Mesenteric injury after cardiopulmonary bypass: Role of poly(adenosine 5’-diphosphate-ribose) polymerase*

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**Objectives:** To investigate the effects of the ultrapotent poly(adenosine 5'-diphosphate-ribose) polymerase (PARP) inhibitor INO-1001 on cardiac and mesenteric function during reperfusion in an experimental model of cardiopulmonary bypass with cardioplegic arrest.

**Design:** Prospective, randomized, and blinded experimental study.

**Setting:** Research laboratory.

**Subjects:** Twelve anesthetized dogs underwent cardiopulmonary bypass with hypothermic cardioplegic cardiac arrest.

**Interventions:** After 60 mins of hypothermic cardiac arrest, either PARP inhibitor INO-1001 (1 mg/kg, n = 6) or vehicle (control, n = 6) was administered during reperfusion.

**Measurements and Main Results:** Left ventricular hemodynamic variables were measured by combined pressure-volume-conductance catheters. Coronary and mesenteric blood flow and vasodilatory responses to acetylcholine and sodium nitroprusside as well as mesenteric lactate and creatinine phosphokinase release were also determined. The administration of INO-1001 led to a significantly improved recovery of left ventricular systolic function (p < .05) after 60 mins of reperfusion. Coronary and mesenteric blood flow were also significantly higher in the INO-1001 group (p < .05). Although the vasodilatory response to sodium nitroprusside was similar in both groups before and after cardiopulmonary bypass and similar in response to acetylcholine before cardiopulmonary bypass, PARP-inhibited dogs had lower mesenteric vascular resistance after cardiopulmonary bypass (p < .05). Mesenteric lactate and creatinine phosphokinase release was significantly lower in the PARP inhibitor treated group (p < .05).

**Conclusion:** PARP inhibition with INO-1001 improves the recovery of myocardial function and prevents mesenteric vascular dysfunction and tissue injury after cardiopulmonary bypass with hypothermic cardiac arrest. (Crit Care Med 2004; 32:2392–2397)

**Key Words:** poly(adenosine 5'-diphosphate-ribose) polymerase; cardioplegia; cardiopulmonary bypass; heart surgery; reperfusion injury; mesenteric injury

To date, the majority of routine cardiac surgery is performed using cardiopulmonary bypass (CPB) with cardioplegic arrest. Despite technological and medical advances, CPB still imposes considerable physiologic stress on the patient (1). Independent of the technique of cardioplegia, temporary cardiac dysfunction can be observed frequently as a consequence of ischemia/reperfusion injury (2). In addition, CPB is also known to induce a systemic inflammatory reaction (3–5) with free radical release (6) or vehicle (7) leading to secondary organ injury. There is an evidence that pulmonary (7), renal (8) or gastrointestinal (9) injury may occur in the context of cardiac surgery as a consequence of CPB-induced inflammatory reaction and reduced organ perfusion (6, 10) ranging from subclinical functional changes in most patients to full-blown clinical complications. Gastrointestinal complications have a low incidence, between 1% and 3% (9, 11, 12). Once a gastrointestinal complication occurs, however, the overall mortality rate ranges from 13.5% to 72%. In particular, patients with gastric bleeding or cholecystitis are most likely to survive, whereas the lethality of mesenteric ischemia is extremely high (9, 12). In previous studies (6, 13), we showed that intestinal injury can be observed during routine CPB as a result of hypoperfusion, impaired endothelial function, and free radical generation.

Poly(adenosine 5'-diphosphate-ribose) polymerase (PARP) is an abundant nuclear enzyme of eukaryotic cells. Free radical production and related cytotoxicity during inflammation or ischemia/reperfusion may lead to DNA strand-breakage that activates PARP. Activated PARP catalyzes an energy-consuming cycle by transferring adenosine 5'-diphosphate (ADP) ribose units to nuclear proteins. The results of this process are rapid depletion of the intracellular oxidized nicotinamide adenine dinucleotide and adenosine 5'-triphosphate pools, which slows the rate of glycolysis and mitochondrial respiration leading to cell necrosis (14). Both the genetic disruption of the PARP pathway and the pharmacologic...
blockade of PARP effectively protect against reactive oxygen and nitrogen species induced toxicity in vitro (14). PARP has recently been proposed to play a role in the pathogenesis of myocardial reoxygenation injury (15). Myocardial reperfusion injury in vitro and in vivo has been shown to be ameliorated by genetic disruption or pharmacologic blockade of PARP (14, 15). It has also been demonstrated that PARP inhibition leads to a significant improvement of endothelial function ex vivo in peroxynitrite-treated thoracic aortic rings (16) and in isolated mesenteric arteries in the setting of splanchnic ischemia/reperfusion (17). We recently demonstrated that PARP inhibition effectively reduces CBP-induced myocardial and pulmonary injury as well as coronary and pulmonary endothelial dysfunction (18, 19).

