

Postconditioning the Human Heart

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Background—In animal models, brief periods of ischemia performed just at the time of reperfusion can reduce infarct size, a phenomenon called postconditioning. In this prospective, randomized, controlled, multicenter study, we investigated whether postconditioning may protect the human heart during coronary angioplasty for acute myocardial infarction.

Methods and Results—Thirty patients, submitted to coronary angioplasty for ongoing acute myocardial infarction, contributed to the study. Patients were randomly assigned to either a control or a postconditioning group. After reperfusion by direct stenting, control subjects underwent no further intervention, whereas postconditioning was performed within 1 minute of reflow by 4 episodes of 1-minute inflation and 1-minute deflation of the angioplasty balloon. Infarct size was assessed by measuring total creatine kinase release over 72 hours. Area at risk and collateral blood flow were estimated on left ventricular and coronary angiograms. No adverse events occurred in the postconditioning group. Determinants of infarct size, including ischemia time, size of the area at risk, and collateral flow, were comparable between the 2 groups. Area under the curve of creatine kinase release was significantly reduced in the postconditioning compared with the control group, averaging $208\,984 \pm 26\,576$ compared with $326\,095 \pm 48\,779$ (arbitrary units) in control subjects, ie, a 36% reduction in infarct size. Blush grade, a marker of myocardial reperfusion, was significantly increased in postconditioned compared with control subjects: 2.44 ± 0.17 versus 1.95 ± 0.27 , respectively ($P < 0.05$).

Conclusions—This study suggests that postconditioning by coronary angioplasty protects the human heart during acute myocardial infarction. (*Circulation*. 2005;112:2143-2148.)

Key Words: ischemia ■ myocardial infarction ■ postconditioning ■ reperfusion

Although the prognosis of acute myocardial infarction (AMI) has significantly improved, it represents a major cause of death and heart failure in industrialized countries.¹ Infarct size is an important determinant of the short- and long-term outcome after AMI.^{2,3} Reperfusion therapy for AMI has been shown to reduce mortality, yet it may also have deleterious effects, including myocardial necrosis and no reflow.⁴⁻⁶ Although major therapeutic advances have been made to improve AMI patients' prognosis, adjunct treatment to reperfusion that would actually reduce infarct size in humans is still lacking.

Editorial p 2085

Two decades ago, great hope arose from the description of ischemic preconditioning. Brief episodes of ischemia-reperfusion performed just before a prolonged coronary artery occlusion trigger an endogenous protection and dramatically limit infarct size in experimental preparations.⁷ Unfortunately, ischemic preconditioning is not feasible in clinical practice because the coronary artery is already occluded at the time of hospital admission of the AMI patient.

Recently, Zhao et al⁸ described in the dog model a phenomenon they called "postconditioning." Whereas preconditioning is triggered by brief episodes of ischemia-reperfusion performed just before a prolonged coronary artery occlusion, postconditioning is induced by a comparable sequence of reversible ischemia-reperfusion but is applied just after the prolonged ischemic insult. Protection afforded by postconditioning is as potent as that provided by preconditioning, whatever the species and experimental preparation.⁹⁻¹²

Unlike preconditioning, the experimental design of postconditioning theoretically allows direct application to the clinical settings, especially during PTCA. In this case, inflation and deflation of the angioplasty balloon after reopening of the coronary artery can mimic repetitive coronary artery clamping performed in postconditioning animal models.

Therefore, the objective of the present study was to determine whether brief episodes of ischemia-reperfusion performed during the first minutes of reperfusion by PTCA in patients with ongoing AMI can limit infarct size, ie, postcondition the human heart, and attenuate no reflow.

