JACC: CARDIOVASCULAR IMAGING VOL. 7, NO. 6, 2014

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2014.01.017

iCONCEPTS

CONCEPTS ON THE VERGE OF TRANSLATION

Clinical Pacing Post-Conditioning During Revascularization After AMI

Johannes Waltenberger, MD,*† Marloes Gelissen, BS,*‡ Sebastiaan C. Bekkers, MD, PhD,* Jindra Vainer, MD,* Vincent van Ommen, MD, PhD,* Filip Eerens, MD,* Alexander Ruiters, MD,* Alexa Holthuijsen, RN,* Paqui Cuesta, PhD,§ Racho Strauven, MS, MS,§ Eric Mokelke, MS,‖ Anton Gorgels, MD, PhD,* Frits W. Prinzen, MD, PhD‡

Maastricht, the Netherlands; Münster, Germany; Diegem, Belgium; and St. Paul, Minnesota

Intermittent dyssynchrony, induced by ventricular pacing, during early reperfusion reduces infarct size in pre-clinical studies. We evaluated cardioprotection by pacing post-conditioning (PPC) in ST-segment elevation myocardial infarction in a randomized, controlled, single-center, single-blinded, first-in-man study. Patients with first ST-segment elevation myocardial infarction received either PPC plus percutaneous coronary intervention (PCI) (n = 30) or PCI (n = 30). PPC consisted of 10 episodes of 30-s right ventricular pacing. Infarct size was measured as the area under the curve of creatine kinase (CK) (primary endpoint) and by contrast-enhanced cardiac magnetic resonance. The CK area under the curve was not significantly different between study groups. Adjusted contrast-enhanced cardiac magnetic resonance data showed ~25% smaller infarct size in PPC + PCI than in PCI patients after 4 days (p = 0.01), 4 months (p = 0.02), and 1 year of PCI (p = 0.08). In PPC + PCI, (uncomplicated) ventricular fibrillation (n = 3) and paroxysmal atrial fibrillation (n = 4) were observed as opposed to 1 and 0 cases in PCI, respectively. We conclude PPC is feasible and may induce cardioprotection during PCI treatment of ST-segment elevation myocardial infarction, but technical improvements are needed to improve safety. (PROTECT: Pacing to Protect Heart for Damage From Blocked Heart Vessel and From Re-opening Blocked Vessel[s]; NCT00409604) (J Am Coll Cardiol Img 2014;7:620–6) © 2014 by the American College of Cardiology Foundation

From the *Department of Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, the Netherlands; †Department of Cardiovascular Medicine, University Hospital Münster, Münster, Germany; ‡Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical Center, Maastricht, the Netherlands; §Boston Scientific, Diegem, Belgium; and ‖Boston Scientific, St. Paul, Minnesota. This study was supported by a research grant from Boston Scientific (Dr. Prinzen) and the Cardiovascular Research Institute Maastricht (Drs. Waltenberger and Prinzen). Dr. Cuesta owns shares of Boston Scientific Corporation. Dr. Prinzen has received research grants from Medtronic Inc., EBR Systems, Boston Scientific Corporation, MSD Sharp & Dohme, and Biological Delivery Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received November 5, 2013; revised manuscript received January 22, 2014, accepted January 23, 2014.

One of the most interesting and promising ways to protect the heart during an ischemic attack is post-conditioning through interventions in the early reperfusion phase. Post-conditioning has been proven to be effective in many studies and has the potential to be applied in the clinic as it can be performed at the time of reperfusion. Various triggers may induce post-conditioning, such as repeated coronary reocclusion in the early reperfusion phase (ischemic post-conditioning [IPoC]). Also drugs (cyclosporine-A) and remote ischemic conditioning can exert cardioprotection (see Hausenloy and Yellon (1) for review).

We previously demonstrated that in rabbit and pig hearts protection can also be achieved by brief periods of ventricular pacing in the early reperfusion phase (pacing post-conditioning [PPC]). PPC appears to act through a different trigger than IPoC does, which presumably is related to mechanical stimuli. The aim of the present study was to determine whether the application of PPC during primary percutaneous coronary intervention (PCI) in STEMI can protect the human heart from ischemia/reperfusion injury.

