Hepatic oxygen exchange and energy metabolism in hyperdynamic porcine endotoxemia: effects of the combined thromboxane receptor antagonist and synthase inhibitor DTTX30

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Abstract Objective: We compared the effects of thromboxane receptor antagonist and synthase inhibitor DTTX30 on systemic and liver blood flow, oxygen (O₂) exchange and energy metabolism during 24 h of hyperdynamic endotoxemia with untreated endotoxemia. Design: Prospective, randomized, experimental study with repeated measures. Setting: Investigational animal laboratory. Subjects: Twenty-seven domestic pigs: 16 during endotoxemia with volume resuscitation alone; 11 with endotoxemia, volume resuscitation and treatment with DTTX30. Interventions: Continuous infusion of Escherichia coli lipopolysaccharide (LPS) for 24 h together with volume resuscitation. After 12 h of endotoxemia, DTTX30 was administered as a bolus of 0.12 mg kg⁻¹ followed by 12 h continuous infusion of 0.29 mg kg⁻¹ per h. Measurements and results: DTTX30 effectively counteracted the endotoxin-associated increase in TXB₂ levels and increased 6-keto-PGF₁α with a significant shift of the thromboxane/prostacyclin ratio towards predominance of prostacyclin. DTTX30 prevented the significant progressive endotoxin-induced decrease of mean arterial pressure (MAP) below baseline while maintaining cardiac output (CO), and increased the fractional contribution of liver blood flow to CO without an effect on either hepatic O₂ delivery or O₂ uptake. The mean capillary hemoglobin O₂ saturation (HbO₂) on the liver surface and HbO₂ frequency distributions remained unchanged as well. Conclusions: DTTX30 significantly attenuated the endotoxin-induced derangements of cellular energy metabolism as reflected by the diminished progressive decrease in hepatic lactate uptake rate and a blunted increase in hepatic venous lactate/pyruvate ratios. While endotoxin significantly increased the endogenous glucose production (EGP) rate, EGP returned towards baseline levels in the DTTX30-treated group. Thus, in our model DTTX30 resulted in hemodynamic stabilization concomitant with improved hepatic metabolic performance.

Key words Endotoxin · Thromboxane · Prostacyclin · Hemodynamics · Oxygen transport · Gluconeogenesis
Introduction

Eicosanoids play an important role in the pathophysiology of sepsis and septic shock [1]. The main cyclooxygenase (COX)-based metabolites of arachidonic acid, thromboxane A2 (TXA2) and prostacyclin (PGI2), and in particular their ratio, may be linked with the pathogenesis of sepsis and septic organ failure: TXA2 is both a potent vasoconstrictor and a platelet activator [2] and exerts proinflammatory action by upregulating tumor necrosis factor-α (TNF-α) production and neutrophil adhesion receptor activation [3]. By contrast, prostacyclin results in vasodilation, inhibits thrombocyte aggregation and shows cytoprotective effects [4, 5, 6]. Therefore, influencing the equilibrium between TXA2 and PGI2 may have a therapeutic potential in situations where sepsis is known to occur [7, 8]. The splanchic organs represent a key component in the pathogenesis of septic shock and multiple organ failure. In particular, disturbances in microcirculatory organ blood flow are suggested to be major players in the development of progressive organ dysfunction. Again, arachidonic acid metabolites such as PGI2 are involved in the regulation of microcirculation as well as the preservation of organ function [5]. Moreover, data collected in patients with gram-negative septic shock [11] demonstrated that eicosanoids play a potential role in organ function as the predominance of PGI2 over TXA2 was associated with improved organ function. In addition, a recent human study investigating the role of COX inhibition suggested a potential protective role of the endogenous PGI2 release for the barrier function of the intestinal wall [12].

Pharmacological modulation of the TXA2/PGI2 ratio in favor of PGI2 is considered as a potential therapeutic approach in different models, such as liver ischemic injury [13], after splanchic artery occlusion [14] and, finally, during ovine endotoxemia [15]. Since non-selective COX inhibition influences both the TXA2 and the PGI2 pathway, a selective TXA2 synthesis inhibition together with a TXA2 receptor blockade ought more effectively to shift the TXA2/PGI2 ratio in favor of the latter. In small animal models combined TXA2 synthase inhibition and receptor blockade in a pre-treatment approach demonstrated beneficial effects both after splanchic artery occlusion [14, 16] and endotoxin challenge [17]. In large animal models, pre-treatment with thromboxane receptor antagonists and synthase inhibitor resulted in preserved circulatory function [18] both after burn injury in pigs [19] and after endotoxin challenge in sheep [15]. However, when thromboxane synthase inhibition was administered after endotoxin challenge in a rabbit model of endotoxemia, hemodynamic perturbations were ineffectively influenced [20].

We therefore tested the hypothesis that a combined thromboxane receptor antagonist and synthase inhibitor, that should modulate the TXA2/PGI2 ratio in favor of PGI2, may beneficially affect (1) global and regional hemodynamics and (2) oxygen availability in the hepatosplanchnic area as well, and (3) thereby improve energy metabolism. For this purpose we investigated DTTX50 (5-hexenoic acid, 6-[4-[2-[[4-(chlorophenyl)sulfonyl]aminoethyl]phenyl]-6-(3-pyridinyl)-E-], a potent and selective, combined thromboxane receptor antagonist and synthase inhibitor [21, 22] in a porcine model of long-term, volume-resuscitated, hyperdynamic and hypermetabolic endotoxemia as described recently [23]. The results presented in this paper focus on hepatic hemodynamics, O2 transport and liver metabolism, whereas the effects on intestinal perfusion and metabolism are reported separately elsewhere [24].

Methods

Animal preparation
The study protocol was approved by the University Animal Care Committee as well as the federal authorities for animal research of the Regierungspräsidium Tübingen, Baden-Württemberg, Germany. Twenty-seven domestic pigs (Deutsches Landschwein) of either sex with a median body weight of 42 kg (40–49 interquartile range) were included. Here, the number of animals is greater than in the complementary report [24] on intestinal energy balance since, for that analysis, one animal in each group had to be excluded for surgical problems with the ileostomy and the tonometric measurements, respectively.

The surgical procedure for the placement of a central venous catheter, a balloon-tipped thermistorulation pulmonary artery catheter (93A7547F, Baxter Healthcare, Irvine, Calif., USA) and an arterial line for continuous blood pressure recording and thermal-dye double indicator dilution measurements (FT-Pulsio cath PV2023, Pulsion, Munich, Germany) is described in detail elsewhere [23, 25]. After instrumentation a stabilization period of 8 h was allowed before baseline measurements were recorded.

Measurements and calculations
Cardiac output (CO) was determined by thermodilution (66S Monitor, Hewlett Packard, Palo Alto, Calif., USA). The intrathoracic blood volume was measured by arterial thermal-green dye double indicator dilution (COLD Z-021, Pulsion, Munich, Germany). Portal venous and hepatic arterial blood flow rates were continuously recorded. Arterial, portal and hepatic venous blood samples were analyzed for partial pressures of oxygen and carbon dioxide and pH (Nova Stat Profile Ultra, Nova Biomedical, Waltham, Mass., USA) as well as total hemoglobin and hemoglobin O2 saturation (IL682 CO-oximeter [Instrumentation Laboratories, Lexington, Mass., USA], calibrated for pig blood). Systemic and regional O2 transport parameters were calculated according to standard formulas as previously described [23, 25]. Arterial blood glucose levels were measured every 2 h using an automatic enzymatic glucose analyzer (Glucometer Elite, Bayer, Leverkusen, Germa-