Intracoronary Poloxamer 188 Prevents Reperfusion Injury in a Porcine Model of ST-Segment Elevation Myocardial Infarction

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VISUAL ABSTRACT

HIGHLIGHTS

• STEMI remains a significant cause of in-hospital mortality, and up to 20% of people go on to develop heart failure.
• P188 is a nonionic triblock copolymer believed to prevent cellular injury after ischemia and reperfusion. The CORE trial examined P188 for STEMI patients showing no benefit when it was infused through a peripheral IV catheter approximately 30 min after revascularization with thrombolytic therapy.
• STEMI was induced in pigs using endovascular coronary artery occlusion to compare intracoronary infusion of P188 immediately after revascularization to infusion of P188 through a peripheral IV catheter 30 min after revascularization. Immediate intracoronary infusion of vehicle control and PEG, a rheological control, were also compared.
• Intracoronary infusion of P188 immediately upon reperfusion reduced infarct size by 68% compared with delayed peripheral P188 infusion, which was similar to vehicle control.
• Mitochondrial respiration and calcium stress tolerance were preserved in the ischemic tissue of pigs treated with immediate intracoronary P188 infusion. Mitochondria from pigs with delayed peripheral P188 infusion were no different from control pigs.
• By reducing infarct size and mitochondrial dysfunction, immediate intracoronary infusion of P188 may provide a therapeutic strategy to improve post-STEMI outcomes. The timing and route of delivery were critical to the observed benefit.
SUMMARY

Poloxamer 188 (P188) is a nonionic triblock copolymer believed to prevent cellular injury after ischemia and reperfusion. This study compared intracoronary (IC) infusion of P188 immediately after reperfusion with delayed infusion through a peripheral intravenous catheter in a porcine model of ST-segment elevation myocardial infarction (STEMI). STEMI was induced in 55 pigs using 45 min of endovascular coronary artery occlusion. Pigs were then randomized to 4 groups: control, immediate IC P188, delayed peripheral P188, and polyethylene glycol infusion. Heart tissue was collected after 4 h of reperfusion. Assessment of mitochondrial function or infarct size was performed. Mitochondrial yield improved significantly with IC P188 treatment compared with control animals (0.25% vs. 0.13%), suggesting improved mitochondrial morphology and survival. Mitochondrial respiration and calcium retention were also significantly improved with immediate IC P188 compared with control animals (complex I respiratory control index: 7.4 vs. 3.7; calcium retention: 1,152 nmol vs. 386 nmol). This benefit was only observed with activation of complex I of the mitochondrial respiratory chain, suggesting a specific effect from ischemia and reperfusion on this complex. Infarct size and serum troponin I were significantly reduced by immediate IC P188 infusion (infarct size: 13.9% vs. 41.1%; troponin I: 19.2 μg/l vs. 77.4 μg/l). Delayed P188 and polyethylene glycol infusion did not provide a significant benefit. These results demonstrate that intracoronary infusion of P188 immediately upon reperfusion significantly reduces cellular and mitochondrial injury after ischemia and reperfusion in this clinically relevant porcine model of STEMI. The timing and route of delivery were critical to achieve the benefit. (J Am Coll Cardiol Basic Trans Science 2016;1:224–34) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Coronary heart disease accounts for 1 of 6 deaths each year in the United States, with an estimated 595,000 people experiencing myocardial infarction, of whom approximately 30% experience ST-segment elevation myocardial infarction (STEMI) (1). STEMI leads to in-hospital mortality in 6% of cases, and 13% to 20% of people go on to develop heart failure (2). STEMI-induced injury occurs in 2 stages. The first stage, ischemic injury, varies in severity depending on the pre-ischemic condition of the tissue, the duration of the ischemia, and the degree of revascularization. The second stage, reperfusion injury, is the injury initiated when blood flow returns to the ischemic tissue (3-5). Multiple cell injury pathways are thought to contribute to reperfusion injury, including membrane destabilization, dysregulation of calcium entry into the cell, free radical production, mitochondrial injury, and activation of pro-apoptotic pathways (6,7). Unfortunately, there is currently no clinical treatment available to prevent or reverse reperfusion injury.