Trial. The PROTECT (Pacing to Protect Heart for Damage From Blocked Heart Vessel and From Reopening Blocked Vessel[s]) study was a prospective, single-center, randomized, single-blinded, controlled first-in-man trial. The study was performed in accordance with the Declaration of Helsinki (revised version, 2004) and with ISO (International Organization for Standardization) guidelines 14155-1:2003 and 14155-2:203. In accordance with Dutch law, the study protocol was approved by the ethics committee of the Maastricht University Medical Center. All subjects gave witnessed oral informed consent before inclusion in the study (before PCI) and an extended written informed consent 1 to 6 days after PCI.

We included men and women ≥18 years of age who presented with their first documented myocardial infarction and were admitted to the hospital 1 to 6 h after symptom onset with clinical decision for treatment with primary PCI.

We excluded patients with any of the following: clinical or hemodynamic instability requiring mechanical or pharmacological circulatory support; bradycardia (second- or third-degree atrioventricular block) requiring antibradycardia pacing prior to enrollment; tachycardia (>120 beats/min) at the time of enrollment; permanent atrial fibrillation (AF), history of ventricular fibrillation (VF), implanted pacemaker, implantable cardioverter-defibrillator or cardiac resynchronization therapy device; previous PCI and/or coronary artery bypass graft; stroke or cerebrovascular surgery (within 12 months); receiving thrombolytics upon clinical presentation; mechanical tricuspid valve; and diabetes treated by peroxisome proliferator-activated receptor agonists and/or fibrates.

Dropout criteria include the following: reference vessel diameter <3.0 mm at coronary angiography; TIMI (Thrombolysis In Myocardial Infarction) flow grade ≥2; non–infarct-related coronary lesions that cannot be left untreated during the follow-up period (physician's discretion).

Withdrawal criteria include the following: failure to position right ventricular pacing lead; atrial fibrillation at the time of PCI; intrinsic heart rate >120 beats/min between the time of guidewire advancement across the lesion (t0) and t0 + 10 min, or at the time of ventricular pacing; bradycardia (second- or third-degree atrioventricular block) causing symptomatic hypotension or heart failure, requiring antibradycardia pacing during PCI procedure; loss to follow-up; refusal of testing; consent withdrawal; and investigator's decision.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CE-CMR = contrast-enhanced cardiac magnetic resonance
CK = creatine kinase
IPoC = ischemic post-conditioning
LV = left ventricular
PCI = percutaneous coronary intervention
PPC = pacing post-conditioning
TIMI = Thrombolysis In Myocardial Infarction
VF = ventricular fibrillation

Pacing protocol. Patients randomized to the PPC + PCI group received a temporary pacing wire (Pacel bipolar pacing catheter, St. Jude Medical, St. Paul, Minnesota) via the femoral vein, positioned in the right ventricular apex and connected to an external pacemaker (Medtronic 5348, Medtronic Inc., Minneapolis, Minnesota). PPC started when the guidewire crossed the lesion and consisted of 10 cycles of 30 s pacing off and 30 s pacing on. Pacing was performed in the ventricular inhibited mode, 10 to 20 beats/min above intrinsic sinus rhythm.

Infarct size assessment. The primary endpoint was infarct size as assessed by plasma levels of creatine kinase (CK). Blood samples were obtained at hospital admission and after 3, 6, 9, 12, 24, 36, 48, 60, and 72 h. Also lactate dehydrogenase was analyzed and the area under the curve was determined. In addition, infarct size was assessed by serial contrast-enhanced cardiac magnetic resonance (CE-CMR), which is currently the gold standard in infarct size determination.

CMR imaging protocol. CMR was performed 4 days, 4 months, and 12 months after PCI. Left ventricular (LV) function was assessed using breath-hold electrocardiogram-gated steady-state free-precession cine imaging in the cardiac short

axis and vertical and horizontal long axes. Contrast-enhanced images were acquired 10 min after intravenous administration of 0.2 mmol/kg gadolinium-diethylenetriaminepentaacetic acid (Magnevist, Schering, Germany) using single breath-hold, 3-dimensional inversion recovery gradient-echo sequence completely covering the LV.

