, %	10	12	0.61
History of coronary artery disease, %	9	0	0.30
Admission blood glucose levels, μmol/L	8.4±2.3	8.8±2.8	0.65
Admission hemodynamics			
Heart rate, bpm	73±13	72±12	0.67
Systolic blood pressure, mm Hg	133±23	136±20	0.62
Diastolic blood pressure, mm Hg	84±13	83±12	0.87
Admission ST-segment elevation			
Contiguous leads with >1-mm ST shift, n	4.0±1.8	3.9±0.8	0.80
Maximum ST shift, mm	4.2±2.3	4.2±2.0	1.00
LV and coronary angiography			
Single-/multiple-vessel coronary artery disease, %	86/14	82/18	0.56
Culprit artery (left anterior descending), %	52	56	0.47
LV ejection fraction, %	46±5	44±8	0.51
Abnormally contracting segments, %	39±14	40±8	0.60
Ischemia time, min	297±104	283±82	0.35
Stenting of culprit lesion	100	100	1.00
Treatment before angioplasty, %			
Intravenous nitrates	48	50	0.57
Morphine	48	56	0.43
Treatment at time of angioplasty, %			
Heparin	91	100	0.30
Antiaggregants	100	100	1.00
Treatment at discharge, %			
β-Blockers	83	94	0.56
Angiotensin-converting enzyme inhibitors	88	89	0.60
Statins	94	89	0.42
Antiaggregants	100	100	1.00
Long-acting nitrates	12	11	0.65
Diuretics	33	6	0.07

Data are presented as percentage or as mean±SD. Patients' characteristics and treatment at hospital admission and discharge are presented.

Table 2. Infarct Size and LV Function

	Control Group (n=21)	Postconditioned Group (n=17)	P
Cardiac enzyme infarct size (at days 1 to 3)			
CK release (AUC $\times 10^4$)	37.9±19.5	22.7±9.3*	0.01
TnI release (AUC $\times 10^4$)	24.6±20.6	13.0±7.0*	0.02
SPECT infarct size (at 6 months)			
Perfusion defect index (%)	19.5±13.3	11.8±10.3*	0.04
LV function by echocardiography (at 12 months)			
LV ejection fraction, %	49±13	56±8*	0.04
Wall motion score index	1.6±0.4	1.4±0.4*	0.04
Strain rate, s^{-1}	0.6±0.4	1.2±0.8*	0.0002

Data are presented as mean±SD. AUC indicates area under the curve. Infarct size was assessed early (cardiac enzyme release) and at 6 months by SPECT imaging. LV function was evaluated at 12 months by echocardiography.
*$P<0.05$ vs control.

clinical benefit in patients with AMI. We report that, several months after AMI, postconditioning by angioplasty results (1) in a persistent infarct size limitation and (2) in a significant improvement in myocardial contractile function.

Persistent Infarct Size Reduction at 6 Months After Postconditioning

Our group demonstrated previously that postconditioning by angioplasty reduces infarct size, as assessed by early CK release, in the human heart.[16] This was the first study demonstrating that postconditioning can reduce lethal reperfusion injury in the human heart. In a retrospective study, Darling et al[23] similarly reported a reduced release of CK in ST-segment–elevation MI patients who underwent >4 inflations of the angioplasty balloon at the time of reperfusion compared with those who received <3 inflations. The present study is in agreement with the initial results of the Staat study, further reporting a mean reduction of 47% of the area under the curve of TnI in postconditioned versus control groups. This infarct size reduction was observed with the control and postconditioned groups having similar duration of ischemia and size of the area at risk, ie, 2 major determinants of infarct size. Area at risk was assessed by measurement of the percentage of abnormally contracting segments on admission LV angiography, according to the technique of Feild et al.[19] SPECT (eg, with the use of ^{99}technetium sestamibi) or magnetic resonance imaging might have afforded a more accurate estimation of the size of the area at risk. In this type of emergency situation, a rapid preparation of sestamibi and access to the Nuclear Medicine Department on a 24-hour basis was unfortunately not feasible in our study. Aletras et al[24] recently reported that magnetic resonance imaging could delineate the area at risk within 48 hours after AMI in the dog heart. To our knowledge, this interesting new technique has, however, not been reported in AMI patients. Meanwhile, estimation of the size of the area at risk with the use of LV angiography, as performed here, has been correlated with the area at risk as measured by SPECT imaging by Feild et al.[19]