Poloxamer 188 (P188) is a nonionic triblock copolymer with a hydrophobic polyoxypropylene core flanked by hydrophilic polyoxyethylene segments (8,400 Da molecular weight; 0.17 PPO/PEO ratio). P188 has previously been shown to reduce red blood cell aggregation (8), facilitate clot lysis by recombinant tissue plasminogen activator (9), and reduce leukocyte chemotaxis (10). More recent studies have demonstrated that P188 stabilizes cellular membranes (11) and prevents lipid peroxidation induced by Fe²⁺ and H₂O₂ (12). Despite these effects, the CORE (Collaborative Organization for RheothRx Evaluation) trial found no clinical benefit of P188 when given to patients receiving thrombolytic therapy for STEMI (13). Subsequent decades have led to significant changes in...
the standard of care for patients with STEMI, providing additional opportunities for treatment of myocardial injury.

We hypothesized that P188 would prevent reperfusion injury and reduce infarct size when infused immediately upon reperfusion with localized delivery of the same dose of P188 through a peripheral intravenous (IV) catheter would demonstrate no benefit.

**METHODS**

All studies were performed with approval from the Institutional Animal Care and Use Committee of the Minneapolis Medical Research Foundation and the National Research Council’s 1996 Guidelines for the Care and Use of Laboratory Animals (Protocol 15-02-03).

**ANIMAL MODEL.** Yorkshire pigs, 38 to 42 kg, were used for all studies. The anesthesia, surgical preparation, and data monitoring and recording were performed as described in detail previously (14). Briefly, pigs were anesthetized with ketamine (10 ml of 100 mg/ml) followed by inhaled isoflurane at a dose of 0.8% to 1.2% for the remainder of the study. Animals were intubated with a 7.0-mm endotracheal tube. Temperature was measured with an esophageal temperature probe and was maintained at 37.5 ± 0.5°C with a warming blanket throughout the study. Vascular access was obtained in the bilateral femoral arteries with 8-F sheaths placed percutaneously under ultrasound guidance. An 8-F sheath was placed in the right external jugular vein. A right ear vein IV catheter was placed. The central aortic pressure was monitored continuously with a micromanometer-tipped catheter (Millar Instruments, Houston, Texas) placed through the left femoral sheath, and the right atrial pressure was measured with a second micromanometer-tipped catheter placed in the right external jugular sheath. All animals received an IV heparin bolus (100 U/kg) and 1,000 U heparin every 2 h thereafter. The animals were ventilated with room air using volume-controlled ventilation (Narkomed, Draeger Medical, Telford, Pennsylvania) with tidal volume of 10 ml/kg and a respiratory rate adjusted to maintain PaCO₂ of 40 mm Hg and arterial O₂ saturation >95% as measured from arterial blood (Gem 300, Instrumentation Laboratory, Bedford, Massachusetts). Surface electrocardiographic tracings were continuously recorded. All data were recorded with a BIOPAC digital acquisition system (BIOPAC Systems Inc., Goleta, California).

**EXPERIMENTAL PROTOCOLS.** Animals (n = 55) were randomized into 1 of 4 treatment groups: control, P188, delayed P188, and polyethylene glycol (PEG) 8,000 Da. Each treatment group was further divided into 2 groups: mitochondrial studies or assessment of infarct size (Figure 1). The protocol details were described previously (15) and are described briefly in the following text.

**Blood viscosity assessment.** Arterial blood was collected from animals prior to ischemia. Heparin was added (10 U/ml) to prevent thrombus formation. Hematocrit was measured at 28%. Blood was added to
inhibiting the area adjacent to the LAD (nonischemic).