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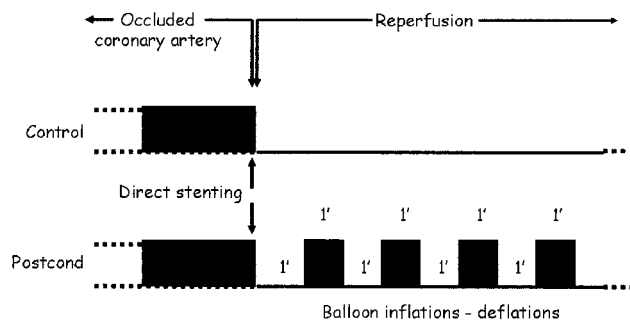


Figure 1. Experimental protocol. All patients underwent reperfusion of the occluded coronary artery by direct stenting. After reflow, control patients underwent no further intervention. In postconditioned patients, within 1 minute after direct stenting, the angioplasty balloon was reinflated 4 times during 1 minute (with a 1-minute intervening period). Thereafter, the angioplasty procedure was completed similarly in all patients. Black boxes indicate periods of ischemia.

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. The study protocol was approved by the ethics committee of our institution. All subjects gave written informed consent before inclusion.

Study Population

Male and female patients who were >18 years of age, presented within 6 hours after the onset of chest pain (consistent with ischemia lasting >30 minutes), and had ST-segment elevation >0.1 mV in 3 contiguous leads in whom the clinical decision had been made to treat with PTCA were eligible for enrollment. Patients with cardiac arrest, cardiogenic shock, or previous AMI were not included. The culprit coronary artery had to be either the left anterior descending or right coronary artery (to encompass large areas at risk), had to be occluded at the time of admission (TIMI 0 flow grade), and had to be adequately reperfused (TIMI 2 to 3 flow grade) after PTCA.¹³ Patients with evidence of coronary collaterals (Rentrop grade ≥ 1) to the risk region were excluded from the study.¹⁴

Experimental Design

This was a prospective, multicenter, randomized, open-label, controlled study. After the patients gave informed consent, they were randomly allocated to either the control or the postconditioned group (Figure 1).

Coronary Angioplasty

All patients were premedicated with hydroxyzine (Atarax, UCB Pharma) (50 mg per os, given 15 to 30 minutes before catheterization) and received aspirin (250 mg IV) and heparin (30 IU/kg). Coronary angiography was performed using a standard Seldinger technique. Sodium plus meglumine ioxaglate (Hexabrix, Guerbet) was used as contrast agent for coronary angiography. Acute biplane left ventriculography (30° right anterior oblique, 60° left anterior oblique) was performed just before revascularization. The size of the area at risk in each patient was estimated by measuring the circumferential extent of abnormally contracting segments (ACSs) according to the method of Feild et al.¹⁵ Coronary angiography allowed identification of the culprit coronary artery and checked that reperfusion had not occurred before PTCA (TIMI 0 flow grade) and that no collateral filling from homolateral or contralateral coronary vessels was present.¹⁴ Coronary angioplasty was performed according to the direct stenting technique to reperfuse in 1 time the coronary artery. After implantation of the coronary stent, the angioplasty balloon was quickly deflated and withdrawn just upstream of the stent; then, reperfusion was checked by a single

contrast shot. Only patients with a TIMI grade 2 to 3 TIMI coronary flow after stent implantation were kept in the study.

Experimental Protocol

In the control group, no additional intervention was performed during the first 8 minutes of reperfusion (Figure 1). In the postconditioned group, within 1 minute of reflow after the direct stenting, the angioplasty balloon was positioned just upstream of the implanted stent (so that it would not be damaged and to prevent possible thrombi embolization during in-stent balloon reinflation) and re-inflated 4 times for 1 minute with low-pressure (4 to 6 atm) inflations, each separated by 1 minute of reflow (Figure 1).¹⁶ This sequence of 4 brief episodes of ischemia-reperfusion was chosen arbitrarily because we recently demonstrated that a similar regimen triggers postconditioning in the rabbit heart.¹⁷ When the balloon was positioned just upstream of the implanted stent in the postconditioned group, care was taken not to encompass a coronary branch. At minute 8, coronary angiography was performed in both groups to assess coronary patency and to estimate the myocardial perfusion index using the blush grade evaluation.¹⁸ The angioplasty procedure was then completed according to physician judgment with respect to patient status.