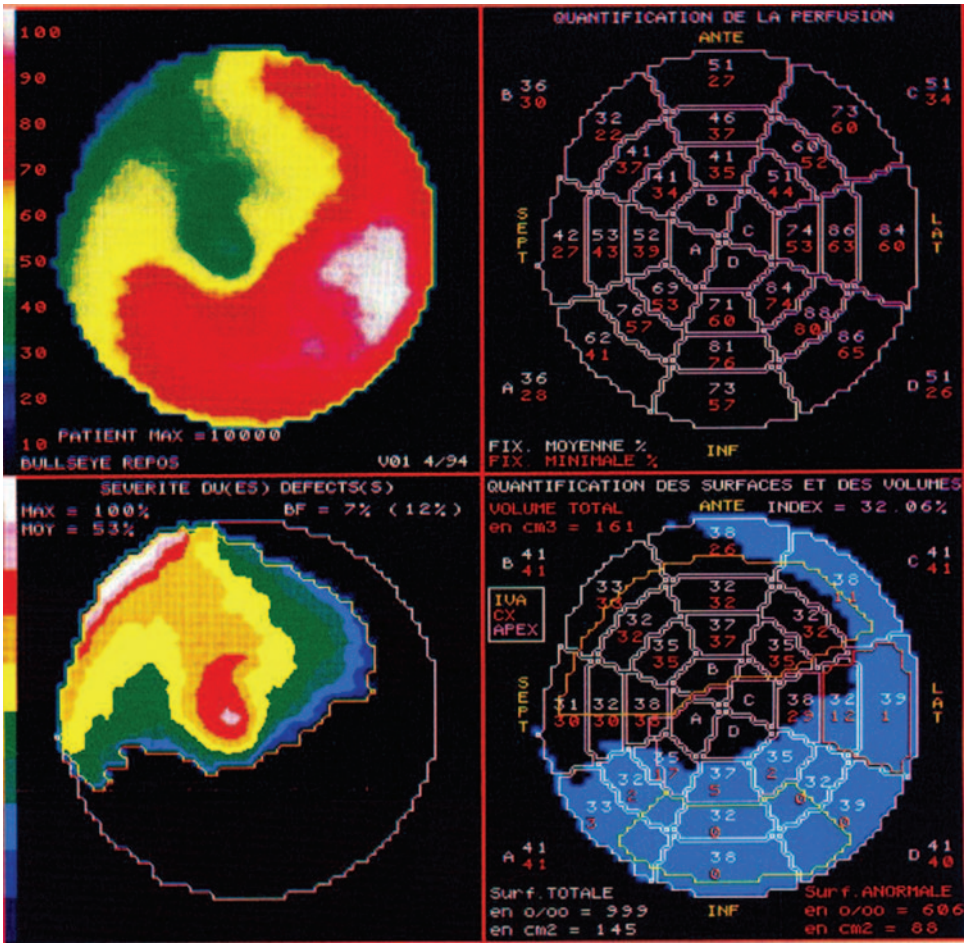

Figure 2. SPECT imaging at 6 months after infarction (typical example). Typical ^{201}thallium scintigraphy at 6 months after AMI. Color encoding depicts normal perfusion as red or white. Injured myocardium encompasses yellow, green, and blue zones.

One might question whether morphine, known as a preconditioning mimetic in experimental studies, might have modified infarct size in our patients. In the present study, morphine was administered intravenously at a dose of 2 to 4 mg, before hospital admission, in nearly 50% of patients in each group. Infarct size in the control group was not smaller than that reported in previous studies in ST-segment–elevation MI patients, and the amplitude of infarct size reduction observed in postconditioned patients was comparable to that reported in experimental preparations (30% to 40%) in the absence of morphine. Primarily, a subgroup analysis of the present study indicated that infarct size was not smaller in both control and postconditioned patients who received morphine versus those who did not. This suggests that morphine did not alter infarct size evaluation in our study.