Image analysis. CE-CMR images were analyzed using CAAS MRV software (version 3.0, Pie Medical Imaging, Maastricht, the Netherlands) blinded to clinical information. After tracing endocardial and epicardial borders, infarct size was assessed using a signal intensity threshold of 5 SD above the signal intensity of remote non-infarcted myocardium in the same slice. Infarct size was expressed as percent of LV mass and included any central areas of hypoenhancement within the area of hyperenhancement (microvascular obstruction).

Analysis of arrhythmias. Immediately upon inclusion, the patients received a Holter monitor (DR180+, NorthEast Monitoring Inc., Maynard, Massachusetts) for 24-h recording. Data were analyzed using Holter LX Pro software (NorthEast Monitoring). Arrhythmias evaluated by the core laboratory were VF, ventricular tachycardia, ventricular extrasystoles (discriminating among nonsustained ventricular tachycardia and pairs and single extrasystoles), and AF.

Power calculation and statistical analysis. Assuming an effect of therapy on infarct size reduction of 40% and a SD of infarct size within groups of 30%, a group size of 25 patients was required to reach a level of significance of 0.05 with a power of 0.90. Descriptive statistics for randomized groups were generated and comparisons of baseline characteristics were performed using Student *t* or chi-square tests as appropriate. The analyses of differences in infarct size and ventricular dimensions were performed using linear models, taking into account the repeated nature of these measurements. After finding significant interactions of the variables treated artery, absolute ST-segment deviation, and time from first symptom with infarct size, as measured by CE-CMR, data were adjusted for these 3 variables using analysis of covariance. A p value <0.05 was considered significant.

Results. Patient flow is depicted in Figure 1. In the control group, 3 patients were withdrawn due to unsuccessful PCI. In the therapy group, 2 patients were withdrawn due to VF before pacing, 1 due to AF before pacing, and 1 due to consent withdrawal. One additional patient in the control group was excluded from analysis because of a gross error in estimating ischemia time (on the basis of clinical information). Thus, following patient withdrawal and exclusion, primary endpoint data was analyzed from 52 patients.

Characteristics of the control and therapy groups are presented in Table 1. Groups were generally comparable, but on average, the therapy group had longer time from symptom onset to hospital admission and higher ST-segment deviations than did the control group, whereas the latter had a higher number of right coronary artery occlusions.

Figure 2 shows typical examples of CE-CMR images obtained at 4 days, 4 months, and 1 year after PCI in 1 patient of the control group and 1 from the therapy group. CE-CMR infarct size showed a significant correlation to the maximum ST-segment deviation before PCI. The slope of the regression line was smaller in the therapy group than in the control group (Fig. 3A). Of note, the 5 largest values for ST-segment deviation belonged to patients in the therapy group. In the subgroup of patients with right coronary artery occlusion, infarct size determined by CE-CMR was significantly smaller in the therapy group than in the control group (10.6 ± 6.1% vs. 15.9 ± 8.1%, p = 0.04) (Fig. 3B).

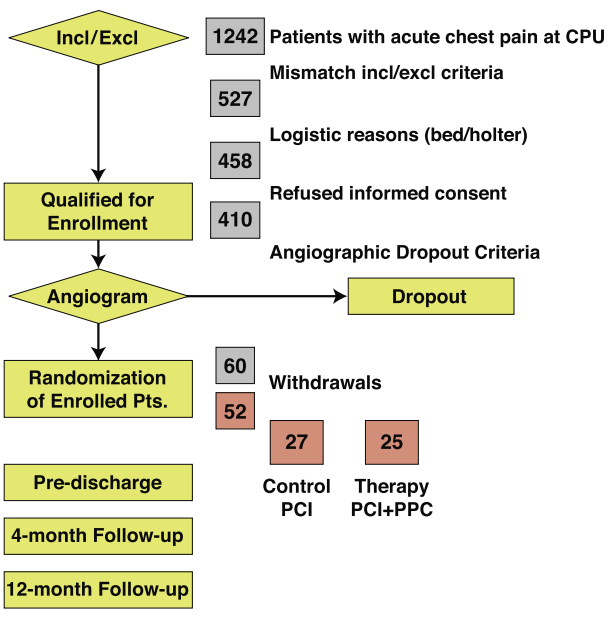

Figure 1. Patient Flow From Initial Screening to Follow-Up

CPU = chest pain unit; Excl = exclude; F-up = follow-up; Incl = include; PCI = percutaneous coronary intervention; PPC = pacing post-conditioning; Pts = patients.

