Research Article

Intraportal versus Systemic Pentoxifylline Infusion after Normothermic Liver Ischemia: Effects on Regional Blood Flow Redistribution and Hepatic Ischemia-Reperfusion Injury

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Pentoxifylline (PTX) has been shown to have beneficial effects on microcirculatory blood flow. In this study we evaluate the potential hemodynamic and metabolic benefits of PTX during hepatic ischemia. We also test the hypothesis that portal PTX infusion can minimize the I/R injury when compared to systemic infusion.

Methods. Twenty-four dogs (18.1 ± 0.7 kg) were subjected to portal triad occlusion (PTO) for 45 min. The animals were assigned to 3 groups: CT (control, PTO, n = 8), PTX-syst (PTO + 25 mg/Kg of PTX IV, n = 8), and PTX-pv (PTO + 25 mg/Kg of PTX in the portal vein, n = 8). Animals were followed for 120 min. Systemic hemodynamics, gastrointestinal tract perfusion, oxygen-derived variables, and liver enzymes were evaluated throughout the experiment.

Results. Animals treated with PTX presented significantly higher CO in the first hour after reperfusion, when compared to the CT (∼3.7 vs. 2.1 L/min, P < 0.05). Alanine aminotransferase (ALT) was similar in the PTX groups two hours after reperfusion but significantly higher in the CT (227 vs. ∼64 U/L, P < 0.05).

Conclusion. PTX infusion was associated with hemodynamic benefits and was able to minimize liver injury during normothermic hepatic I/R. However, local PTX infusion was not associated with any significant advantage over systemic route.

1. Introduction

Despite technical advances in liver surgery in the last decades, the consequences of liver ischemia/reperfusion injury remain a major concern for surgeons. Liver ischemia/reperfusion (I/R) injury is a complex cascade of events mediated by numerous inflammatory cells and molecular mediators, resulting in hepatocyte death and systemic inflammatory response. The degree of inflammatory response and organ dysfunction is dependent on duration of liver ischemia and underlying liver disease. In this setting, activation of hepatic macrophages plays an important role. Macrophages have been responsible for the release of various inflammatory mediators, including but not limited to tumor necrosis factor alpha (TNF-α). Several studies have shown that the inhibition of TNF-α production or its neutralization after isolated hepatic I/R decreases polymorphonuclear neutrophil infiltration with further reduction of the I/R injury [1–3].

Pentoxifylline (PTX) is a methylxanthine derivative that displays vasodilatory effects on peripheral blood vessels, particularly on the liver [4–8]. In addition, PTX has other important pharmacological properties that may be responsible for the minimization of hepatic I/R including; attenuation of leukocyte-endothelial interactions, reduction of blood viscosity, and suppression of cytokine release by the overstimulated Kupffer cells [9–13].

Previously, we and others have shown the cardiovascular benefits of PTX infusion in a canine model of hemorrhagic
shock [10, 14]. However, no existing study has ever examined
the effects of PTX infusion on systemic and locoregional
hemodynamics in a large animal model of hepatic I/R.
With that in mind, we have designed this study to evaluate
the potential hemodynamic and metabolic benefits of PTX
infusion during normothermic hepatic ischemia. We have
also tested the hypothesis that regional PTX infusion (i.e.,
portal) can minimize the I/R injury when compared to
systemic infusion.

2. Methods

The experimental protocol was approved by the Institutional
Review Board, in adherence with the “Principles of Labora-
tory Animal Care” formulated by the National Society for
Medical Research and the “Guide for the Care and Use of
Animals” by the National Institutes of Health.

