

Lactated Ringer's solution for preventing myocardial reperfusion injury[☆]



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ABSTRACT

Reperfusion of ischemic myocardium is crucial for salvaging myocardial cells from ischemic cell death. However, reperfusion itself induces various deleterious effects on the ischemic myocardium. These effects, known collectively as reperfusion injury, comprise stunned myocardium, reperfusion-induced arrhythmia, microvascular reperfusion injury, and lethal reperfusion injury. No approach has proven successful in preventing any of these injuries in the clinical setting. My colleagues and I recently proposed a new postconditioning protocol, postconditioning with lactate-enriched blood (PCLeB), for the prevention of reperfusion injury. This new approach consists of intermittent reperfusion and timely coronary injections of lactated Ringer's solution, aiming to achieve controlled reperfusion with cellular oxygenation and minimal lactate washout from the cells. This approach appeared to be effective in preventing all types of reperfusion injury in patients with ST-segment elevation myocardial infarction (STEMI), and we have already reported excellent in-hospital outcomes of patients with STEMI treated using PCLeB. In this review article, I discuss a possible mechanism of reperfusion injury, which we believe to be valid and which we targeted using this new approach, and I report how the approach worked in preventing each type of reperfusion injury.

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1. Introduction

Reperfusion of ischemic myocardium is crucial for salvaging myocardial cells from ischemic cell death. However, reperfusion itself induces various deleterious effects on the ischemic myocardium; this has become known as reperfusion injury. Originally, reperfusion injury was classified into four types of injury [1]: 1. stunned myocardium (stunning); 2. reperfusion-induced arrhythmia; 3. microvascular reperfusion injury (the no-reflow phenomenon or, more recently, microvascular obstruction); and 4. lethal reperfusion injury. No approach has proven successful in preventing any of these injuries in the clinical setting.

My colleagues and I recently reported a new modified postconditioning protocol, postconditioning with lactate-enriched blood (PCLeB), which appeared to be effective against all four types of reperfusion injury [2–6]. In this review article, I discuss a possible mechanism of reperfusion injury, which we believe to be valid and which we targeted using the new postconditioning protocol, and I report how

this new approach worked in preventing each type of reperfusion injury.

2. Hypercontracture as a new target for the prevention of reperfusion injury

Hypercontracture develops within the reperfused ischemic myocardium and mechanically disrupts myocardial cell skeletons that ischemic insults have already made vulnerable to such strong forces. Consequently, contraction band necrosis ensues in the myocardium [7,8]. This has been included among the mechanisms of lethal reperfusion injury [1,9–12]. However, hypercontracture has not been regarded as the primary cause or trigger, but only as one component of the cascade of events that eventually results in reperfusion injury.

Currently, the most popular mechanism for reperfusion injury involves mitochondrial disorders that result from a permeability transition [11–13]. During ischemia, the mitochondrial permeability transition (MPT) pore remains closed, but it opens within minutes of reperfusion [14,15]. This transition is thought to initiate the irreversible process of reperfusion injury. Meanwhile, a well-developed hypercontracture (contraction band necrosis) is reportedly observed within 120 s of reperfusion of ischemic myocardium in animal experiments [16]. Although a causal relationship between hypercontracture and MPT has not been established, development of a mature hypercontracture appears to coincide chronologically with the onset of MPT. Although MPT may play an important role in the development of

Abbreviation: CAG, coronary angiography; CK, creatine kinase; CRP, C-reactive protein; ECG, electrocardiography; MI, myocardial infarction; MPT, mitochondrial permeability transition; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PCLeB, postconditioning with lactate-enriched blood; PVC, premature ventricular contraction; TIMI, thrombolysis in myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

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reperfusion injury, its role in hypercontracture development is rather questionable. We therefore targeted hypercontracture for the prevention of reperfusion injury, rather than MPT.

In a recent large-scale clinical trial, cyclosporine, a potent inhibitor of MPT, failed to improve the long-term outcomes of patients with ST-segment elevation myocardial infarction (STEMI) and failed to prevent left ventricular remodeling [17]. Thus, for an effective breakthrough, a new strategy for the prevention of reperfusion injury would appear to be essential.

3. PCLeB, a novel postconditioning protocol

In 2005, Staat et al. reported that four brief cycles of intermittent reperfusion applied immediately after reopening of the culprit coronary artery, a procedure called “postconditioning”, reduced the infarct size in patients with STEMI [18]. The beneficial effects of postconditioning were attributed to the delay in recovery from tissue acidosis produced during ischemia. However, recent larger clinical trials did not demonstrate any protective effects of postconditioning in patients with STEMI [19,20]. To achieve more consistent results, my colleagues and I modified the original protocol of postconditioning to increase the delay in recovery from intracellular acidosis during the early reperfusion period [2]. Fig. 1 shows an overview of the protocol of PCLeB. In our postconditioning protocol, the duration of each brief reperfusion is prolonged from 10 s 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. Lactated Ringer’s solution (20–30 mL) containing 28 mM lactate is injected directly into the culprit coronary artery at the end of each brief reperfusion and the balloon is quickly inflated at the site of the lesion, so that the lactate is trapped inside the ischemic myocardium. Each brief ischemic period lasts 60 s. After 7 cycles of balloon inflation and deflation, full reperfusion is performed. This approach aims 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 postconditioning, may be increased through this approach.