To address interaction of treated artery, ST-segment deviation and time from symptom onset to hospital admission with infarct size, these variables were used as covariates to evaluate infarct size. No statistically significant difference was found between the adjusted area under the curve of CK in the control group and the therapy group, the primary endpoint of this study ($p = 0.70$) (Table 2). However, infarct size as measured by CE-CMR was 29% and 27% smaller in the therapy group than in the control group at 4 days and 4 months, respectively ($p = 0.01$) and still tended to be smaller after 1 year (23%, $p = 0.08$) (Table 2, Fig. 4). LV ejection fraction tended to be higher in the therapy group, especially at 4 days and 1 year (Table 2).

Arrhythmias during and after reperfusion. During the PCI procedure, 4 patients developed VF (3 in the therapy group) and 4 other patients AF (all in the therapy group) (Table 3). In all cases, VF could be immediately defibrillated. VF in the control patient occurred when the guidewire passed the occlusion, VF in the therapy group occurred in 1 patient before placing the guidewire and pacing lead, in 1 patient during positioning of the pacing lead, and in 1 patient during pacing (applying the withdrawal rule that rhythm should be <120 beats/min at time of reperfusion and no history of VF). (Data from the VF patient in the control group and 2 VF patients in the therapy group were excluded for analysis of all other parameters.) No significant differences were found between the groups with respect to single and multiple premature ventricular capture beats.

Table 1. Patient Characteristics

	Control	Therapy	p Value
Patients	27	25	
Age, yrs	60 ± 10	60 ± 11	0.80*
Male	19 (70)	17 (68)	0.85†
Diabetes mellitus	2 (7.4)	3 (12)	0.57†
Hypertension	9 (33)	12 (48)	0.28†
Hypercholesterolemia	3 (11)	3 (12)	0.92†
Smoking	15 (55)	15 (60)	0.75†
Time from first symptoms to admission, h	2.0 ± 0.9	2.4 ± 1.2	0.16*
Time from first symptoms to PCI, h	2.8 ± 1.0	3.3 ± 1.2	0.12*
Time from first symptoms to revascularization, h	3.2 ± 1.0	3.7 ± 1.2	0.07*
Treated coronary artery			
RCA (prox/mid/dist)	20 (74)	16 (64)	0.31†
LAD (prox/mid/dist)	7 (26)	7 (28)	
Other	0 (0)	2 (8)	
Rentrop grade			
Grade 0	3 (11)	3 (12)	0.43†
Grade 1	13 (48)	16 (64)	
Grade 2	11 (41)	6 (24)	
ST-segment deviation, mm	5.5 ± 2.8	6.1 ± 3.4	0.52*

Values are n, mean ± SD, or n (%). *Determined by Student *t* test. †Determined by chi-square test.
dist = distal; LAD = left anterior descending; PCI = percutaneous coronary intervention; prox = proximal; RCA = right coronary artery.

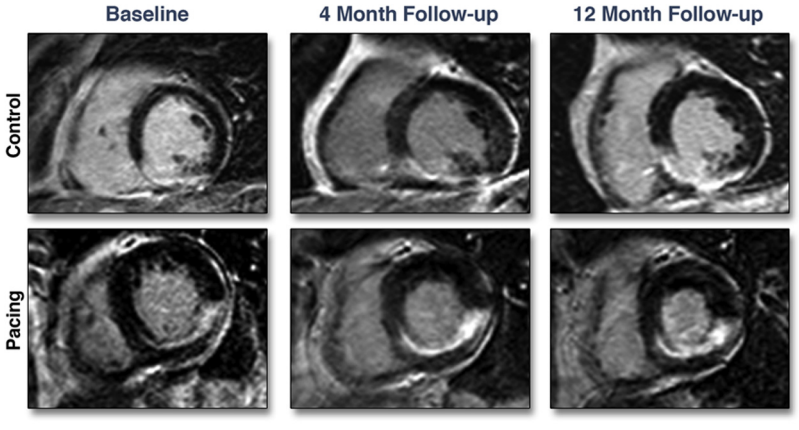

Figure 2. PPC-Induced Infarct Size Reduction Demonstrated by CE-CMR

Short-axis delayed-enhancement cardiac magnetic resonance images at baseline, 4-month follow-up, and 12-month follow-up of 2 patients with inferior wall myocardial infarction on the basis of a proximal right coronary artery occlusion. Infarct size was 26%, 19%, and 17% in the control patient and 17%, 15%, and 13%, respectively, in the patient who underwent right ventricular pacing. CE-CMR = contrast-enhanced cardiac magnetic resonance; PPC = pacing post-conditioning.