2.1. Animal Preparation. Twenty-four male mongrel dogs,
weighing 17.9 ± 0.7 kg, were fasted for 12 hours prior to the
study, with free access to water. Anesthesia was induced with
an intravenous injection of 0.1 mg/kg of morphine sulfate
followed by 25 mg/kg of pentobarbital sodium. Additional
doses of pentobarbital, 2 mg/kg, were used as necessary. A
cuffed endotracheal tube was placed to allow mechanical
ventilation with a 1.0 fraction of oxygen inspired, at a tidal
volume of 15 mL/kg (670 Takaoka, ventilator, São Paulo, SP,
Brazil). The respiratory rate was adjusted to maintain an ini-
tial arterial pCO2 at 40 ± 5 mmHg. A urinary bladder catheter
was placed for urinary drainage. During surgical preparation,
a heating pad was used to maintain normothermia. The
animals received lactated Ringer solution, 10 mL/kg/h, to
compensate for fluid losses.

A polyethylene cannula (P240) was placed in the right
carotid artery to measure mean arterial pressure and to collect
arterial blood samples for blood gas, pH, bicarbonate, base
deficit, hematocrite and hemoglobin analyses. A 7.5 Fr flow-
directed thermodilution fiberoptic pulmonary artery catheter
with thermal filament (CCOmbo 744H7.5F, Edwards Swan-
Ganz, Baxter Edwards Critical Care, Irvine, CA, USA) was
introduced through the right external jugular vein with its
tip placed in the pulmonary artery, guided by the pressure
wave tracings. This catheter was connected to a cardiac
computer (Vigilance, Baxter Edwards Critical Care, Irvine,
CA, USA) to measure cardiac output using 3-mL bolus
injections of isotonic saline at 20°C. Each deter-
mation was the arithmetic mean of three consecutive
measurements when their differences did not exceed 10%.
Arterial, portal, and mixed venous base deficits, pH, pCO2,
pO2, oxygen saturation, hemoglobin, bicarbonate levels, and
ALT and DHL were measured at baseline (BL), at the end of
hepatic ischemia (P45) and 15, 60, and 120 after reperfusion
(R15, R60, and R120, resp.). All blood samples were analyzed,
immediately after their collection, by a Stat Profile Ultra
Analyzer (Nova Biomedical, Waltham, MA, USA). Systemic
and splanchnic oxygen delivery, consumption, and extraction
(DO2syst, VO2syst, O2ERsyst, DO2splanch, VO2splanch, and
O2ERsplanch, resp.) were calculated using standard formu-
lae.

2.3. Statistical Methodology. Results are presented as mean ±
standard error of mean. Statistical analysis was performed
using a Statistic Package for Social Sciences for Windows soft-
ware (version 10.0, SPSS, Chicago, IL). Differences between
Table 1: Mean arterial and pulmonary artery pressures (MAP and MPAP, mmHg), arterial hemoglobin (g/dL), arterial pH in CT (control, portal triad clamping, \( n = 8 \)), PTX-sys (portal triad clamping + 25 mg/Kg of PTX intravenous systemically, \( n = 8 \)), and PTX-pv (portal triad clamping + 25 mg/Kg of PTX in the portal vein, \( n = 8 \)) groups.