More specifically, this method precisely targets the prevention of hypercontracture. My colleagues and I have previously reported that abrupt washout of lactate during the reperfusion following simulated ischemia induced contracture in guinea-pig myocytes. This occurred despite a substantial decrease in their intracellular Ca^{2+} concentrations, which were elevated during the simulated ischemia [21]. Based on these findings, we attempted to create a transition period between ischemia and reperfusion. This transition period allowed the elevated intracellular Ca^{2+} concentration to normalize safely, while suspending

the restoration of vigorous myocardial contraction by keeping the tissue lactate concentrations high (maintaining tissue acidosis). This was the basic concept of our novel postconditioning protocol. To summarize our protocol, lactate was employed as an inherent contractile activity blocker with the aim of preventing the rapid recovery of contractile force immediately following reperfusion, which otherwise might result in the development of hypercontracture.

This idea was fueled by previous experimental studies. Garcia-Dorado et al. reported that inhibition of the contractile apparatus of ischemic myocardium using 2,3-butanedione monoxime during the first 30 min of reperfusion reduced the infarct size in pigs [22]. Buckberg and colleagues also showed that reperfusion for 20 to 30 min with hyperkalemic blood prevented contraction and reduced myocyte death during totally vented bypass in the canine heart [23,24]. This approach is currently widely used in the field of open-heart surgery as a method of cardioprotection, and is called terminal warm blood cardioplegia. Thus, inhibition of myocardial contraction during the early reperfusion period may be an effective approach for cardioprotection.

4. Effects of PCLeB on microvascular reperfusion injury (the no-reflow phenomenon or microvascular obstruction)

Mechanical restoration of coronary blood flow by percutaneous coronary intervention (PCI) often results in tissue hypoperfusion in patients with STEMI; this is reperfusion injury in the microvasculature, known as the no-reflow phenomenon [25,26], or more recently as microvascular obstruction [27,28]. My colleagues and I reported that PCLeB was consistently followed by angiographically excellent microcirculation recovery [2–6]. The coronary angiography findings of a representative patient are presented in Fig. 2. This patient had a totally occluded obtuse marginal artery. After completion of PCI using PCLeB, coronary blood flow in the obtuse marginal artery appeared to be faster than that in the other coronary arteries. Furthermore, the washout of the contrast medium from the obtuse marginal artery appeared to be faster still, indicating that microcirculation recovery was apparently augmented. These angiographic observations have been confirmed by a more quantitative approach. We reported that the mean corrected Thrombolysis in Myocardial Infarction (TIMI) frame count of 55 consecutive STEMI patients treated using PCLeB was 20.1 ± 10.1 frames (normal value 21 frames) [5]. Among these patients, 30 so far have returned for follow-up coronary angiography and have shown no angiographic restenosis. In these 30 patients, the corrected TIMI frame counts immediately after PCI completion (19.1 ± 9.3 frames) were significantly smaller than those in the chronic phase (27.4 ± 12.2 frames, $p < 0.0001$). These results were in stark contrast to the no-reflow phenomenon, and the results obtained indicated more than its prevention.

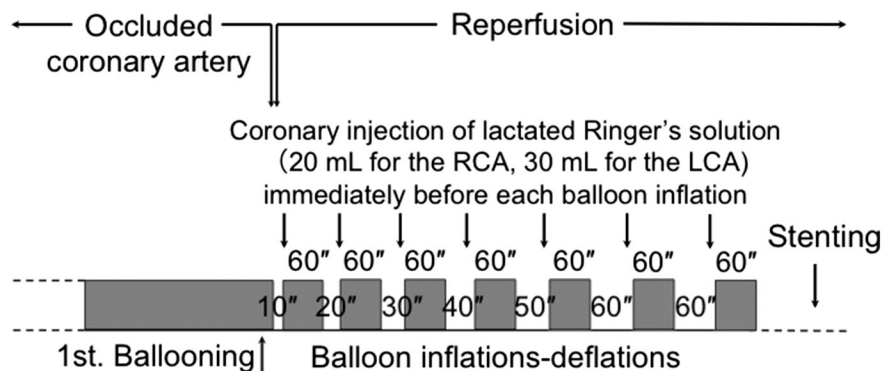


Fig. 1. Overview of the protocol for postconditioning with lactate-enriched blood. The duration of each brief reperfusion was prolonged from 10 to 60 s in a stepwise manner. At the end of each brief reperfusion, lactate was supplied by injecting lactated Ringer’s solution into the culprit coronary artery. 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; RCA, right coronary artery. (Reprinted from Koyama et al. [3]).

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