As PARP inhibition is a promising therapeutic concept in both cardiac ischemia/reperfusion and secondary inflammatory organ injury, we tested the hypothesis that INO-1001, a novel ultrapotent PARP inhibitor (20, 21), improves cardiac function and reduces mesenteric injury in a clinically relevant canine model of CBP and cardiopulmonary arrest.

MATERIALS AND METHODS

Animals and Experimental Groups. Twelve female dogs (foxhounds) weighing 23–32 kg (25 ± 4 kg) were used in this experiment. All animals received humane care in compliance with the “Principles of Laboratory Animal Care” formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals (22). The experiments were approved by the Ethical Committee of the Land Baden-Württemberg for Animal Experimentation. The animals were divided into two groups in a randomized blinded fashion. Six animals received 1 mg/kg INO-1001 (Inotek Pharmaceuticals, Beverly, MA), an isoidosinolone-based, novel, ultrapotent, water-soluble PARP-inhibitor (20, 21), as a single bolus intravenous injection (20, 21), as a short infusion starting 5 mins before aortic declamping and continuing during the first 25 mins of reperfusion. Six vehicle-treated animals served as controls. The applied dose of INO-1001 is based on previous dose-response and pharmacokinetic studies (unpublished data).

General Management and Cardiopulmonary Bypass. The dogs were sedated with propofol and anesthetized with pentobarbital (15 mg/kg initial bolus and then 0.5 mg/kg/hr intravenously), paralyzed with pancuronium bromide (0.1 mg/kg as a bolus and then 0.2 mg/kg/hr intravenously), and endotracheally intubated. The dogs were ventilated with a mixture of room air and oxygen (FiO2 60%) at a frequency of 12–15/min and a tidal volume starting at 15 mL/kg/min. The settings were adjusted to maintain arterial partial carbon dioxide pressure levels between 35 and 40 mm Hg. The femoral artery and vein were cannulated to record aortic pressure and to take blood samples for biochemical analysis. Basic intravenous volume substitution was carried out with Ringer’s solution. According to the values of potassium, bicarbonate, and base excess, substitution included administration of potassium chloride and sodium bicarbonate (8.4%). Neither catecholamines nor other hormonal or pressor substances were administered.

Through a midline laparotomy, an ultrasonic flow probe (Transonic Systems, Ithaca, NY) was positioned around the origin of the superior mesenteric artery and connected to a flow monitor. A 2.5-Fr catheter was introduced in the superior mesenteric vein through an ideal tributary. The cannula was flushed with heparinized saline and secured with a purse string suture. After preparation, the intestine was reintroduced into the abdomen.

After left anterolateral thoracotomy in the fourth intercostal space and pericardiotomy, the great vessels were dissected. A combined 6-Fr Millar pressure-conductance catheter with 6-mm spacing was inserted via the apex (Millar Instruments, Houston, TX). Ultrasonic flow probes were positioned around the left anterior descending coronary artery and the ascending aorta and connected to a flow monitor.

