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Bulletin of the National Research Centre (2022) 46:277
https://doi.org/10.1186/s42269-022-00966-y

Bulletin of the National Research Centre

RESEARCH

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Postconditioning with lactate-enriched blood in ST-segment elevation myocardial infarction

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Abstract

Background: Ischemic postconditioning failed to demonstrate improved outcomes in patients with ST-segment elevation myocardial infarction (STEMI) in large-scale studies. We examined the cardioprotective effects of a modified postconditioning protocol, which was named postconditioning with lactate-enriched blood (PCLeB).

Methods: This study included 100 consecutive patients with STEMI treated in the Saitama Municipal Hospital within 12 h of symptom onset since March 2014 to July 2020 with one-year follow-up. PCLeB was implemented at the beginning of reperfusion. PCLeB comprised intermittent reperfusion and timely coronary injections of lactated Ringer's solution, aimed at achieving controlled reperfusion with myocardial oxygenation and minimal washout of lactate to prolong tissue acidosis in comparison with the original protocol. Outcome measures were in-hospital and one-year mortality and re-hospitalization rates for heart failure within one year.

Results: In-hospital and one-year mortality were zero and none was re-hospitalized for heart failure during the one-year follow-up period among the 100 study patients.

Conclusions: PCLeB was associated with zero mortality and no re-hospitalization for heart failure at one year among 100 consecutive patients with STEMI who underwent reperfusion therapy.

Keywords: Cardioprotection, Ischemia reperfusion injury, Outcome

Background

Ischemic myocardium cannot survive without reperfusion. However, myocardial reperfusion injury attenuates the beneficial effects of reperfusion therapy for ST-segment elevation myocardial infarction (STEMI) (Heusch 2020). Various approaches that were successful in experimental studies have been attempted to prevent reperfusion injury in clinical settings. However, none of these approaches has proven to be successful to date (Bøtker et al. 2018; Davidson et al. 2019). Ischemic postconditioning is one such approach. In 2005, Staat et al. reported that four brief cycles of ischemia and reperfusion implemented at the start of reperfusion reduced enzymatic infarct size by 36% in their small pilot study (Staat et al. 2005). However, subsequent large-scale studies using the same protocol failed to demonstrate improved outcomes in patients with STEMI (Xing et al. 2019). We thought that these failed results for ischemic postconditioning were attributable to inadequacies of the protocol rather than inappropriateness of the method itself. Therefore, we modified the original protocol of ischemic postconditioning to potentiate the supposed cardioprotective effects. Because the cardioprotective effects of ischemic postconditioning are thought to result from delayed recovery from intracellular acidosis (Inserte et al. 2009), we modified the original protocol to increase the delay in recovery from intracellular acidosis. Our new approach, named postconditioning with lactate-enriched

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blood (PCLeB), consists of intermittent reperfusion and timely coronary injections of lactated Ringer's solution (Koyama et al. 2014, 2019; Koyama 2019). With this approach, we aimed to achieve controlled reperfusion with cellular oxygenation and minimal lactate washout from the cells to prolong intracellular acidosis more than the original protocol could. Here, we present the outcomes in 100 patients with STEMI who were treated using PCLeB.

Methods

Study participants

Consecutive patients with STEMI undergoing primary percutaneous coronary intervention (PCI) using PCLeB within 12 h of symptom onset at our hospital from March 2014 to July 2020 were included in this study. STEMI was defined as prolonged chest pain (duration > 30 min) and ST-segment elevation > 1 mm in ≥ 2 adjacent leads. We excluded patients with (1) an infarct-related coronary artery with a thrombolysis in myocardial infarction (TIMI) flow grade of II or III, (2) grade III collateral circulation, (3) occlusion of the left main trunk, (4) serum creatinine levels ≥ 2.0 mg/dL, and (5) cancer as well as those who had undergone reperfusion using technically flawed PCLeB procedures (most often by undertrained operators).

Postconditioning protocol

Figure 1 depicts an overview of the PCLeB protocol. The duration of each brief reperfusion was extended from 10 to 60 s in a stepwise manner. At the end of each brief reperfusion, lactated Ringer's solution (Lactec Injection; Otsuka Pharmaceutical, Tokyo, Japan) containing 28 mM lactate was injected 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, a balloon was quickly inflated with low pressure at the site of the lesion. Each ischemic period lasted 60 s. After seven cycles of balloon inflation and deflation, full reperfusion was performed; subsequently, stenting was performed, thus completing the PCI.

