IJC Metabolic & Endocrine 2 (2014) 30–34

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

journal homepage: http://www.journals.elsevier.com/ijc-metabolic-and-endocrine

Impact of ischemic postconditioning with lactate-enriched blood on early inflammation after myocardial infarction☆,☆☆

Takashi Koyama [a,*], Hiroki Niikura [b], Masaru Shibata [a], Kazunori Moritani [a], Megumi Shimada [c], Akiyasu Baba [c], Makoto Akaishi [c], Hideo Mitamura [a]

[a] Cardiovascular Center, Tachikawa Hospital, 4-2-22 Nishiki-cho, Tachikawa, Tokyo 190-8531, Japan
[b] Cardiology Division, Ota Memorial Hospital, 455-1 Oshima-cho, Ota, Gunma 373-8585, Japan
[c] Cardiology Division, Kitasato Institute Hospital, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan

ARTICLE INFO

Article history:
Received 15 December 2013
Received in revised form 31 January 2014
Accepted 4 February 2014
Available online 14 February 2014

Keywords:
Acidosis
C-reactive protein
Microcirculation
No reflow
Ischemia reperfusion injury

ABSTRACT

Background: Excessive early inflammation after myocardial infarction (MI) is associated with poor outcomes. However, an approach for suppressing this early inflammation has not been reported. We previously reported that postconditioning with lactate-enriched blood (PCLeB) induced excellent microcirculation recovery in patients with acute MI. We therefore tested the hypothesis that early inflammation after MI could be suppressed by PCLeB.

Methods and results: We treated 17 consecutive patients with ST-elevation MI using primary percutaneous intervention with our modified postconditioning protocol within 12 h of onset. In this protocol, the duration of each brief reperfusion was prolonged from 10 to 60 s in a stepwise manner. Lactated Ringer's solution (20–30 mL) was injected directly into the culprit coronary artery at the end of each brief reperfusion, and the balloon was quickly inflated at the site of the lesion to trap lactate within the ischemic myocardium. Each brief ischemic period lasted 60 s. After 7 cycles of balloon inflation and deflation, full reperfusion was performed; subsequently, stenting was performed. C-reactive protein (CRP) levels were measured daily and the peak values within the first 7 days post-admission were recorded. Peak CRP values were compared with those in matched control patients with acute MI treated without postconditioning. In both groups, only patients with CRP values <0.3 mg/dL on admission were included. Peak CRP values were significantly lower in the postconditioned group (control group vs. postconditioned group, 5.05 ± 4.85 vs. 1.66 ± 1.57 mg/dL; $p < 0.01$).

Conclusion: PCLeB may suppress early inflammation after MI.

Introduction

Excessive early inflammation after myocardial infarction (MI) is associated with adverse left ventricular remodeling [1,2] and poor outcomes [3]. However, an approach that effectively suppresses early post-MI inflammation during/after reperfusion therapy has not been reported. We previously reported that ischemic postconditioning with lactate-enriched blood (PCLeB) induced excellent microcirculation recovery in patients with acute MI [4,5]. This has not been demonstrated in patients with acute MI treated with the original postconditioning procedures [6].

The protective effects of postconditioning are thought to result from a delayed recovery from intracellular acidosis during the early phase of reperfusion [7]. Therefore, our modified postconditioning protocol was designed based on the assumption that prolonging the delay in intracellular acidic recovery may increase the protective effects of postconditioning. The improved microcirculation recovery achieved by our approach is expected to induce a healthier healing process in the reperfused ischemic myocardium. If this is true, excessive inflammatory responses will not be evoked by reperfusion. Therefore, we tested the hypothesis that early post-MI inflammation can be suppressed by our modified postconditioning protocol.

Methods

This matched case–control study was approved by the ethics review boards of Tachikawa Hospital, Ota Memorial Hospital, and Kitasato Institute Hospital; all study patients provided informed consent.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
☆☆ This work has no relation with industry.

* Corresponding author at: Cardiology Division, Saitama Municipal Hospital, 2460 Mimuro, Midori-ku, Saitama City, Saitama 336-8522, Japan. Tel.: +81 48 873 4111; fax: +81 48 873 5451.
E-mail address: koyamas@me.com (T. Koyama).

http://dx.doi.org/10.1016/j.ijcme.2014.02.002
2214-7624

Study patients

The inclusion criteria were as follows: hospital admission within 12 h of a first ST-elevation MI; a C-reactive protein (CRP) level <0.3 mg/dL upon admission; no collagen-related diseases, malignancies, or any infectious diseases; and eligibility for primary percutaneous coronary intervention (PCI). An ST-elevation MI was defined as prolonged chest pain (duration, >30 min) and an ST-segment elevation >1 mm in ≥2 adjacent leads. Patients having an infarct-related coronary artery with a Thrombolysis in Myocardial Infarction (TIMI) flow grade II or III were excluded from the study. The relevant patient characteristics are shown in Table 1.