Cardiopulmonary Bypass. The cardiopulmonary bypass model is described in detail elsewhere (18, 19). Briefly, after systemic anticoagulation with sodium heparin (300 units/kg), the left subclavian artery was cannulated for arterial perfusion. The venous cannula was placed in the right atrium. The extracorporeal circuit consisted of a heat exchanger, a venous reservoir, a roller pump, and a membrane oxygenator primed with Ringer’s lactate solution (1000 mL) supplemented with heparin (150 units/kg) and 20 mL of sodium bicarbonate (8.4%). After initiation of CPB, the body temperature was cooled to 28°C. After cross-clamping of the aorta, the heart was arrested with 25 mL/kg HTK solution (in mmol: 15 NaCl, 9 KCl, 4 MgCl2, 6 H2O, 18 histidine hydrochloride monohydrate, 180 histidine, 2 tryptothphan, 30 mannitol, 0.015 CaCl2, 1 potassium-hydrogen-2-oxopentanodiantio, 0.6 Na2HPO4·12H2O). The time between initiation of CPB and cardiac arrest was standardized at 10 mins. During cardiac arrest, the pump flow was set at 100 mL/kg/min to maintain perfusion pressure above a value of 35–40 mm Hg at any time point, and alpha-stat management was applied. Twenty minutes before cross-clamp removal, rewarming was initiated. After 60 mins of cardiac arrest, the aorta was declamped and the heart was reperfused with normothermic blood in the bypass circuit. If necessary, ventricular fibrillation was counteracted with DC cardioversion of 40 J. Ventilation was restarted with 100% oxygen. All animals were weaned from CPB without inotropic support 20 mins after the release of the aortic cross-clamp. Each animal underwent 90 mins of CPB with 60 mins of cardiac arrest.

Data Acquisition and Analysis. Left ventricular systolic and diastolic pressures and volumes signals were collected by Sigma 5 device (CD-Leycom, Leiden, Netherlands). Stroke volume was calculated from the integrated flow signal measured by an ultrasonic flow probe and was used to calibrate the volume signal from the conductance catheter. Parallel conductance was estimated by rapid injection of 1 mL of hypertonic saline into the pulmonary artery. Venous occlusions were performed to obtain a series of pressure-volume loops. The slope and intercept of the left ventricular end-systolic pressure-volume relationships and preload recruitable stroke work were calculated as load-independent indexes of myocardial contractility.

Mesenteric and coronary blood flows were measured as described previously. Mesenteric endoluminal-dependent vasodilation was assessed after intra-arterial administration of a single bolus of acetylcholine (10−7 M) and endoluminal-independent vasodilation after sodium-nitroprusside (10−4 M). The vasoresponse was expressed as percent change of baseline mesenteric vascular resistance.

Hemoglobin, P O2, P CO2, H CO3−, and pH were measured in arterial and venous blood by a blood-gas analyzer (AVL 995-HB). Laboratory analyses were performed (Cobas Mira Plus, Roche Diagnostic Systems, Switzerland) to determine arterial and venous plasma levels of lactate and creatinine phosphokinase. Plasma myeloperoxidase concentrations—an index of neutrophil accumulation—were determined by standard enzyme-linked immunosorbent assay kits from IBL (Hamburg, Germany). Mesenteric lactate and creatinine phosphokinase gradient and myeloperoxidase release were derived as the difference between mesenteric venous and systemic arterial concentrations multiplied by mesenteric blood flow, respectively.

The immunohistochemical detection of poly(ADP-ribose) (PAR), the product of PARP, was used to detect the activation of PARP in tissues (19). Mesenteric biopsy specimens were taken at baseline and after 60 mins of reperfusion and fixed in formalin and embedded in paraffin. After section of the probes, slides were deparaffinized, antigen was retrieved by incubation in boiling 0.1 M sodium citrate (pH 6), and then slides were rinsed in water. Slides were incubated in 10% (W/V) trichloroacetic acid for 10 mins to prevent catalysis of the polymer by PAR glycohydrodase. Slides were rinsed in phosphate buffered saline, and then endogenous peroxidase activity was quenched with 1.5% (vol/vol) hydrogen peroxide in methanol for 15 mins. Non-
specific binding sites were blocked using 2% (vol/vol) normal goat serum in phosphate buffered saline for 1.5 hrs at 37°C. Preliminary experiments determined optimal antibody concentrations. Chicken antibody against PAR was a generous gift from Dr. John R. Simon (Tulip BioLabs, West Point, PA) and was used in 1:250 or 1:500 dilutions. Slides were incubated overnight at 4°C and then washed in phosphate buffered saline, and as a secondary antibody, biotinylated goat anti-chicken immunoglobulin G (Vector Laboratories, Burlingame CA) was used for 30 min at 30°C. After phosphate buffered saline washes, slides were incubated with Vectastain Elite ABC (peroxidase) standard kit (Vector Laboratories) for 30 mins at 30°C and developed using diaminobenzidine substrate. Slides were counterstained with nuclear fast red.