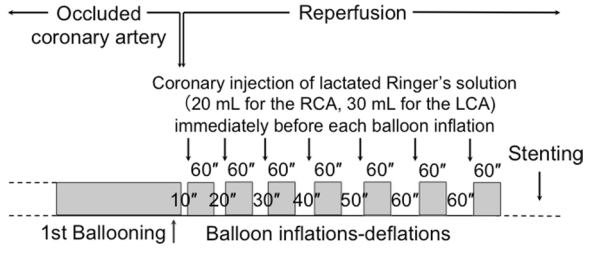

Fig. 1 Overview of the protocol for postconditioning with lactate-enriched blood. LCA, left coronary artery; RCA, right coronary artery. (Reprinted from Koyama et al. 2014)

Measurements

Serum creatine kinase and creatine kinase-MB levels were measured at 4-h intervals after reperfusion until they peaked. Serum C-reactive protein (CRP) levels were measured daily, and the peak value during the first 7 days after admission was recorded. Data from the patients with concomitant extracardiac inflammatory disorders were excluded from the analysis. Corrected TIMI frame counts in the culprit coronary arteries were measured after PCI completion in all patients.

We retrospectively collected chronic phase data for NT-proBNP levels from medical records. Although we excluded patients with serum creatinine levels ≥ 2.0 mg/dL, aged patients may also have masked renal insufficiency that affects NT-proBNP levels. We therefore excluded the NT-proBNP data of 14 patients aged ≥ 80 years from the analysis. Additionally, two patients aged < 80 years had not undergone measurement of NT-proBNP levels after discharge. Therefore, the analyses were performed after excluding these 16 patients. Since the timing of the measurements during follow-up visits was arbitrary, we tried to select data as close as possible to one year after STEMI, resulting in data acquisition dates ranging from six to 18 months (mean ± SD, 11.0 ± 2.8 months) after STEMI.

Outcomes

In-hospital and one-year mortality and re-hospitalization rates for heart failure within one year were evaluated.

This single center, interventional, uncontrolled study was approved by the ethics review boards of the Saitama Municipal Hospital, and all study patients provided written informed consent. All data are expressed as means ± SD.

Results

In total, 105 patients with STEMI treated using PCLeB were eligible for this study. Among them, however, we excluded five patients (all aged ≥ 80 years) who were lost to follow-up within one year; thus, 100 patients were included in this study (Table 1). During reperfusion therapy, no patient experienced severe ventricular arrhythmia, as reported in our previous smaller study (Akima et al. 2016). DC cardioversion was never implemented except for patients who required cardioversion before PCI. With regard to the resumed coronary blood flow, the mean corrected TIMI frame count was close to the normal value of 21, which may indicate preservation of microvascular function after PCI using PCLeB.

Table 1 Clinicodemographic characteristics and outcomes of the study patients ($N = 100$)

Age, yr (range)	64.7 ± 13.3 (30–92)
Male sex, *n*	77
Hypertension, *n*	58
Dyslipidemia, *n*	61
Diabetes mellitus, *n*	35
Time to reperfusion, *h*	4.1 ± 2.5
Occluded coronary artery, n	
Left anterior descending artery	41
Left circumflex artery	18
Right coronary artery	41
Peak creatine kinase level, IU/L	2873 ± 2036
Peak creatine kinase-MB level, IU/L	267 ± 167
Peak C-reactive protein level, mg/dL ($n = 91$)*	3.94 ± 3.71
Corrected TIMI frame count	22.8 ± 16.8
NT-proBNP level in the chronic phase, pg/mL ($n = 84$)†	247 ± 312
In-hospital deaths, *n*	0
Diuretic use at discharge, *n*	1
Diuretic use at one year, *n*	3
Deaths within one year, *n*	0
Re-hospitalization for heart failure within one year, *n*	0

TIMI, thrombolysis in myocardial infarction

* Nine patients with extracardiac inflammatory disorders were excluded from the analysis

† Fourteen patients aged ≥ 80 years were excluded from the analysis. Data were missing in two additional patients aged < 80 years

In reality, we had never observed the no-reflow phenomenon among the 100 study patients. Therefore, intra-aortic balloon counterpulsation (IABP) for poor coronary flow recovery or hemodynamic deterioration had never been implemented after reperfusion therapy.

No in-hospital deaths were recorded in this study (Table 1). As reported in our previous smaller study (Koyama et al. 2016), in most patients initially presenting with heart failure, the signs and symptoms of heart failure subsided without using diuretics after reperfusion therapy using PCLeB. This was true even in the present study and only one patient required an oral diuretic, at the minimum dose, at discharge. After discharge, none of the 100 study patients died or was re-hospitalized for heart failure during the one-year follow-up period. Only three patients were taking an oral diuretic at one year.

As for the five patients excluded from our study because of being lost to follow-up within one year, none of them died or was re-hospitalized for heart failure during the shortened follow-up period.

Discussion

In this study, none of the 100 patients with STEMI who were treated using PCLeB died or were re-hospitalized for heart failure at one year. As reported in our previous smaller studies, the peak CRP levels in the acute phase (Koyama et al. 2014) and NT-proBNP levels in the chronic phase (Koyama et al. 2020) were also substantially low in this study, both of which indicate a generally fair prognosis. These findings in the laboratory data may support the positive outcomes observed in this study.