Analysis

We prospectively decided that patients with the following characteristics would be excluded from the study: (1) evidence of coronary collaterals (Rentrop grade ≥ 1) to the risk region as assessed by coronary angiography, (2) preinfarction angina within 48 hours, and (3) failure to obtain a reperfusion TIMI grade 2 to 3 flow.

Left Ventricular Angiography

Left ventricular angiography (30° right anterior oblique, 60° left anterior oblique) was performed just before coronary angioplasty. It was used to evaluate the size of the risk region, a major determinant of infarct size.¹⁹ For each patient, the circumferential extent of wall motion abnormality (severely hypokinetic, akinetic, or dyskinetic segments) was measured according to the method of Feild et al.¹⁵ 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 1.29x software). ACS was expressed (percentage) as follows: ACS equals abnormally contracting length of end-diastolic circumference divided by total end-diastolic circumference times 100.^{15,20} This measure was performed by an experienced investigator unaware of the patient's group. TIMI flow grades, assessing coronary flow at the epicardial coronary artery level, were assessed as previously described: grade 0=no perfusion, grade 1=penetration without perfusion, grade 2=partial perfusion, and grade 3=complete perfusion.¹³ Grading of myocardial blush, which estimates reperfusion at the myocardial level, was performed according to the description of van't Hof et al.¹⁸: grade 0=no myocardial blush, grade 1=minimal myocardial blush, grade 2=moderate myocardial blush, and grade 3=normal myocardial blush. Both TIMI flow and myocardial blush were graded on the angiograms performed immediately before and after PTCA by 2 experienced investigators who were blinded to all data apart from the coronary angiograms.

ECG

Standard 12-lead ECGs were recorded at admission and 48 hours later. Maximal ST-segment change was measured by a cardiologist unaware of the patient's group. At all time points, ST-segment shift was measured 80 ms after the J point.

Serum Creatine Kinase Release During the First 72 Hours After PTCA

Blood samples were taken at admission, every 4 hours after opening of the coronary artery during day 1, and every 6 hours on days 2 and 3. Area under the curve (AUC; arbitrary units) of serum creatine kinase CK release (Beckman Kit, expressed in IU/L) was measured

Baseline Characteristics of the Study Population

	Control	Postconditioned	P
Age, y	56±3	58±4	NS
Sex, M/F	13/14	12/16	NS
BMI, kg/m ²	27±1	28±1	NS
HBP, %	36	38	NS
Smokers, %	56	57	NS
Dyslipidemia, %	50	80	NS
Diabetes, %	13	20	NS
LV and coronary angiography			
Culprit artery (LAD/RCA), n	6/8	6/10	NS
Ejection fraction, %	49±4	52±2	NS
ACS, % endocardial end-diastolic circumference	34±2	37±3	NS

Age, sex, body mass index (BMI), percentage of patients with high blood pressure (HBP), smokers, dyslipidemia, and diabetes are presented. Distribution of the culprit lesion between left anterior descending (LAD) and right coronary artery (RCA), percentage of left ventricular (LV) ejection fraction, and percentage of ACS are described.

in each patient by computerized planimetry (Image J 1.29x) and used as a surrogate marker of infarct size.

Statistical Analysis

Comparison between the AUC of serum CK release, time of ischemia, ACS (circumferential extent of ACSs), blush grade, and ST-segment shift was performed with the Student *t* test. For analysis of the difference between groups in the relationship between CK release and ACS, we used a conventional general linear model procedure. We adjusted the treatment effect on infarct size of postconditioning on the size of the area at risk (covariate) and applied a protected least significant difference (PLSD) Fisher's test (Statview software). All values are expressed as mean±SEM. A value of *P*<0.05 was considered statistically significant.

Results

Characteristics of the Study Population

Thirty-three patients (6 women, 27 men) 58±3 years of age were included in the present study. The Table summarizes the main characteristics of the study population. Three patients were excluded from the study: 2 because of Rentrop grade 2 and 3 collateral coronary circulation to the area at risk and 1 because of failure to obtain adequate reperfusion (TIMI flow grade 1 after PTCA). There was no difference between the 2 groups with regard to ongoing medication at the time of admission. Time from onset of chest pain to reperfusion (ie, ischemia time) averaged 331±40 minutes in the control compared with 318±38 minutes in the postconditioned group (*P*=NS). Mean heart rate and blood pressure at hospital admission were comparable between the 2 groups.