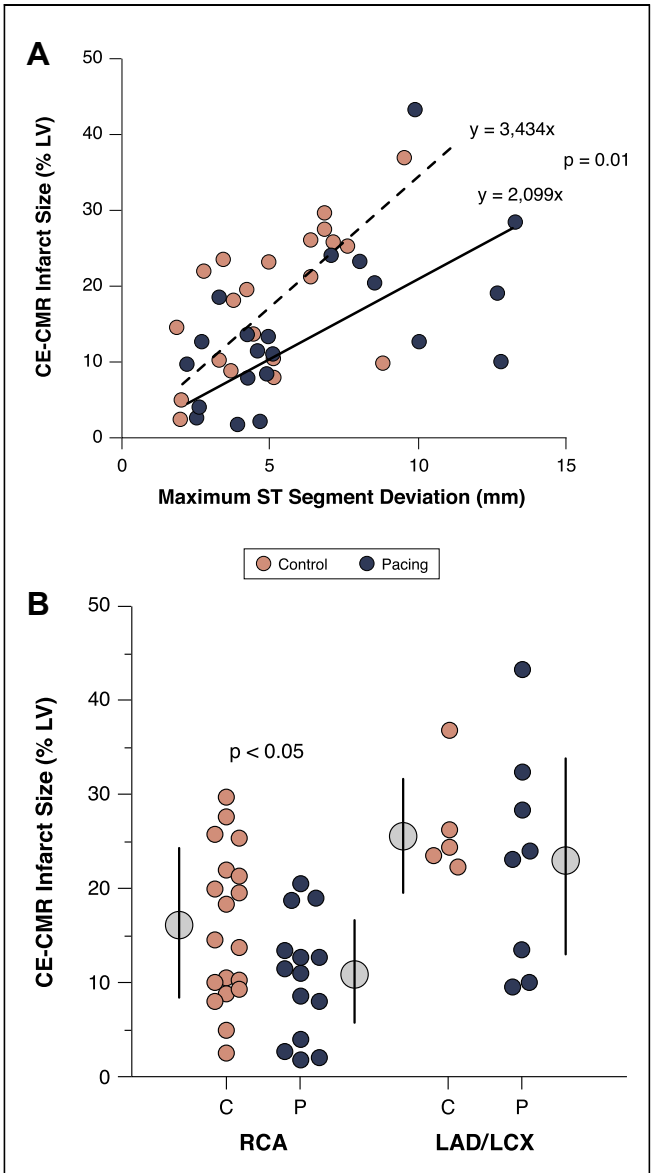

Figure 3. Infarct Size (CE-CMR) in Relation to ST-Segment Deviation and Localization

Infarct size (% LV), determined using CE-CMR at 4 days after percutaneous coronary intervention for the control **(pink circles)** and the therapy patients **(blue circles),** in relation to **(A)** maximal ST-segment deviation and **(B)** treated artery (**bars** represent mean ± SE). CE-CMR = contrast-enhanced cardiac magnetic resonance; LV = left ventricle.

Concept. This first-in-man study to evaluate the feasibility and efficacy of PPC during acute reperfusion of STEMI indicates the following: 1) the primary endpoint of the study (enzyme release) was not met; 2) CE-CMR data demonstrate a smaller infarct size by PPC + PCI as compared to PCI alone at 4 days and 4 months after PCI; 3) PPC + PCI is feasible, but additional attention may be required to improve safety. Therefore, the present study shows that it would be worthwhile to investigate in more detail whether PPC is a useful adjunct treatment algorithm to attenuate reperfusion damage following STEMI and reperfusion.

The reduction in infarct size, as measured by the CE-CMR data is in agreement with previous observations from experiments in rabbits and pigs, where PPC reduced infarct size by 40% to 50%, both acutely and chronically (2). The percent reduction observed in PROTECT (29% after 4 days and 27% after 4 months) is in the same range as that shown for IPoC in patients.