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>BL</th>
<th>P45</th>
<th>R15</th>
<th>R60</th>
<th>R120</th>
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<tbody>
<tr>
<td><strong>MAP mmHg</strong></td>
<td>CT</td>
<td>100.5 ± 20.4</td>
<td>91.0 ± 21.5</td>
<td>83.3 ± 25.2</td>
<td>67.5 ± 26.4&lt;sup&gt;a&lt;/sup&gt;&lt;sup&gt;b&lt;/sup&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>73.5 ± 29.4&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>PTX-syst</td>
<td>115.3 ± 17.7</td>
<td>85.0 ± 22.2</td>
<td>94.1 ± 21.5</td>
<td>80.2 ± 18.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>87.0 ± 31.2</td>
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<td>PTX-pv</td>
<td>111.6 ± 21.4</td>
<td>84.0 ± 14.8</td>
<td>89.2 ± 20.6</td>
<td>78.0 ± 14.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>87.2 ± 19.2</td>
</tr>
<tr>
<td><strong>MPAP mmHg</strong></td>
<td>CT</td>
<td>15.6 ± 2.2</td>
<td>16.8 ± 2.8</td>
<td>16.2 ± 3.9</td>
<td>15.0 ± 4.2</td>
<td>13.0 ± 3.6</td>
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<td>PTX-syst</td>
<td>14.7 ± 3.7</td>
<td>14.6 ± 5.0</td>
<td>16.1 ± 3.2</td>
<td>14.0 ± 2.6</td>
<td>13.7 ± 2.8</td>
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<tr>
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<td>PTX-pv</td>
<td>15.6 ± 4.8</td>
<td>16.5 ± 5.2</td>
<td>17.5 ± 5.7</td>
<td>16.4 ± 5.1</td>
<td>15.7 ± 4.9</td>
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<td><strong>Hemoglobin g/dL</strong></td>
<td>CT</td>
<td>12.9 ± 2.1</td>
<td>10.2 ± 2.4</td>
<td>10.5 ± 2.8</td>
<td>11.4 ± 3.1</td>
<td>11.4 ± 3.2</td>
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<tr>
<td></td>
<td>PTX-syst</td>
<td>13.6 ± 1.7</td>
<td>11.2 ± 2.0</td>
<td>11.1 ± 2.2</td>
<td>10.4 ± 2.2</td>
<td>10.3 ± 2.7</td>
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<tr>
<td></td>
<td>PTX-pv</td>
<td>12.9 ± 1.7</td>
<td>10.4 ± 1.7</td>
<td>10.4 ± 1.2</td>
<td>10.1 ± 1.5</td>
<td>9.6 ± 1.4</td>
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<tr>
<td><strong>Arterial pH</strong></td>
<td>CT</td>
<td>7.36 ± 0.06</td>
<td>7.30 ± 0.07</td>
<td>7.23 ± 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.21 ± 0.07&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.21 ± 0.05&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>PTX-syst</td>
<td>7.41 ± 0.06</td>
<td>7.32 ± 0.08</td>
<td>7.25 ± 0.09&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.24 ± 0.11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.24 ± 0.11&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>PTX-pv</td>
<td>7.36 ± 0.06</td>
<td>7.28 ± 0.06</td>
<td>7.22 ± 0.07&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.24 ± 0.09&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.24 ± 0.08&lt;sup&gt;a&lt;/sup&gt;</td>
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</table>

Legends: BL: baseline; P45: 45 min after Pringle’s maneuver; R15, R60, and R120: 15, 60, and 120 min after reperfusion. Data are shown as mean ± SEM. *Indicates \( P < 0.05 \) versus BL; \( \text{a} \) indicates \( P < 0.05 \) versus PTX-sys; \( \text{b} \) indicates \( P < 0.05 \) versus PTX-pv.

Groups were analyzed using repeated measure analysis of variance and post hoc Tukey’s test. Statistical significance was considered for \( P \) values less than 0.05.

3. Results

3.1. Systemic Hemodynamic Parameters. Portal triad occlusion promoted a slight reduction in MAP in all animals (Table 1). During early reperfusion (R60) lower MAP levels were observed in all three groups in comparison to baseline measurements. However, there was no significant difference between groups. At the end of experiment the MAP in both PTX-sys and PTX-pv presented a partial recovery (Table 1). Mean pulmonary arterial pressure remained stable throughout the experiment, with no differences between groups.

Baseline cardiac output was similar in all three groups. However, animals treated with PTX presented significantly higher CO in the first hour after reperfusion, when compared to the control group (Figure 1(a)). Cardiac output was similar to baseline levels in all three groups by the end of the experiment (R120). After portal vein declamping, a significant acidosis was observed without any difference between groups throughout the reperfusion period.