Aortic and left ventricular pressures as well as aortic, coronary, and mesenteric blood flows were recorded continuously. Left ventricular pressure-volume relationships and coronary and mesenteric vascular function were assessed before cardiopulmonary bypass and after 60 mins of reperfusion. Biochemical measurements were performed at baseline and after 60 mins of reperfusion. All values were expressed as mean ± SEM. Paired Student’s t-test was used to compare two means within groups. Individual means between the groups were compared by one-way analysis of variance. A probability value <.05 was considered statistically significant.

**RESULTS**

Hemodynamic variables are shown in Table 1. Baseline variables did not differ between the groups and were within the physiologic range. Heart rate did not change in either the control or the INO-1001 group. Mean arterial pressure during cardiopulmonary bypass was 55 ± 3 vs. 58 ± 7 mm Hg in the control and in the INO-1001 group, respectively (non-significant). After 60 mins of cardioplegic arrest and 60 mins of reperfusion, mean arterial pressure decreased significantly (p < .05) in the control group whereas it remained unchanged in the INO-1001 group. Cardiac output did not differ significantly between the groups. However, cardiac output showed a clear decreasing tendency within the control group without reaching the level of significance (Table 1). The load-independent indexes of myocardial contractility slope of the end-systolic pressure-volume relationship and preload recruitable stroke work showed a significant decrease (p < .05) after extra-corporal circulation and reperfusion in the control group, whereas they remained unchanged in the INO-1001-treated group.

Mesenteric blood flow was nearly identical at baseline in both groups and showed a significant decrease during CPB and hypothermic cardiac arrest (Fig. 1). During the reperfusion phase, mesenteric blood flow remained impaired in the control group whereas it recovered at baseline levels in the INO-1001 group.

Vasomotor function did not differ between the groups at baseline. Endothelium-dependent vasodilation after acetylcholine was significantly (p < .05) reduced in the control group after 60 mins of reperfusion compared with values before CPB (Fig. 2), whereas it remained unchanged in the INO-1001 group. Endothelium-independent vasodilation after sodium-nitroprusside showed no significant differences over the time and between the groups (Fig. 2).

Mesenteric myeloperoxidase release did not differ between the groups before CPB. At 60 mins of reperfusion, myeloperoxidase release increased significantly in the control group but remained unchanged in the INO-1001 group (Fig. 3).

Mesenteric lactate production and creatinine phosphokinase release were significantly (p < .05) higher in the control group after 60 mins of reperfusion compared with baseline as well as with the INO-1001 group (Fig. 3).

There was no detectable PAR at baseline in the mesenteric specimens (not shown). After 60 mins of reperfusion, extensive PAR staining was observed in mesenteric specimens of the control group: In all intestinal layers, the cell nuclei showed a characteristic, somewhat inhomogeneous staining against PAR. In a considerable part of the cell nuclei, however, PAR staining was even homogeneous. This staining was almost completely abrogated in the INO-treated group. Two representative specimens are shown in Figure 4. The arrows indicate exemplary homogeneous and inhomogeneous staining against PAR in different intestinal layers. If we compare the control and INO-treated specimens in Figure 4, almost all cell nuclei show more (homogeneous) or less (inhomogeneous) staining than controls.