Our new approach was developed to potentiate the supposed cardioprotective effects of the original postconditioning protocol by increasing the delay in recovery from intracellular acidosis. Intermittent reperfusion delays the recovery from intracellular acidosis with respect to time. However, it is not known whether intermittent reperfusion actually delays recovery physiologically. Reoxygenation, replenishment of substrates, and washout of metabolites (e.g., lactate) occur simultaneously upon reperfusion. Intermittent reperfusion slows down all of these processes, thus, re-establishing the physiological state simultaneously. In contrast, acidic reperfusion, which has been demonstrated to reduce myocardial infarct size in animal models of ischemia and reperfusion (Preckel et al. 1998), selectively delays recovery from intracellular acidosis (Fig. 2). The failure of "intermittent reperfusion" postconditioning to improve the outcomes of patients with STEMI can be explained by the inability of this maneuver to selectively delay the recovery from intracellular acidosis. To produce the same cardioprotective effects as acidic reperfusion in STEMI treatment, we thought that lactate washout needed to be further delayed relative to the rate of reoxygenation during the postconditioning procedures, since lactate accumulation is mainly responsible for intracellular acidosis during ischemia. PCLeB was designed on the basis of this concept. To further delay the lactate washout, timely coronary injections of lactated Ringer's solution were incorporated into the "intermittent reperfusion" postconditioning in PCLeB. The positive results of this study appear to indicate that this modification was in the right direction.

This study did not include control patients, which is a major limitation of this study. However, the 0% mortality and re-hospitalization rates for heart failure at one year among the 100 consecutive patients, which were supported by the laboratory findings showing substantially low levels of both CRP in the acute phase and NT-proBNP in the chronic phase, can be considered to be encouraging results outlining the potential

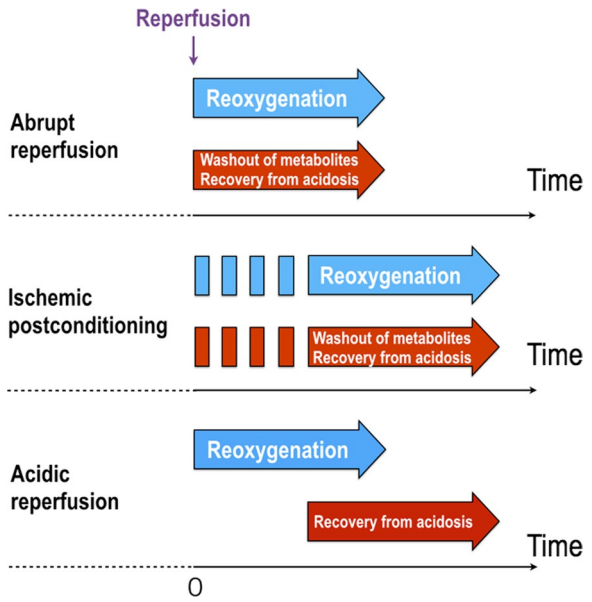

Fig. 2 Schematic representation of the difference between ischemic postconditioning and acidic reperfusion. Abrupt reperfusion simultaneously induces reoxygenation of the tissue and washout of metabolites including lactate, which is mainly responsible for intracellular acidosis produced during ischemia (upper panel). Ischemic postconditioning delays both reoxygenation and recovery from intracellular acidosis on a similar timescale (middle panel). In contrast, acidic reperfusion selectively delays the recovery from intracellular acidosis (bottom panel)

cardioprotective effects of PCLeB. The absence of serious ventricular arrhythmia and the fact that IABP was not required after reperfusion may represent another aspect of the possible cardioprotective effects of this approach. Apart from the cardioprotective efficacy, the avoidance of both DC cardioversion and IABP after reperfusion were themselves favorable for patients' health.

Because PCLeB does not involve any pharmacological agents or technically demanding procedures, it can be considered safe and feasible; this was demonstrated by the good short- and long-term outcomes for the 100 patients in this study. Multicenter randomized controlled trials are required to elucidate the true cardioprotective effects of PCLeB.

Conclusions

In conclusion, PCLeB was associated with zero mortality and no re-hospitalization for heart failure at one year among 100 consecutive patients with STEMI who underwent reperfusion therapy.

Abbreviations

CRP: C-reactive protein; IABP: Intra-aortic balloon counterpulsation; NT-proBNP: *N*-terminal pro-brain natriuretic peptide; PCI: Percutaneous coronary intervention; PCLeB: Postconditioning with lactate-enriched blood; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis in myocardial infarction.

Acknowledgements

Not applicable.

Author contributions

TK designed the study, performed the protocol, analyzed the data, and wrote the manuscript. TA performed the protocol, collected the data, and critically reviewed the manuscript. All authors have read and approved the manuscript.

Funding

No funding was obtained for this study.

Availability of data and materials

Further information on the data and methodologies will be made available by the author for correspondence, as requested.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics review boards of the Saitama Municipal Hospital, and all study patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interest relevant to this work.

Received: 16 October 2022 Accepted: 3 December 2022
Published online: 09 December 2022

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