Mitochondrial experiments were performed as described previously (16). Briefly, excised cardiac tissue was immediately placed in ice cold isolation buffer containing 200 mmol/l mannitol, 50 mmol/l sucrose, 5 mmol/l K\textsubscript{2}HPO\textsubscript{4}, 5 mmol/l 3-(n-morpholino)propanesulfonic acid (MOPS), 1 mmol/l ethylene glycol tetraacetic acid, and 0.1% bovine serum albumin (BSA), pH 7.15. The tissue was then manually minced and homogenized with a blade homogenizer (CAT Scientific, Paso Robles, California) in the presence of 5 U/ml protease (Bacillus licheniformis). The protease was then diluted 10-fold, and homogenization was repeated. Mitochondria were isolated by differential centrifugation including 10 min at 8,000 \( \times \) g followed by resuspension of the pellet and centrifugation at 750 \( \times \) g for 10 min to remove cellular debris. Isolated mitochondria were quantified by Bradford protein quantification assay (Sigma, St. Louis, Missouri). The mitochondrial yield was calculated as the ratio of total protein mass of isolated mitochondrial to total protein mass of the excised heart tissue from which they were isolated.

**Mitochondrial respiration.** Mitochondrial oxygen consumption was measured at 25°C using a Clark-type \( O_2 \) electrode (Model 1302, Strathkelvin Instruments, North Lanarkshire, Scotland) in a water-jacketed chamber. Mitochondria (275 \( \mu \)g) were added to the respiration chamber with experimental buffer containing 130 mmol/l KCl, 5 mmol/l \( K_2 \text{HPO}_4 \), 20 mmol/l MOPS, and 0.1% BSA, pH 7.15. State 2 respiration was initiated with the addition of substrate specific for either complex I (10 mmol/l pyruvate/malate) or complex II (10 mmol/l succinate and 10 mmol/l rotenone, a complex I blocker) of the mitochondrial respiratory chain. State 3 respiration then began with addition of 250 mmol/l adenosine diphosphate. State 4 was observed when the phosphorylation of adenosine diphosphate to adenosine triphosphate was complete. The respiratory control index (RCI) was calculated as the ratio of state 3 to 4 respiration.

**Mitochondrial calcium retention.** Mitochondria (0.5 mg/ml) were combined with complex I (10 mmol/l pyruvate/malate) or complex II (10 mmol/l succinate and 10 \( \mu \)mol/l rotenone) substrates and buffer containing 130 mmol/l KCl, 5 mmol/l \( K_2 \text{HPO}_4 \), 20 mmol/l MOPS, and 0.1% BSA, pH 7.15. CaGreen-5N hexapotassium salt (100 nmol/l) was added to monitor extra-mitochondrial calcium at excitation 510 nm and emission 531 nm (Life Technologies, Grand Island, New York). CaCl\textsubscript{2} (5 mmol/l) was infused at a rate of 150 mmol/min until the CaGreen fluorescence reached steady state. A sudden increase in CaGreen emission suggested an opening of the mitochondrial permeability transition pore (mPTP). The calcium retention capacity is quantified as the calcium required to trigger mPTP opening.

**Infarct size assessment.** After 4 h of reperfusion, the left main coronary artery was again engaged with a 6-F AL 0.75 guide. The right coronary artery was engaged with a 6-F hockey stick guide. The 0.014-inch guidewire was again advanced into the LAD,
Blood viscosity was measured at increasing shear rates with various concentrations of PEG or P188. All data points represent n = 4. Error bars represent SEM. Statistical significance (p < 0.05) denoted as: †comparing PEG and P188 at shear rate 0.1 s⁻¹; ††comparing shear rate 0.1 s⁻¹ vs. 1, 10, and 100 s⁻¹ for PEG; †††comparing shear rate 0.1 s⁻¹ vs. 1, 10, and 100 s⁻¹ for P188; *comparing shear rate 1 s⁻¹ vs. 10 and 100 s⁻¹ for PEG and P188; and #comparing shear rate 0.1 s⁻¹ vs. 100 s⁻¹ for PEG. Abbreviations as in Figure 1.