**Table 1.** Hemodynamic variables before cardiopulmonary bypass and after 60 mins of reperfusion

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<thead>
<tr>
<th></th>
<th>Control</th>
<th>INO-1001</th>
<th>Control</th>
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<tr>
<td><strong>Baseline</strong></td>
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<tr>
<td>HR, beats/min</td>
<td>110 ± 6</td>
<td>112 ± 7</td>
<td>126 ± 9</td>
<td>112 ± 8</td>
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<tr>
<td>MAP, mm Hg</td>
<td>98 ± 7</td>
<td>93 ± 5</td>
<td>73 ± 5</td>
<td>89 ± 6</td>
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<td>CO, L/min</td>
<td>2.32 ± 0.51</td>
<td>2.97 ± 0.79</td>
<td>2.03 ± 0.37</td>
<td>3.67 ± 0.88</td>
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<td>Ees, mm Hg/mL</td>
<td>5.5 ± 1.1</td>
<td>4.8 ± 0.4</td>
<td>2.6 ± 0.3</td>
<td>4.2 ± 0.4</td>
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<tr>
<td>PRSW, kerg</td>
<td>75 ± 4</td>
<td>76 ± 8</td>
<td>56 ± 6</td>
<td>70 ± 7</td>
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<td>CBF, mL/min</td>
<td>42 ± 6</td>
<td>48 ± 5</td>
<td>21 ± 3</td>
<td>52 ± 4</td>
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<td><strong>60 Mins of Reperfusion</strong></td>
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<tr>
<td>HR, beats/min</td>
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<td>MAP, mm Hg</td>
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<td>CO, L/min</td>
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<td>Ees, mm Hg/mL</td>
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<td>PRSW, kerg</td>
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<td>CBF, mL/min</td>
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*p < .05 vs. baseline; *p < .05 INO-1001 vs. control. All values are given as mean ± SEM.
staining against PAR in the control group, yet practically no staining could be observed after INO-1001 treatment.

**DISCUSSION**

In this study, the benefits of the application of the novel ultrapotent PARP-inhibitor INO-1001 during reperfusion were assessed in a canine model of CPB and cardiac arrest. In accordance with the literature (2, 18, 19), hypothermic cardioplegic arrest and reperfusion resulted in a decline of contractile function and coronary blood flow, which can be reversed by PARP inhibition. We have shown that PARP inhibition improves mesenteric vascular function and reduces mesenteric injury.

Previous studies have shown PARP activation in the reperfused heart (14, 15) and reduced reperfusion injury in PARP knockout animals (14, 15) or after PARP inhibition (14, 15, 18, 19). The current study confirms our previous findings, which show the effectiveness of PARP inhibition in a clinically relevant large animal model of cardiopulmonary bypass. The mechanisms of INO-1001’s protective action are multiple. In various types of ischemia/reperfusion, the prevention of PARP activation results in a better preservation of the high-energy phosphophosphate content resulting in an improved energy status (14, 15, 23). Beside its direct effects on myocardial metabolism, PARP activation contributes to the expression of P-selectin and intracellular adhesion molecule-1 during cardiac ischemia/reperfusion (14, 15, 23) and consequently to the recruitment of neutrophils into the jeopardized tissue. It is likely that both an inhibition of the energetic component of PARP-mediated cell dysfunction and the suppression of proinflammatory pathways contribute to cardioprotective effects (14, 15).

Until now only a few studies had investigated the pathophysiologic effects of CPB on the mesenterium (6, 13, 24–28). Summarizing these studies, CPB-associated mesenteric hypoperfusion (6, 13) and inflammatory reaction (24–26) with subsequent free radical generation (6, 29) lead to mesenteric vascular dysfunction as a result of the imbalance between local vasodilative and vasoconstrictor substances. This may trigger a vicious cycle with vascular dysregulation and flow redistribution resulting in shunting of blood flow away from the metabolically active gut mucosa. These processes may lead to anaerobic conversion of gut metabolism (13) and tissue damage. The data of the control group confirm these previous findings in terms of reduced mesenteric blood flow despite normal cardiac output, impaired endothelial function, conversion toward anaerobic metabolism (increased lactate levels), and cell injury (increased creatinine-phosphokinase levels). Furthermore, increased plasma myeloperoxidase levels indicate increased neutrophil accumulation and subsequently increased oxidative stress in the mesenterium.

The present study is the first to prove immunohistologically that the complex pathophysiologic processes during and after CPB lead to PARP activation in the mesenterium. Both local hypoperfusion and systemic inflammatory reaction may contribute to oxidative stress. Free radical mediated DNA strand breaks lead, in turn, to a subsequent activation of PARP. Although PAR-positive staining could be observed in all layers, the most intensive staining occurred in the lamina propria and the submucosal layers. This is in agreement with previous studies (30–32) where also the submucosal layers showed the most intensive PARP staining in rodent models of splanchnic occlusion and reperfusion. Also, the mesenteric injury was significantly less in our model as the
mesenteric artery was not completely occluded.