3.2. Hepatic Blood Flow. Systemic and intraportal infusion of PTX promoted a significant improvement in portal vein blood flow during reperfusion when compared to CT animals. In all groups a rapid but not sustained restoration of PVBF was observed after portal triad declamping. However, animals in the control group demonstrated a progressive reduction in portal blood flow during the reperfusion phase when compared to PTX-treated animals. Moreover, 30 minutes after reperfusion, until the end of the observation, animals which received systemic PTX presented significantly higher PVBF when compared with baseline values and to the CT group (Figure 1(b)).

All animals presented a sustained recovery of hepatic artery blood flow during reperfusion, with no differences between groups (Figure 1(c)). Fifteen minutes after reperfusion, animals treated with systemic PTX presented higher hepatic artery blood flows when compared with the other two groups, but no differences were observed afterwards (Figure 1(c)). In Table 2, we can observe the significant decrease of systemic and splanchnic oxygen delivery in CT group. On the other hand, animals treated with PTX did not present significant changes on DO\(_2\). A compensatory increase of systemic and regional oxygen extraction was observed in CT group (Table 2).

3.3. Serum ALT and LDH Levels. Pentoxifylline exerted a protective effect against ischemia/reperfusion injury. Serum markers of liver injury remained stable throughout the experiment in animals treated with both systemic PTX and intraportal PTX. However, a progressive increase of serum ALT and LDH was observed in CT group after reperfusion (Figures 2(a) and 2(b)).

4. Discussion

This study confirms that intravenous systemic infusion of PTX is an effective strategy to prevent liver damage after normothermic I/R. Locoregional PTX infusion (i.e., portal vein) also has demonstrated a protective effect on liver cells, but no advantage was obtained over standard systemic infusion. PTX has been studied in hemorrhagic shock models in combination with different strategies of fluid resuscitation. Besides the beneficial hemodynamic and metabolic effects, we and others have demonstrated that PTX infusion reduces the circulation of inflammatory cytokines, bacterial translocation, and polymorphonuclear neutrophil-endothelial interactions, thus attenuating the systemic inflammatory response syndrome triggered by trauma and hemorrhage [10, 11].
Figure 1: (a) Cardiac output (L/min), (b) and (c) portal vein and hepatic artery blood flows (mL/min) during the experimental protocol. The animals were randomly assigned into three groups: CT (control, portal triad clamping, \( n = 8 \)), PTX-syst (portal triad clamping + 25 mg/Kg of PTX intravenously systemically, \( n = 8 \)), and PTX-pv (portal triad clamping + 25 mg/Kg of PTX in the portal vein, \( n = 8 \)). BL: baseline; P45: 45 min after Pringle’s maneuver; R15, R60, and R120: 15, 60, and 120 min after reperfusion. Data are shown as mean ± SEM. *Indicates \( P < 0.05 \) for PTX-pv and PTX-sys versus BL; †indicates \( P < 0.05 \) for PTX-pv and PTX-sys versus CT; ‡indicates \( P < 0.05 \) for PTX-sys versus BL; ¶indicates \( P < 0.05 \) for PTX-sys versus CT.

Figure 2: (a) Alanine transaminase (ALT, U/L) and (b) lactate dehydrogenase (LDH, U/L) during the experimental protocol. BL: baseline; P45: 45 min after Pringle’s maneuver; R15, R60, and R120: 15, 60, and 120 min after reperfusion. Groups are the same as in Figure 1. Data are shown as mean ± SEM. †Indicates \( P < 0.05 \) for CT versus PTX-pv and PTX-sys.
In this study, no differences between the groups were observed regarding systemic arterial pressure and pulmonary arterial pressure. However, during reperfusion cardiac output was significantly higher in animals treated with PTX. The precise mechanism responsible for the improvement in cardiac function observed after PTX administration remains unknown. A combination of factors may have contributed to this beneficial effect of PTX on CO including, but not limited to: (1) the improvement in systemic blood flow and the systemic delivery of hypoxia to the tissue via improved systemic oxygen delivery, consumption, and extraction (DO₂, VO₂, and O₂ ER, resp.) in CT (control, portal triad clamping, n = 8), PTX-syst (portal triad clamping + 25 mg/Kg of PTX intravenously systemically, n = 8), and PTX-pv (portal triad clamping + 25 mg/Kg of PTX in the portal vein, n = 8) groups.