Until now, whether infarct size reduction by postconditioning represents long-lasting protection was unknown. Cardiac enzyme release after reperfusion has long been used as a surrogate marker for infarct size.[25,26] Because cardiac enzyme release depends largely on the rate of reperfusion and myocardial healing takes several weeks after reperfusion, it cannot be ruled out that postconditioning might only delay, but not actually reduce, lethal reperfusion injury. We therefore measured infarct size 6 months after AMI, a time at which infarct healing is complete. We used rest-redistribution ^{201}thallium SPECT to quantify infarct size. The rest-redistribution index was reduced by 39% in postconditioned versus control patients, an amount of myocardial salvage comparable to that observed with the use of either CK or TnI release. One might wonder whether some degree of myocardial hibernation in the months after AMI might have modified the SPECT rest-redistribution index. Hibernating myocardium may display a reduced contractile function matched with a reduced myocardial blood flow.[27] Areas of hypoperfusion on SPECT scans would not then depict infarcted tissue only but a mixture of necrotic and peri-infarct hibernating myocardium. Assessment of perfusion-contraction matching was not possible in the present study because measurements of myocardial blood flow by SPECT and of LV function by echocardiography were not performed simultaneously. However, all study patients underwent a full revascularization of the infarcted territory by PCI. Although we did not repeat coronary angiography at 6 or 12 months, the fact that none of the patients underwent recurrent ischemia suggests that the dilated culprit coronary artery remained patent at 6 to 12 months after AMI. Therefore, the perfusion defect observed on SPECT images at rest very likely corresponded to irreversible myocardial damage rather than to a partial reduction of flow redistribution to an abnormally contracting peri-infarct tissue. This is further supported by the fact that, in

agreement with Licka et al,[28] we found a good correlation between the rest-redistribution perfusion index and CK release. In addition, the uptake of ^{201}thallium on rest-redistribution scans has been shown to correlate closely with sestamibi, which has been validated to measure infarct size and predict functional recovery.[3,29,30] The regional abnormality of contraction observed at 1 year by echocardiography likely did not represent "hibernating" myocardium per se but rather was probably the consequence of a tethering effect of the reperfused viable peri-infarct tissue to the underlying necrotic myocardium. Overall, rest-redistribution ^{201}thallium SPECT performed 6 months after AMI demonstrated that angioplasty postconditioning does not simply delay but truly and persistently reduces infarct size.

Improved Functional Recovery at 1 Year After AMI

Although reduction of infarct size is a major therapeutic goal, the long-term clinical benefit of any adjunctive treatment to reperfusion will rather result from the improvement of LV contractile function and prevention of heart failure. The control and postconditioned groups exhibited comparable LV ejection fraction at admission. One year later, the postconditioned group exhibited a significant 7% improvement in LV ejection fraction, above benefits afforded by established strategies to promote functional recovery after AMI, including PCI, β-blockers, and angiotensin-converting enzyme inhibitors. Quantitative analysis of regional contractile function clearly indicated a better functional recovery of the reperfused myocardium in postconditioned hearts. SPECT was performed at 6 months because healing of MI is considered complete at this time. Echocardiography was performed later than SPECT because LV remodeling is slower than infarct healing, and a potential moderate improvement of LV function was likely to be more easily detectable after 12 than after 6 months after AMI.

There is little doubt that improvement in contractile function at 1 year after AMI in postconditioned patients was a direct consequence of infarct size reduction. Myocardial stunning, which might mask any beneficial effect of infarct size reduction within days to weeks after AMI, no longer interferes after several months. Whether postconditioning might have any beneficial effect on contractile function per se remains unknown. However, Zhao et al[9] first reported that postconditioning does not improve myocardial segment shortening in the first 3 hours after reflow in the dog heart. Recently, Couvreur et al[31] and Vinten-Johansen et al[32] reported in dog and rabbit models of pure (ie, in the absence of irreversible tissue injury) myocardial stunning that postconditioning does not improve recovery of regional contractile function. By analogy, preconditioning that reduces infarct size to an extent comparable to that of postconditioning in animal models has no effect on contractile function early after reflow.[33] Once stunning of the still viable peri-infarct myocardium wanes as reperfusion time elapses, improved functional recovery is revealed, likely resulting from the diminished tethering effect of a reduced amount of infarcted tissue.[34,35]