The reduction in infarct size by CE-CMR was not paralleled by a significant reduction in enzyme release. The explanation for the mismatch between enzyme and CE-CMR analysis is currently unclear and remains to be determined. CE-CMR is the current gold standard for assessing infarct size and can be used to detect structural abnormalities in the myocardium indicating low reflow or no reflow. In contrast, although frequently used in clinical practice, plasma enzyme levels are an indirect reflection of infarct size, because the circulating enzyme levels are dependent on the rate of release, breakdown, and clearance, as well as distribution between intravascular and extravascular space.

In the present study, no direct stenting was used. Rather, the PPC protocol was added to the routine PCI procedure, which allowed, for example, thrombosuction for establishing reperfusion. Also, in order to achieve proper reperfusion and stent positioning, a variable number of balloon inflations (ranging from 1 to 8) were used, which may mimic the repeated reocclusions used for achieving IPoC.

In the therapy group, 2 patients experienced VF that was potentially related to the pacing therapy: 1 due to positioning of the pacing lead in the right ventricle; and 1 during pacing. Moreover, 4 patients in the PPC group developed atrial fibrillation. These findings indicate that final implementation of PPC in the clinic requires technical improvements that warrant higher safety, such as better sensing and inhibition functions and a dedicated, automated pacing equipment.

The optimal pacing location relative to the infarct may be an important consideration in this therapy as well. It may also be advisable to modify PPC delivery as well as the PPC pacing algorithm. In that respect, it is of interest that our recent animal studies showed that pacing cycles as short as 5 s may provide the same protection as

Table 2. Enzyme Release and Cardiac Function

	Control	Therapy	Difference	p Value
CK, AUC	68,840 ± 8,816 (51,094 to 86,587)	65,772 ± 7,952 (49,765 to 81,778)	3,069 ± 8,001 (−13,037 to 19,174)	0.70
Infarct size, % LV				
4 days	21.7 ± 2.3 (17.0 to 26.4)	15.4 ± 2.1 (11.3 to 19.6)	6.3 ± 2.2 (1.9 to 10.7)	0.01
4 months	18.6 ± 2.0 (14.5 to 22.7)	13.9 ± 1.7 (10.4 to 17.4)	4.7 ± 1.9 (0.9 to 8.5)	0.02
12 months	16.2 ± 2.2 (11.7 to 20.6)	12.5 ± 1.9 (8.7 to 16.3)	3.7 ± 2.0 (−0.4 to 7.8)	0.08
LVEF, %				
4 days	52.2 ± 2.2 (47.8 to 56.7)	55.3 ± 1.9 (51.4 to 59.2)	−3.1 ± 2.0 (−7.2 to 1.1)	0.14
4 months	53.5 ± 2.0 (49.4 to 57.7)	53.7 ± 1.8 (50.2 to 57.3)	−0.2 ± 1.9 (−4.0 to 3.6)	0.92
12 months	49.6 ± 2.7 (44.2 to 55.0)	53.6 ± 2.3 (49.0 to 58.2)	−4.0 ± 2.4 (−9.0 to 1.0)	0.11

Values are mean ± SE (95% confidence intervals) after adjustment for treated artery, time from first symptom to admission, and ST-segment deviation as explained in the methods. The p values are from adjusted linear regression models.
AUC = area under the curve; CK = creatine kinase; LV = left ventricle; LVEF = left ventricular ejection fraction.

the 10 × 30 s algorithm used in the present study. These short "trigger" times may relate to the supposed mechanism of PPC. Animal studies suggest that PPC is mediated by abnormal mechanical loading, induced by ventricular pacing (dyssynchrony). Through pathways not yet unraveled (but that do not include G-coupled proteins, as is the case in IPoC) PPC leads to activation of well-known protective molecules such as phosphoinositide 3-kinase, mitochondrial adenosine triphosphate–sensitive potassium channel, and protein kinase C (2).