Table 2: Systemic (syst) and splanchnic (splanc) oxygen delivery, consumption and extraction (DO₂, VO₂, and O₂ ER, resp.) in CT (control, portal triad clamping, n = 8), PTX-syst (portal triad clamping + 25 mg/Kg of PTX intravenously systemically, n = 8), and PTX-pv (portal triad clamping + 25 mg/Kg of PTX in the portal vein, n = 8) groups.

<table>
<thead>
<tr>
<th>DO₂ syst mL/min</th>
<th>Group</th>
<th>BL</th>
<th>P45</th>
<th>R15</th>
<th>R60</th>
<th>R120</th>
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<tbody>
<tr>
<td>CT</td>
<td>483 ± 76</td>
<td>449 ± 58</td>
<td>367 ± 40&lt;sup&gt;a&lt;/sup&gt;</td>
<td>254 ± 29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>211 ± 61&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>PTX-syst</td>
<td>454 ± 39</td>
<td>496 ± 62</td>
<td>580 ± 76</td>
<td>479 ± 62</td>
<td>381 ± 56</td>
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<tr>
<td>PTX-pv</td>
<td>411 ± 89</td>
<td>530 ± 43</td>
<td>707 ± 109&lt;sup&gt;a&lt;/sup&gt;</td>
<td>578 ± 83&lt;sup&gt;a&lt;/sup&gt;</td>
<td>416 ± 63</td>
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<th>VO₂ syst mL/min</th>
<th>Group</th>
<th>BL</th>
<th>P45</th>
<th>R15</th>
<th>R60</th>
<th>R120</th>
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<tr>
<td>CT</td>
<td>10 ± 3.1</td>
<td>12.8 ± 7.8</td>
<td>4.7 ± 0.8</td>
<td>6.9 ± 0.5</td>
<td>7.5 ± 2.1</td>
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<tr>
<td>PTX-syst</td>
<td>8.5 ± 2</td>
<td>8.5 ± 2.1</td>
<td>8.1 ± 0.6</td>
<td>7.7 ± 1.2</td>
<td>8.8 ± 1.8</td>
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<td>PTX-pv</td>
<td>6.8 ± 0.3</td>
<td>7.7 ± 1.6</td>
<td>10.5 ± 2.9</td>
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<td>8.4 ± 1</td>
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<th>O₂ ER syst%</th>
<th>Group</th>
<th>BL</th>
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<th>R15</th>
<th>R60</th>
<th>R120</th>
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<tr>
<td>CT</td>
<td>16.9 ± 2.9</td>
<td>17.7 ± 3.9</td>
<td>14.8 ± 3.5</td>
<td>23.7 ± 1.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.9 ± 2.4&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>PTX-syst</td>
<td>16.7 ± 1.7</td>
<td>16.5 ± 3.4</td>
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<td>18 ± 3.4</td>
<td>19.9 ± 2.4</td>
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<td>PTX-pv</td>
<td>15.3 ± 1.5</td>
<td>14.2 ± 2.2</td>
<td>18.8 ± 4.5</td>
<td>14 ± 20</td>
<td>20.6 ± 2.9&lt;sup&gt;a&lt;/sup&gt;</td>
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<th>DO₂ splanc mL/min</th>
<th>Group</th>
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<th>R15</th>
<th>R60</th>
<th>R120</th>
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<tr>
<td>CT</td>
<td>103 ± 28&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>85 ± 55</td>
<td>71 ± 48</td>
<td>54 ± 39&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>PTX-syst</td>
<td>95 ± 5</td>
<td>—</td>
<td>150 ± 20</td>
<td>93 ± 12</td>
<td>69 ± 7&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>PTX-pv</td>
<td>80 ± 16</td>
<td>—</td>
<td>156 ± 31</td>
<td>137 ± 11</td>
<td>111 ± 20</td>
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<th>VO₂ splanc mL/min</th>
<th>Group</th>
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<tr>
<td>CT</td>
<td>6.4 ± 0.4</td>
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<td>8.2 ± 1.5</td>
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<td>10 ± 1.1</td>
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<td>PTX-syst</td>
<td>10 ± 1.4</td>
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<td>17.7 ± 3.4</td>
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<td>PTX-pv</td>
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<th>O₂ ER splanc%</th>
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<tr>
<td>CT</td>
<td>80 ± 16&lt;sup&gt;b&lt;/sup&gt;</td>
<td>—</td>
<td>124 ± 35</td>
<td>156 ± 13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>192 ± 13&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>PTX-syst</td>
<td>121 ± 5</td>
<td>—</td>
<td>108 ± 12</td>
<td>92 ± 4</td>
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<tr>
<td>PTX-pv</td>
<td>104 ± 1.3</td>
<td>—</td>
<td>115 ± 36</td>
<td>82 ± 13</td>
<td>87 ± 17</td>
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Legends: BL: baseline; P45: 45 min after Pringle’s maneuver; R15, R60, and R120: 15, 60, and 120 min after reperfusion. Data are shown as mean ± SEM. *Indicates P < 0.05 versus BL; a indicates P < 0.05 versus PTX-syst; b indicates P < 0.05 versus PTX-pv.