Postconditioning Amends Lethal Reperfusion Injury in Humans

The study population of the present trial was small. On the one hand, this can be considered a limitation to the generalizability of its findings to the population at large. On the other hand, the fact that only 38 patients were sufficient to show such a clinical benefit of postconditioning clearly indicates the power of the protection. It further means that lethal reperfusion injury can damage a large amount of myocardial tissue in AMI patients (nearly 40% of the final infarct size). Besides conventional treatments that target either ischemia-induced damage (eg, early reperfusion or prevention of coronary reocclusion by antiaggregants), arrhythmogenesis (eg, β-blockers), or detrimental LV remodeling (eg, angiotensin-converting enzyme inhibitors), no treatment is currently aimed at attenuating lethal reperfusion injury. This study identifies lethal reperfusion injury as a new target that is amenable by a simple and safe intervention, ie, postconditioning. It further indicates that the long-term beneficial effects of postconditioning are due to a timely intervention performed within the first minutes of reflow. Consequently, it suggests that this major myocardial injury is initiated by intracellular molecular abnormalities, possibly including the opening of the mitochondrial permeability transition pore, that occur within the first minutes of reflow.[10,11,35,36]

Study Limitations

An important limitation of the present trial is the small size of the study population and the lack of outcome data. However, the primary objective was met, and we report that angioplasty postconditioning affords persistent benefit. Whether the conclusions of this trial can be extrapolated to a much larger number of AMI patients requires additional large-scale trials. However, this study population is typical of most populations of AMI patients. The baseline characteristics, catheterization laboratory procedures, and treatment at admission or at discharge were similar to those of the much larger populations of recent large-scale trials also performed in ST-segment–elevation MI patients treated by PCI.[37–40]

Conclusion

The present study supports the idea that postconditioning can afford persistent benefit after AMI. Additional trials are required to address the best strategies for a widespread use of postconditioning protection against lethal reperfusion injury in patients with ongoing AMI.

Acknowledgments

The authors are grateful to Valerie Prost and Alice Dubois for their excellent technical assistance in data monitoring.

Sources of Funding

This study was supported in part by a grant from Programme Hospitalier de Recherche Clinique 2005 from the French government. The funding source had no role in the design and conduct of the study, in the data collection, analysis, or interpretation, or in the preparation, review, or approval of the manuscript.

Disclosures

None.