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tissue (7.4 vs. 8.2; p = 0.85), suggesting near total preservation of mitochondrial respiration through complex I. Complex I RCI for infarct tissue from delayed P188 and PEG-treated animals were similar to infarct tissue from control animals (3.9 and 4.2 vs. 3.7 for delayed P188 [p = 0.85] and PEG [p = 0.61], respectively).

Complex II RCI was significantly reduced for mitochondria isolated from infarct tissue in all treatment groups when compared with nonischemic tissue (2.1 vs. 3.4, 2.7 vs. 3.5, 2.2 vs. 3.9, 2.3 vs. 3.8 for control, P188, delayed P188, and PEG, respectively; p < 0.01) (Figure 4B). There were no significant differences between the treatment groups when comparing ischemic tissues or nonischemic tissues.

Calcium retention, a measure of mitochondrial membrane integrity and mitochondrial function, was significantly reduced in the infarct tissue of all groups in the presence of complex I substrates when compared with nonischemic tissue (Figure 4B). However, calcium retention of mitochondria isolated from P188-treated animals was significantly preserved compared with control, delayed P188, and PEG animals (1,152 nmol vs. 386, 451, and 423 nmol, respectively; p < 0.001).

In the setting of complex II substrates, mitochondria isolated from the infarct territory of P188-treated animals continued to tolerate higher levels of calcium compared with control, delayed P188, and PEG animals (1,481 nmol vs. 848, 843, and 881 nmol, respectively; p < 0.005) (Figure 5B). However, mitochondria from infarct tissue from P188-treated animals also retained significantly greater levels of calcium than the nonischemic mitochondria from P188-treated animals (1,481 vs. 1,005 nmol; p = 0.019). There were no significant differences in calcium retention capacity of the mitochondria taken from control, delayed P188, and PEG animals when infarct and nonischemic tissues were compared.
INFARCT SIZE AND TROPNIN RELEASE ARE REDUCED WITH P188 TREATMENT. Infarct size, as a percentage of area at risk, was significantly reduced with immediate IC P188 infusion compared with control, delayed P188, and PEG treatment animals (13.9% vs. 41.1%, 42.8%, and 45.6%, respectively; p < 0.001) (Figures 6A to 6D). The infarct size with control, delayed P188, and PEG treatments were not significantly different. Serum cTnI was significantly reduced at 4 h in the P188-treated animals as compared with the control, delayed P188, and PEG groups (19.2 μg/l vs. 77.4, 68.8, and 65.1 μg/l, respectively; p < 0.05) (Figure 6E). There were no significant differences between the control, delayed P188, and PEG groups.

SAFETY ENDPOINTS. Ventricular arrhythmias including ventricular tachycardia and ventricular fibrillation occurred in 18% of animals overall. Of the ventricular arrhythmias, 40% developed during ischemia, whereas 60% occurred during reperfusion. There were no significant differences between treatment groups. All animals achieved return of spontaneous circulation and completed the 4-h reperfusion time. Angiography was performed immediately after deflation of the coronary balloon and before medication infusion, demonstrating Thrombolysis In Myocardial Infarction flow grade 3 and similar myocardial blush in all animals. There were no significant differences in creatinine levels between groups at baseline or 4 h after reperfusion. The 4-h creatinine values for control, P188, delayed P188, and PEG groups were 1.1, 1.2, 0.96, and 1.1 mg/dl, respectively.

DISCUSSION

This study reports a significant reduction in cardiac injury with decreased infarct size and preserved mitochondrial function after STEMI using a first-class membrane stabilizing block copolymer called P188. These findings highlight the importance of copolymer delivery route and timing to achieve meaningful myocardial preservation in reperfusion, as we find that immediate and direct IC infusion, but not delayed peripheral delivery, is essential to prevent myocardial injury. These findings may help explain the negative outcomes of the CORE trial, which applied a delayed and peripheral delivery strategy in an era when thrombolysis was widely used.