Coronary Angiography and PTCA

PTCA was successfully performed in all 30 patients. Left ventricular angiography was performed in 25 of the 30 patients (12 control, 13 postconditioned). The ACS (percentage of ACS) before reperfusion was comparable in the 2 groups, averaging 34.3±2.4% in the control compared with 37.1±2.6% in the postconditioned group (*P*=NS). Similarly, the mean number of ECG leads with a >1-mm segment shift

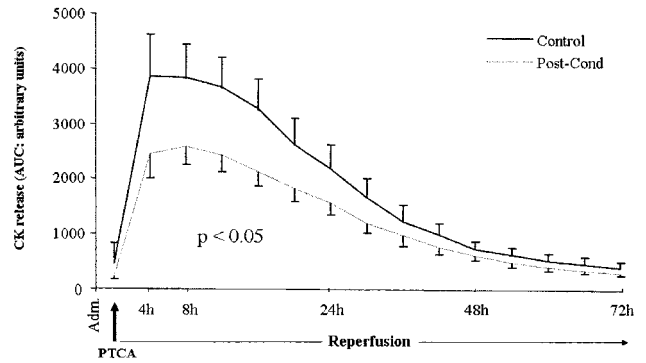


Figure 2. Serum CK release over the first 72 hours of reperfusion. AUC (arbitrary units) of serum CK release was measured in control (solid line) and postconditioned (dotted line) patients. There was a significant 36% reduction in the AUC of CK release for postconditioned vs control (*P*<0.05).

at admission was comparable between the 2 groups, averaging 4.59±0.64 in the control group and 4.22±0.74 in the postconditioned group (*P*=NS).

Enzymatic Infarct Size

The AUC (arbitrary units) of serum CK release during the first 72 hours of reperfusion was significantly reduced in the postconditioned group compared with the control group, averaging 208 984±26 576 in postconditioned compared with 326 095±48 779, which represents a 36% reduction in infarct size (*P*<0.05) (Figure 2). The peak of CK release was markedly lower in the postconditioned (2831±404 IU/L) than in the control (4234±722 IU/L) group (*P*<0.05). In the control group, there was a significant correlation between serum CK release and ACS, with CK=15 996×ACS−198 993 (*r*²=0.52, *P*<0.05). Importantly, most data points for the postconditioned group were below the control regression line, indicating that for any given size of the risk region, postconditioned hearts developed smaller infarcts (Figure 3). This was confirmed by analysis of covariance (*F*=5.33; *P*=0.03).

ST-Segment Shift and Blush Grade During Reflow

The blush grade was significantly higher in postconditioned than in control hearts, averaging 2.44±0.18 and 1.79±0.28, respectively (*P*=0.02) (Figure 4). At the time of admission,

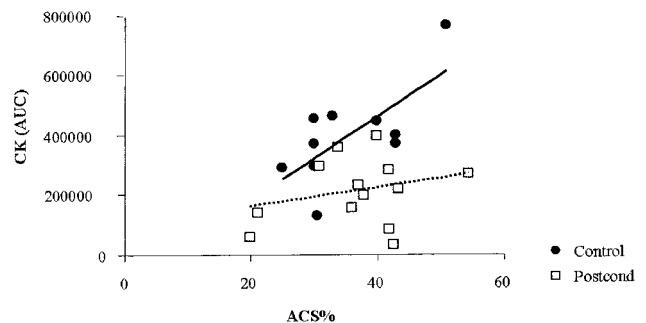


Figure 3. Serum CK release vs area of ACSs. AUC of serum CK release was plotted vs ACS, a surrogate marker of the size of the area at risk. There is a significant correlation between the 2 factors in the control group (●) (*r*²=0.52). Data points for the postconditioned group (□) lie below the control line.