Compared with other protective strategies during PCI, PPC may have advantages. IPoC requires repeated occlusion of a stented coronary artery segment during PCI. In PPC, no additional mechanical contact with the sensitive vessel is required. Also, PPC lacks potential effects in other organs or the circulation, as may occur by administration of drugs, such as adenosine and cyclosporine. Moreover, the demonstration of cardioprotection by PPC in patients also makes it worthwhile to search for new molecular targets of the pathways involved in this protection.

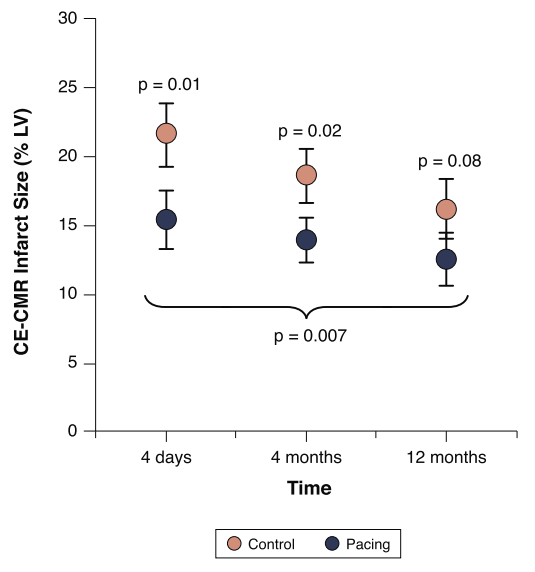

Figure 4. Changes in Infarct Size During the Initial 12 Months After Infarction

Infarct size (% LV) determined by CE-CMR for the control **(pink circles)** and therapy **(blue circles)** patients at 4 days (n = 48), 4 months (n = 44), and 12 months after percutaneous coronary intervention (n = 41). Data represent adjusted mean ± SE. Data were adjusted for ST-segment deviation, time from symptom onset to hospital admission, and affected coronary artery, as explained in the methods. C = control group; LAD = left anterior descending; LCX = left circumflex; P = therapy group; RCA = right coronary artery; other abbreviations as in Figures 2 and 3.

Table 3. Occurrence of Arrhythmias During Treatment and in the Early Post-Treatment Period (Secondary Endpoint: Safety)

		Control	Therapy	p Value
PVC	Single	774 (166, 877)	950 (260, 1,525)	0.52
PVC	Pairs	61 (8, 59)	75 (11, 97)	0.57
	Start to t0	0 (0, 0)	0 (0, 0)	NA
NSVT	t0 to t0 + 1 h	2 (0, 3)	1 (0, 2.5)	0.60
	> t0 + 1 h	2.5 (1, 4.8)	5 (1.5, 8.0)	0.18
AF		0	4	
VF		1	3	

Values are median (interquartile range). The p values were calculated using Mann-Whitney *U* test.
AF = atrial fibrillation; NA = not available; NSVT = nonsustained ventricular tachycardias; PVCs = premature ventricular capture beats; t0 = time of guidewire advancement through lesion; VF = ventricular fibrillation.

JACC: CARDIOVASCULAR IMAGING, VOL. 7, NO. 6, 2014
JUNE 2014:620–6

Conclusions

The PROTECT study missed its primary endpoint of reduction in CK release. However, the CE-CMR data indicate that PPC has the potential to reduce infarct size; moreover, PPC is feasible in the clinical setting. Development of better pacing tools (automated switching and better sensing integrated in PCI tools) may facilitate clinical implementation. Besides, better pacing algorithms may be required to reduce proarrhythmic properties. The results of this study clearly require further corroboration in a larger trial.

Reprint requests and correspondence: Dr. Johannes Waltenberger, Department of Cardiovascular Medicine, Münster University Hospital, Albert-Schweitzer-Campus 1, Building A1, D-48149 Münster, Germany. *E-mail: Waltenberger@ukmuenster.de*.

REFERENCES

1. Hausenloy DJ, Yellon DM. Preconditioning and postconditioning: underlying mechanisms and clinical application. Atherosclerosis 2009;204:334–41.
2. Babiker FA, Lorenzen-Schmidt I, Mokelke E, et al. Long-term protection and mechanism of pacing-induced postconditioning in the heart. Basic Res Cardiol 2010;105:523–33.

Key Words: acute myocardial infarction ■ arrhythmias ■ cardioprotection ■ pacing post-conditioning ■ primary PCI ■ reperfusion injury.