References

1. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report for the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol*. 2004;44:e1–e211.
2. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. *Circulation*. 1998;97:282–289.
3. Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. *J Am Coll Cardiol*. 2004;44:1533–1542.
4. Burns RJ, Gibbons RJ, Yi Q, Roberts RS, Miller TD, Schaer GL, Anderson JL, Yusuf S; CORE Study Investigators. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following acute myocardial infarction treated by thrombolysis. *J Am Coll Cardiol*. 2002;39:30–36.
5. van Domburg RT, Sonnenschein K, Nieuwlaat R, Kamp O, Storm CJ, Bax JJ, Simoons ML. Sustained benefit 20 years after reperfusion therapy in acute myocardial infarction. *J Am Coll Cardiol*. 2005;546:15–20.
6. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet*. 1996;348:771–775.
7. Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 2. *Circulation*. 2001;104:3158–3167.
8. Kloner RA. Does reperfusion injury exist in humans? *J Am Coll Cardiol*. 1993;21:537–545.
9. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, Vinten-Johansen J. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol*. 2003;285:H579–H588.
10. Argaud L, Gateau-Roesch O, Raisky O, Loufouat J, Robert D, Ovize M. Postconditioning inhibits mitochondrial permeability transition. *Circulation*. 2005;111:194–197.
11. Tsang A, Hausenloy DJ, Mocanu MM, Yellon DM. Postconditioning: a form of modified reperfusion protects the myocardium by activating the phosphatidylinositol 3-kinase-Akt pathway. *Circ Res*. 2004;95:230–232.
12. Kin H, Zhao ZQ, Sun HY, Wang NP, Corvera JS, Halkos ME, Kerendi F, Guyton RA, Vinten-Johansen J. Postconditioning attenuates myocardial ischemia-reperfusion injury by inhibiting events in the early minutes of reperfusion. *Cardiovasc Res*. 2004;62:74–85.
13. Yang XM, Proctor JB, Cui L, Krieg T, Downey JM, Cohen MV. Multiple, brief coronary occlusions during early reperfusion protect rabbit hearts by targeting cell signaling pathways. *J Am Coll Cardiol*. 2004;44:1103–1110.
14. Heusch G. Postconditioning: old wine in a new bottle? *J Am Coll Cardiol*. 2004;44:1111–1112.
15. Heusch G, Büchert A, Feldhaus S, Schulz R. No loss of cardioprotection by postconditioning in connexion 43-deficient mice. *Basic Res Cardiol*. 2006;101:354–356.
16. Staat P, Rioufol G, Piot C, Cottin Y, Cung TT, L'Huillier I, Aupetit JF, Bonnefoy E, Finet G, Andre-Fouet X, Ovize M. Postconditioning the human heart. *Circulation*. 2005;112:2143–2148.
17. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P, Markis JE, Mueller H, Passamani ER, Powers ER, Rao AK, Robertson T, Ross A, Ryan TJ, Sobel BE, Willerson J, Williams DO, Zaret BL, Braunwald E. Thrombolysis in Myocardial Infarction (TIMI) trial, phase 1: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation*. 1987;76:142–154.
18. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon on human subjects. *J Am Coll Cardiol*. 1985;5:587–592.
19. Feild BJ, Russell RO Jr, Dowling JT, Rackley CE. Regional left ventricular performance in the year following myocardial infarction. *Circulation*. 1972;66:679–689.
20. Benoit T, Vivegnis D, Foulon J, Rigo P. Quantitative evaluation of myocardial single photon emission tomographic imaging: application to the measurement of perfusion defect size and severity. *Eur J Nucl Med*. 1996;23:1603–1612.
21. Bontemps L, Gabain M, Doudouh A, Felecan R, Ovize M, Bonnefoy E, Itti R. Severity and extent of perfusion defects provoked by transient coronary occlusion compared with myocardial damage observed after infarction. *Nucl Med Commun*. 2000;21:147–154.
22. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2:358–367.
23. Darling CE, Solari PB, Smith CS, Furman MI, Przyklenk K. Postconditioning the human heart: multiple balloon inflations during primary angioplasty may confer cardioprotection. *Basic Res Cardiol*. 2007;102:274–278.
24. Aletras AH, Tilak GS, Natanzon A, Hsu LY, Gonzalez FM, Hoyt RF, Arai AE. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. *Circulation*. 2006;113:1865–1870.
25. Roberts R, Henry PD, Sobel BE. An improved basis for enzymatic estimation of infarct size. *Circulation*. 1975;52:743–754.
26. Hackel DB, Reimer KA, Ideker RE, Mikat EM, Hartwell TD, Parker CB, Braunwald EB, Buja M, Gold HK, Jaffe AS. Comparison of enzymatic and anatomic estimates of myocardial infarct size in man. *Circulation*. 1984;70:824–835.
27. Heusch G, Schulz R, Rahimtoola SH. Myocardial hibernation: a delicate balance. *Am J Physiol*. 2005;288:H984–H999.
28. Licka M, Zimmermann R, Zehelein J, Dengler TJ, Katus HA, Kubler W. Troponin T concentrations 72 hours after myocardial infarction as a serological estimate of infarct size. *Heart*. 2002;87:520–524.
29. Udelson JE, Coleman PS, Metherall J, Pandian NG, Gomez AR, Griffith JL, Shea NL, Oates E, Konstam MA. Predicting recovery of severe regional dysfunction: comparison of resting scintigraphy with 201-T1 and 99m Tc-sestamibi. *Circulation*. 1994;89:2552–2561.
30. Christian TF, O'Connor MK, Hopfenspirger M, Gibbons RJ. Comparison of reinjection thallium 201 and resting technetium 99m sestamibi tomographic images for the quantification of infarct size after acute myocardial infarction. *J Nucl Cardiol*. 1994;1:17–28.
31. Couvreur N, Lucats L, Tissier R, Bize A, Berdeaux A, Ghaleb B. Differential effects of postconditioning on myocardial stunning and infarction: a study in conscious dogs and anesthetized rabbits. *Am J Physiol*. 2006;291:H1345–H1350.
32. Vinten-Johansen J, Zhao ZQ, Jiang R, Zatta AJ, Dobson GP. Preconditioning and postconditioning: innate cardioprotection from ischemia-reperfusion injury. *J Appl Physiol*. 2007;103:1441–1448.
33. Ovize M, Przyklenk K, Kloner RA. Preconditioning does not attenuate myocardial stunning. *Circulation*. 1992;85:2247–2254.
34. Cohen MV, Yang XM, Neumann T, Heusch G, Downey JM. Favorable remodeling enhances recovery of regional myocardial function in the weeks after infarction in ischemically preconditioned hearts. *Circulation*. 2000;102:579–583.
35. Gomez L, Thibault HB, Gharib A, Dumont JM, Vuagniaux G, Scalfaro P, Derumeaux G, Ovize M. Inhibition of mitochondrial permeability transition improves functional recovery and reduces mortality following acute myocardial infarction in mice. *Am J Physiol*. 2007;293:H1654–H1661.
36. Duchen MR, McGuinness O, Brown LA, Crompton M. On the involvement of a cyclosporin A sensitive mitochondrial pore in myocardial reperfusion injury. *Cardiovasc Res*. 1993;27:1790–1794.
37. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boullenger E, Machecourt J, Lacroute JM, Cassagnes J, Dissait F, Touboul P; Comparison of Angioplasty and Prehospital Thromboysis in Acute Myocardial Infarction Study Group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet*. 2002;360:825–829.
38. Granger CB, Mahaffey KW, Weaver WD, Theroux P, Hochman JS, Filloon TG, Rollins S, Todaro TG, Nicolau JC, Ruzyllo W, Armstrong