The current investigation demonstrates for the first time that systemic PARP inhibition prevents mesenteric vascular dysfunction and tissue damage. Prior studies in rodent models of splanchnic occlusion and reperfusion (30–32) described reduced decrease in blood pressure, reduced morphologic injury and neutrophil infiltration, and decreased up-regulation of P-selectin and intracellular adhesion molecule-1 as well as reduced intestinal hyperpermeability after PARP inhibition. These studies suggested that similar to cardiac ischemia/reperfusion, PARP inhibition attenuates both energy depletion and proinflammatory pathways. Mazzon and colleagues (32) proposed a positive feedback cycle: early hydroxyl radical and peroxynitrite production → PARP-related endothelial injury → neutrophil infiltration → more hydroxyl and peroxynitrite production. Inhibition of PARP would interrupt this cycle at the level of endothelial injury. The observations in splanchnic occlusion and reperfusion models are probably not completely transferable to the situation of CPB-associated mesenteric injury, as the mesenteric vessels are not occluded. Nevertheless, functional hypoxia may occur as result of flow redistribution from nutritive capillaries to arteriovenous shunts (13). It was also shown in intravital microscopic studies (24, 25) that CPB facilitates the neutrophil-endothelial interaction both at the early rolling phase mediated by P-selectin and at late firm adhesion mediated by intracellular adhesion molecule-1. In the present study, myeloperoxidase activity—an index of neutrophil accumulation—was increased after CPB, which was abolished by PARP inhibition. Furthermore, we demonstrated endothelial dysfunction after CPB, which could be prevented by PARP inhibition. As discussed previously, probably the reduction of both energy depletion and proinflammatory responses may contribute to the improved endothelial response in the INO-1001-treated group. Whether the PARP pathway has a direct interaction with the L-arginine-nitric oxide pathway remains to be clarified. Even if a growing number of studies report an improvement of endothelial function after PARP inhibition under pathophysio logic conditions, no evidence exists for the direct involvement of nitric oxide synthases and metabolism. Taken together, CPB-induced mesenteric injury is probably the consequence of the combined effects of local malperfusion (6, 13, 26, 27) and systemic inflammatory reaction (1, 3–5, 24–26, 29), which in turn leads to PARP activation, positive feedback cycle of endothelial dysfunction, further free radical generation, and subsequent tissue injury, as described previously (32). The confirmation of this proposed pathomechanism, however, needs further investigation.

It is probable that PARP inhibition has additional direct effects on the intestinal epithelial cell function. Unfortunately, we do not have direct evidence at this point. Also, previous studies assessed only biochemical markers of intestinal tissue injury but not epithelial function.

The present study has some limitations. Similar to the clinical situation, in the present in vivo model, different types of pathophysiologic stimuli are counteracting cardiac ischemia/reperfusion and systemic inflammatory reaction to CPB. The systemic inflammatory reaction may worsen reperfusion injury, and in turn reduced myocardial function may worsen the hemodynamic consequences of the systemic inflammatory reaction. Therefore, it remains unclear how far improved mesenteric vascular function and injury affect improved cardiac function in the INO-1001 group or the local effects of PARP inhibition. However, even though load-independent indexes showed a marked difference between the groups, cardiac output and arterial pressure showed only small differences. Cardiac output differed much less than mesenteric blood flow between the groups. Furthermore, the immunohistochemical staining for PAR clearly demonstrated PARP activation in the mesenterium, which was abolished by INO-1001 during the reperfusion phase. Therefore, we can assume that the observed reduction of mesenteric injury is mainly caused by the local effects of PARP inhibition.

CONCLUSIONS

The results of the present study strengthen the notion that PARP inhibition may represent a novel important therapeutic target in myocardial and secondary—in particular mesenteric—organ injury after CPB and that PARP inhibitors such as INO-1001 may have the potential to ameliorate complications in cardiac surgery.

REFERENCES


P oly(adenosine 5'-diphosphate-ribose) polymerase inhibition with INO-1001 improves the recovery of myocardial function and prevents mesenteric vascular dysfunction and tissue injury after cardiopulmonary bypass with hypothermic cardiac arrest.