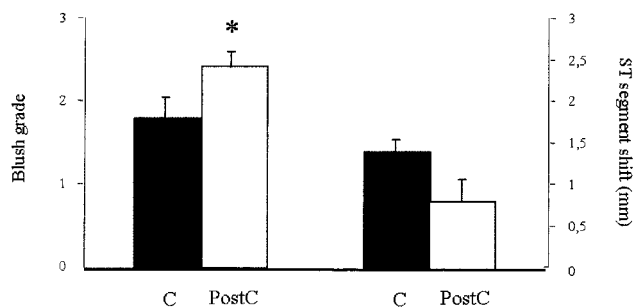


Figure 4. Blush grade and ST-segment shift during reperfusion. The blush grade was significantly higher in postconditioned (PostC) than in control hearts (C). At 48 hours after PTCA, maximal ST-segment elevation was reduced in the postconditioned group ($P=0.09$).

maximal ST-segment shift was comparable in the 2 groups, averaging 4.65 ± 0.68 and 4.28 ± 0.61 mm in the control and postconditioned groups, respectively ($P=NS$). At 48 hours after PTCA, mean ST-segment elevation averaged 1.39 ± 0.30 mm in the control group compared with 0.82 ± 0.27 mm in the postconditioned group ($P=0.09$).

Discussion

This multicenter, randomized, controlled study demonstrates for the first time that postconditioning during coronary angioplasty protects the human heart.

Zhao et al⁸ recently demonstrated in the dog model that repetition of brief episodes of ischemia-reperfusion, performed just at the time of reflow after a prolonged ischemic insult, dramatically reduces infarct size. This observation has been confirmed by several investigators in in vivo and ex vivo animal preparations in which infarct size limitation afforded by postconditioning was very comparable to that observed with ischemic preconditioning.^{9–12} The mechanisms involved in postconditioning protection take place within the first minutes of reperfusion.^{8,11,12} Experimental studies suggest that infarct size reduction involves activation of the PI3-kinase–endothelial nitric oxide synthase–Akt pathway at the time of reflow.^{9,12,21} Argaud et al,¹⁷ Hausenloy et al,²² and Javadov et al²³ recently reported that postconditioning inhibits opening of the mitochondrial permeability transition pore, which had previously been involved in lethal reperfusion injury after sustained ischemia-reperfusion.²⁴ The antinecrotic effect of postconditioning is associated with beneficial anti-inflammatory and antioxidant effects that may not necessarily be directly related to the abovementioned molecular pathways. Zhao et al⁸ demonstrated in the dog model that postconditioning limits tissue edema within the myocardial area at risk, attenuates polymorphonuclear accumulation, and protects endothelial function. Sun et al²⁵ reported in primary cultured neonatal cardiomyocytes that postconditioning reduces reactive oxygen species generation and subsequent lipid peroxidation and attenuates intracellular and mitochondrial calcium concentrations. Galagudza et al²⁶ recently reported that postconditioning may convert ventricular fibrillation into regular rhythm in the isolated rat heart, whereas Halkos et al²⁷ reported a reduced incidence of reperfusion ventricular fibrillation in postconditioned dogs.

Unlike ischemic preconditioning, postconditioning offers the unique opportunity to be applied in clinical practice, because the episodes of brief ischemia-reperfusion can be performed at the time of reflow during the PTCA procedure. In the present study, the angioplasty balloon was inflated and deflated 4 times for 1 minute, starting within 1 minute of reflow. An important observation of the present study is that this angioplasty protocol was feasible and safe. The postconditioning regimen induced no complication (eg, coronary artery dissection, stent damage, acute reocclusion) and was well tolerated by the patients, who displayed no adverse event during the procedure and the 3-day hospital follow-up.