Previous studies have proposed 2 distinct mechanisms for the effects of P188. The first, altered blood viscosity leading to improved tissue perfusion, is not the primary mechanism, as PEG infusion fails to provide a similar benefit despite similar viscosity effects. The second proposed mechanism involves reduction in reperfusion injury through stabilization of sarcolemmal membranes damaged by the metabolic derangements of ischemia (11,12). Although this mechanism was not tested directly in the current study, it may be supported by the improvement in mitochondrial calcium retention capacity observed. Direct effects of P188 on mitochondria in situ have not been shown in prior studies and are beyond the scope of the current study. Further studies will be required to elucidate the specific mechanism of the benefit.
Ischemia-reperfusion has previously been shown to reduce mitochondrial respiration predominantly at complex I in agreement with the current findings (17). This down-regulation may be due to damage incurred by the respiratory complex, or it may be a result of controlled inhibition of complex I activity possibly reducing the formation of reactive oxygen species that can occur at complex I (18). This study demonstrates near normalization of complex I activity with P188 treatment. The significant improvement in mitochondrial yield further supports the hypothesis that mitochondrial health is improved with P188 treatment. Although serving as a marker of mitochondrial health, preserved complex I function may also provide significant bioenergetic benefits for mitochondria experiencing the severe stress of ischemia-reperfusion.

Uncontrolled calcium influx during ischemia-reperfusion presents a severe challenge to the mitochondria with calcium overload leading to mPTP opening, loss of membrane potential, cessation of respiration, and release of pro-apoptotic factors. Immediate IC P188 treatment demonstrated significant improvement in calcium retention in the infarct.
tissue without any significant effect in the non-ischemic tissue. The mechanism of improved calcium retention is unclear, but it may indicate that P188 is preventing mitochondrial calcium loading in an injury-dependent manner. Importantly, the group receiving delayed peripheral P188 infusion did not demonstrate any of these benefits, suggesting that early and direct infusion was critically important.

The CORE trial, a phase II, open-label clinical trial published in 1997, tested the safety and potential benefits of P188 in 2,948 STEMI patients receiving thrombolytic therapy (13). No clinical benefit was observed. However, multiple significant limitations to the protocol can now be observed (Table 1). First, P188 was delivered by peripheral IV approximately 30 min after thrombolytic therapy was administered. Although the detailed timing is not described in the published study, the CORE trial protocol recommended randomization within 15 min of thrombolytic infusion with initiation of the P188 within 15 min of randomization. This provides a 30-min delay in Pt88 therapy from the time of revascularization. Prior studies using cyclosporine, known to prevent reperfusion injury by inhibiting opening of the mPTP in the setting of cardiac arrest, have shown a severe degradation in efficacy of treatment within as little as 3 min after return of spontaneous circulation (19). Therefore, the 30-min delay in the CORE trial may have negated the opportunity to attenuate reperfusion injury. In contrast, our study demonstrates a 68% reduction in infarct size when a similar dose of Pt88 was delivered directly into the affected coronary artery immediately after reperfusion.

Use of primary percutaneous coronary intervention (PCI) in the current study represents the current standard of care for STEMI patients in the United States where catheterization laboratories are available. Until recently, thrombolytic therapy was the standard treatment modality for patients experiencing myocardial infarction. However, 26% of patients failed to achieve reperfusion even in recent trials (20). In the CORE trial, which exclusively enrolled patients receiving thrombolytic therapy, 46% of control subjects did not achieve revascularization after administration of the thrombolytic. If reperfusion is never achieved, treatments that prevent reperfusion injury will be ineffective. PCI has been shown to result in normal coronary artery flow in over 90% of patients (20). Although absolutely necessary, reinitiation of coronary flow increases the potential for reperfusion injury, creating a need for innovative therapies to prevent this damage (4).

Although myocardial infarction is the most common cause of ischemia/reperfusion injury, other medical scenarios trigger similar pathology, including organ transplantation, cardiac surgery using cardioplegia, and cardiac arrest. Other organ systems can also be affected in situations of stroke or cardiac arrest. P188 was recently tested in combination with other pharmacological and mechanical treatments for ischemia/reperfusion injury in a porcine model of prolonged ventricular fibrillation cardiac arrest, where it showed considerable improvement in cardiac function and neurologically intact survival (21). P188 has also shown a direct benefit in neurons exposed to ischemia with prevention of apoptosis and preservation of the blood-brain barrier (22,23).