PW; COMMA Investigators. Pexelizumab, an anti-C5 complement antibody, as adjunctive therapy to primary percutaneous coronary intervention in acute myocardial infarction: the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial. *Circulation*. 2003;108:1184–1190.

39. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW; AMISTAD-II Investigators. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol*. 2005;45:1775–1780.
40. O'Neill WW, Martin JL, Dixon SR, Bartorelli AL, Trabattoni D, Oemrawsingh PV, Atsma DE, Chang M, Marquardt W, Oh JK, Krucoff MW, Gibbons RJ, Spears JR; AMIHOT Investigators. Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT): a prospective, randomized trial of intracoronary hyperoxemic reperfusion after percutaneous coronary intervention. *J Am Coll Cardiol*. 2007;50:397–405.

CLINICAL PERSPECTIVE

Infarct size is a major determinant of prognosis after acute myocardial infarction. Interventions aimed at reducing infarct size may therefore be of major clinical interest. Experimental and clinical reports indicate that reperfusion has deleterious effects, including myocardial stunning, ventricular arrhythmias, and no reflow. Zhao et al recently demonstrated in the dog model that repetition of brief episodes of ischemia immediately at the onset of reperfusion after a prolonged ischemic insult can dramatically reduce infarct size. This phenomenon, termed postconditioning, demonstrates the existence and the importance of reperfusion necrosis. We previously showed that 4 episodes of ischemia/reperfusion (1-minute inflation/1-minute deflation of the angioplasty balloon) immediately after direct stenting of the occluded culprit coronary artery reduced reperfusion release of total creatine kinase, an estimate of infarct size, by 36%. However, widespread use of postconditioning as an adjunct treatment targeting reperfusion injury in patients with acute myocardial infarction requires demonstration of a persistent clinical benefit. In the present prospective randomized controlled trial, we addressed whether postconditioning might (1) afford a sustained infarct size reduction (^{201}thallium single photon emission computed tomography) and (2) improve myocardial contractile function (echocardiography). We report here that postconditioned patients exhibited a persistent reduction of irreversible myocardial injury at 6 months after acute myocardial infarction and an improvement of regional and global left ventricular function at 1 year. Thus, targeting lethal reperfusion injury by postconditioning provides persistent clinical benefit to patients with acute myocardial infarction.

Long-Term Benefit of Postconditioning

Hélène Thibault, Christophe Piot, Patrick Staat, Laurence Bontemps, Catherine Sportouch, Gilles Rioufol, Thien Tri Cung, Eric Bonnefoy, Denis Angoulvant, Jean-François Aupetit, Gérard Finet, Xavier André-Fouët, Jean Christophe Macia, Franck Raczka, Rolland Rossi, Rolland Itti, Gilbert Kirkorian, Geneviève Derumeaux and Michel Ovize

Circulation. 2008;117:1037-1044; originally published online February 11, 2008;
doi: 10.1161/CIRCULATIONAHA.107.729780
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539