Study protocol

We treated 17 consecutive patients who met the inclusion criteria with primary PCI using our modified postconditioning protocol (Fig. 1). In this postconditioning protocol, the duration of each brief reperfusion was prolonged from 10 to 60 s in a stepwise manner. This approach sought to prevent rapid and abrupt washout of lactate during the very early phase of reperfusion. At the end of each brief reperfusion, lactate was supplied by injecting lactated Ringer's solution (Lactec Injection, Otsuka Pharmaceutical, Tokyo, Japan), containing 28 mM lactate, into the culprit coronary artery (20 mL for the right coronary artery, 30 mL for the left coronary artery). To trap the lactate within the ischemic myocardium, the balloon was quickly inflated with low pressure at the site of the lesion. Each brief ischemic period lasted 60 s. This approach aimed to achieve controlled reperfusion with cellular oxygenation and minimal lactate washout from the cells. Lactate accumulation is generally accepted to be responsible for intracellular acidosis during ischemia. Therefore, the delay in recovery from intracellular acidosis, achieved by simple intermittent reperfusion, may be increased through this approach. After 7 cycles of balloon inflation and deflation, full reperfusion was performed; subsequently, stenting was performed, and the PCI was completed. Thrombosuction was implemented only after completion of the postconditioning protocol and only in cases where it was deemed necessary. Follow-up coronary angiography (CAG) was scheduled for each patient 6–9 months after reperfusion therapy, unless the patient refused.

Biomarker measurement

As an indicator of inflammation, each patient's blood CRP level was measured daily using a latex photometric immunoassay; the peak value during the first 7 days after admission was also recorded. Peak CRP values were compared with those in control patients who experienced ST-elevation MI and were successfully treated with primary PCI without postconditioning. Data from control patients, treated before 2012 in our hospitals, were also collected within 12 h of MI onset. Blood creatine kinase (CK) levels were measured every 3–4 h after admission until they peaked. In all control patients, stent implantation was performed after balloon dilation of the culprit lesion. The control patients were matched to the 17 study patients with respect to age, gender, presence or absence of diabetes mellitus, time to reperfusion, and peak CK values (Table 1). In the control group, only patients with CRP values <0.3 mg/dL upon admission were included. Patients having an infarct-related coronary artery with a TIMI flow of grade II or III were not included in the control group. Patients with a collagen-related disease, malignancy, or any infectious disease were also not included in the control group.

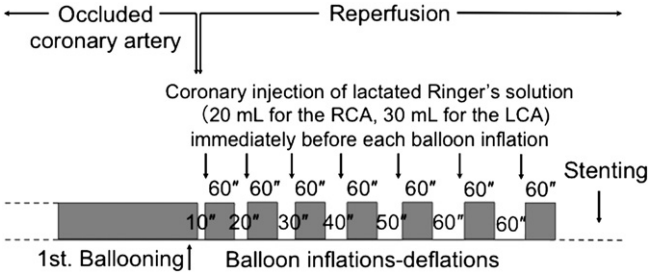

Fig. 1. Overview of the protocol for ischemic postconditioning with lactate-enriched blood. The duration of each brief reperfusion was prolonged from 10 to 60 s in a stepwise manner. At the end of each brief reperfusion, lactate was supplied by injecting lactated Ringer's solution into the culprit coronary artery. Each brief ischemic period lasted 60 s. After 7 cycles of balloon inflation and deflation, full reperfusion was performed; subsequently, stenting was performed. LCA, left coronary artery; and RCA, right coronary artery.

Statistics

All continuous variables are reported as means ± SD. Differences between continuous variables in the 2 patient groups were assessed by a non-paired *t*-test. Categorical variables in the 2 groups were compared using a chi-squared test or Fisher exact test. A p-value <0.05 was considered statistically significant.

Results

The 17 study patients were successfully reperfused, achieving a grade III TIMI flow and a Blush grade of more than II. Marked myocardial staining with contrast medium and/or early visualization of venous drainage on CAG were observed in each patient, indicating unimpaired microcirculation. Figs. 2 and 3 show the final CAG views from 2 representative patients after completion of primary PCI. The figures also show the CAG view of each patient in the chronic phase (6 months after the MI), for comparison. In Fig. 2a, marked myocardial staining with contrast medium was observed in the final CAG view after completion of PCI. The myocardium was stained more densely in the acute phase than in the chronic phase (Fig. 2a and b, Videos 1 and 2). In Fig. 3a, early visualization of venous drainage was observed after PCI completion. Venous drainage was more clearly visualized in the

Table 1
Characteristics of control patients and postconditioned patients.

	Control (n = 20)	PCLeB (n = 17)	p value
Age, years	65.4 ± 11.1	66.6 ± 14.3	NS
Male patients, n (%)	15 (75.0)	13 (76.5)	NS
Patients with diabetes mellitus, n (%)	5 (25.0)	4 (23.5)	NS
Time to reperfusion, h	5.7 ± 3.1	5.8 ± 3.9	NS
Peak CK value, IU/L	2336 ± 1143	2370 ± 1042	NS
Time from reperfusion to peak CK release, h	7.5 ± 4.4 (3–17 h)	4.5 ± 1.5 (2–6 h)	0.013
Proximal occlusion of a coronary artery*, n (%)	12 (60)	16 (94.1)	0.023
Proximal occlusion of LAD, n (%)	5 (25.0)	7 (41.2)	NS

CK, creatine kinase; LAD, left anterior descending artery; PCLeB, postconditioning with lactate-enriched blood.
* "Proximal occlusion of a coronary artery" includes occlusion of segments 1 and 2 of the right coronary artery, segments 6 and 7 of the left anterior descending artery, and segment 11 of the left circumflex artery.