The major finding of this study is that postconditioning reduced infarct size by 36%. The reduced enzymatic infarct size observed here closely resembles that reported in the preconditioned human heart by Kloner et al²⁸ and Ottani et al.²⁹ CK release is a surrogate end point that has been validated with respect to SPECT imaging in several studies and represents a useful and easily available technique to evaluate irreversible myocardial injury in clinical practice.³⁰ In this particular clinical situation of emergency PTCA for AMI, we tried to assess the major determinants of infarct size, ie, ischemia time, size of the area at risk, and collateral flow. Ischemia time was similar in the 2 groups. Area at risk was assessed by measuring the percentage of ACSs on predilatation left ventricular angiography.^{15,20} SPECT imaging using ⁹⁹Tc-sestamibi, likely the more adequate way to assess the size of the risk region in human undergoing PTCA, was not possible on a 24-hour basis in the 4 centers that participated to this study.^{31,32} Yet, the control and postconditioned groups exhibited comparable mean percentages of ACSs, which have otherwise been correlated with ⁹⁹Tc-sestamibi estimation of myocardium at risk.^{33,34} Moreover, we observed a significant correlation between CK release and area of ACS in the control group. This relationship is very similar to what is usually seen in experimental preparations using reference techniques such as blue dye and triphenyltetrazolium staining to delineate risk region and necrotic myocardium, respectively.^{35,36} This strongly suggests that the area of ACS is a valid estimate of the area at risk in the present study. As depicted in Figure 3, most data points for the postconditioned group lie below the control line, indicating that postconditioning limits infarct size for any size of the area at risk. Finally, coronary collateral circulation was assessed with the Rentrop score, and all included patients had a grade 0 coronary collateral flow.¹⁴ Note that the use of coronary flow or pressure Doppler guidewire would have rendered the protocol of postconditioning in the early minutes of reflow impossible. Overall, our data strongly suggest that infarct size reduction was not due to a difference in either major determinant of infarct size but actually reflects a protective effect of postconditioning. Although CK release was assessed over a 72-hour reperfusion period, further studies are needed to confirm, eg, with techniques like SPECT or MRI performed weeks to months after AMI, that infarct size reduction is permanent.

The amplitude of infarct size reduction appears to be in the low range of that reported in animal models, which usually ranges from 25% to 70%.^{8–12,17} Besides species differences, animals are without the comorbidities (eg, hypertension,

hypercholesterolemia, and diabetes) observed in our patients. Note also that experimental preparations are usually set up (especially with regard to the duration of ischemia) to allow demonstration of the largest effect for a given intervention. In clinical practice, a comparable 30% to 40% infarct size reduction has been observed with protective pharmacological interventions (eg, adenosine) performed at the time of reperfusion.³⁷

It is worth noting that the blush grade was significantly improved in the postconditioned group, whereas there was a trend, although not significant, toward a diminution of ST-segment shift at 48 hours of reperfusion. Blush grade has been proposed as a marker of myocardial perfusion in the first minutes of reflow.^{18,38} van't Hof¹⁸ reported blush grade as a marker of long-term mortality in AMI patients. Schröder³⁹ demonstrated that ST regression after reperfusion is another end point that indicate a preserved myocardial perfusion after AMI. Reduction in ST elevation was not significant ($P=0.09$) in the present study, possibly because ECG was performed at 48 hours of reflow instead of 90 minutes, as usually recommended, and because of insufficient statistical power.¹⁸ On the other hand, experimental studies indicate that myocardial blood flow may vary up to 48 hours after reperfusion in the area at risk after prolonged ischemia-reperfusion.⁴⁰ Overall, our data suggest that no reflow was possibly attenuated in postconditioned patients. This is in line with a report by Zhao et al⁸ of a protective effect on endothelial function after ischemia-reperfusion in the dog model of postconditioning, although endothelial dysfunction is only one component of the no-reflow phenomenon. Nevertheless, further studies with long-term follow-up are needed to determine how this early beneficial effect on myocardial perfusion translates into functional improvement in postconditioned patients.

Obtaining such a beneficial effect by simple manipulation of reperfusion is of major potential clinical interest. Whether ischemic postconditioning has to be performed as such in daily clinical practice is an unanswered question. Obviously, it represents a feasible, safe, and efficient cardioprotective intervention. Additional studies are needed to address its effect on postischemic functional recovery, no reflow, and even cardiovascular morbidity within the months after AMI. Unfortunately, all patients with AMI will not be able to benefit from such a treatment, including those who are not selected to receive PTCA. Important research must be done to understand the molecular mechanism of this protection to develop new drugs to apply pharmacological postconditioning to all patients with AMI.

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