In this study, systemic PTX infusion right after reperfusion during liver transplantation could be a useful strategy to improve portal vein blood flow and minimize the deleterious effects of I/R injury. However further investigation is required, in order to evaluate safety and the potential benefits of PTX in preventing liver damage. It has been shown that PTX can inhibit the activation of liver macrophages (Kupffer cells) after an ischemic insult, reducing the production and release of TNF-α, and consequently other inflammatory mediators, resulting in less end-organ injury [15–17].

The short period of observation is an important limitation of our study. Because of our study design, we could not correlate the data presented herein with mortality or development of multiple organ dysfunction, issues that must be addressed in a future study. Also, the use of a venous by-pass is not routine in liver surgery; however, we decided to use an extrahepatic shunt during portal triad clamping to avoid the deleterious effects of intestinal congestion. Small bowel congestion can lead to intestinal mucosal injury, bacterial translocation, and systemic inflammatory response affecting the hemodynamic and metabolic responses during and after normothermic isolated liver I/R [18–20]. We have previously shown that active spleno-femoral shunt maintains the systemic hemodynamic stability, with an effective decompression of splanchnic bed during portal triad occlusion. The deleterious hemodynamic and metabolic effects observed during the reperfusion period, such as transitory hypotension and acidemia, was mainly associated with the isolated hepatic I/R injury, not with the blood congestion in splanchnic bed [19].

We believe that systemic PTX infusion right after reperfusion during liver transplantation could be a useful strategy to improve portal vein blood flow and minimize the deleterious effects of I/R injury. However further investigation is required, in order to evaluate safety and the potential benefits of PTX in preventing liver damage. It has been shown that PTX can inhibit the activation of liver macrophages (Kupffer cells) after an ischemic insult, reducing the production and release of TNF-α, and consequently other inflammatory mediators, resulting in less end-organ injury [15–17].
of continuous PTX infusion in short- and long-term graft function and survival.

Despite these limitations, we were able to demonstrate the systemic and hepatopancreatic hemodynamic benefits of PTX infusion during normothermic hepatic ischemia/reperfusion. We also have shown that pentoxifylline administration could minimize liver damage. However, local PTX infusion was not associated with any significant advantage over systemic route.

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**References**