The CORE trial discovered a significant reduction in the renal function of patients receiving Pt88. This was particularly prominent in elderly patients and in those with pre-existing renal disease. Subsequent studies have demonstrated a reduction in the renal effects of P188 when the compound is purified to reduce low molecular weight contaminants (24). The P188 used in our study was highly purified in its commercial form, presumably limiting the renal effects. No difference was observed in creatinine after 4 h of treatment, although renal dysfunction may not materialize until later in the course and must be studied further.

**STUDY LIMITATIONS.** First, this study does not elucidate a clear mechanism of action for Pt88. Further, although the dose was chosen on the basis of that used in prior animal studies and the CORE trial, dose optimization was not undertaken. It is clear from our study that timing and route of delivery have a significant effect on outcomes, possibly due to the higher effective dose when delivered directly into the coronary arteries. Although this suggests that a significantly higher systemic dose may provide a similar benefit if delivered early in reperfusion, potential side effects of treatment may also become more prominent.

**TABLE 1** Comparison of the CORE Trial and the Current Study

<table>
<thead>
<tr>
<th>CORE Trial</th>
<th>Current Study</th>
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<tbody>
<tr>
<td>Human patients with STEMI</td>
<td>Translational study with a porcine STEMI model</td>
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<tr>
<td>Thrombolytic therapy</td>
<td>Primary angioplasty</td>
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<tr>
<td>Reperfusion in 54% of patients</td>
<td>100% reperfusion</td>
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<tr>
<td>P188 infused via peripheral IV before reperfusion</td>
<td>Intracoronary P188 infusion</td>
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<td>P188 delivered ~ 30 min after reperfusion</td>
<td>P188 infused immediately upon reperfusion</td>
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<tr>
<td>No clinical benefit observed</td>
<td>66% reduction in infarct size</td>
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<tr>
<td>Renal dysfunction in P188-treated patients</td>
<td>No renal dysfunction early after treatment with purified P188</td>
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CORE = Collaborative Organization for RheothRx Evaluation.
Important differences also remain when comparing this pre-clinical porcine model system to human patients. First, this model requires the presence of inhaled anesthetic to maintain animal comfort. This would be expected to mask the effects of P188, as the inhaled anesthetic itself may have pre- and post-conditioning benefits in all animal groups studied (16,25). However, this would be clinically relevant in the setting of cardiac surgery and transplant. The demonstrated benefit with P188 may, therefore, be an underestimate of its true benefit in the typical STEMI patient population. In addition, the animals do not have underlying comorbidities, which often accompany coronary artery disease and may alter the benefits of P188.

Last, this study is limited in the duration of follow-up, with up to 4 h of monitoring post-P188. Further studies with longer follow-up would need to be performed to assess renal function and cardiac benefit. These studies would not be expected to demonstrate a significant reduction in benefit, as the early predictors of infarct size and cTnI release are well-established to correlate with long-term outcomes.

CONCLUSIONS

This study demonstrates a substantial cardiac benefit of P188 after STEMI using a clinically relevant treatment strategy of IC infusion of P188 at the time of reperfusion. The model is clinically relevant, incorporating PCI similar to the current standard of care in human patients. The results demonstrate that early IC infusion is critical to achieving the benefit.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: STEMI causes significant morbidity and mortality. Reperfusion injury, the injury induced by reconstitution of blood flow into the ischemic area, accounts for as much as 50% of the myocardial injury. Treatment at the time of reperfusion provides an opportunity to prevent this injury.

TRANSLATIONAL OUTLOOK: Although the mechanism remains unknown, P188 provides a significant reduction in reperfusion injury in this porcine model of STEMI. Further studies are required to assess the long-term outcomes after P188 treatment in animals. Subsequent studies should focus on human trials.

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KEY WORDS mitochondria, myocardial infarction, poloxamer 188, reperfusion injury, STEMI