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ORIGINAL ARTICLE

# Protective Effects of Sodium Pyruvate during Systemic Inflammation Limited to the Correction of Metabolic Acidosis

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*Abstract*—Protective effects by exogenous sodium pyruvate already have been described in various experimental models of injury, among others during intestinal ischemia-reperfusion injury, hemorrhagic shock, and shock secondary to systemic inflammation (endotoxemic shock). Low doses of sodium pyruvate reduced signs of inflammation, enhanced systemic blood pressure, and ameliorated metabolic acidosis when administered in a prophylactic manner during endotoxemic shock. In the present study, we investigated whether low-dosed infusions of sodium pyruvate exhibited beneficial effects when applied therapeutically after the induction of systemic inflammation. Lipopolysaccharide was infused at a rate of 0.5 mg/kg × h over a period of 360 min to induce systemic inflammation in male Wistar rats. Sodium pyruvate (single dose 50 mg/kg × 15 min) was administered intravenously 180 and 270 min after starting of the lipopolysaccharide infusion. Systemic/vital parameters (*e.g.*, systemic blood pressure and breathing rate) and blood/plasma parameters (*e.g.*, acid-base parameters; electrolytes; glucose and lactate concentration; hemolysis; aminotransferase activities; and parameters of coagulation) were determined in regular intervals. Lipopolysaccharide infusion led to metabolic acidosis, hypoglycemia, electrolyte as well as hemostatic disturbances, and hemolysis. Except for the acid-base status (amelioration of metabolic acidosis) and the plasma chloride concentration (reduction of hyperchloremia), the additional infusion of sodium pyruvate failed in significantly improving lipopolysaccharide-dependent alterations (*e.g.* vital, blood and plasma parameters). Protective effects of a delayed administration of the metabolizable anion pyruvate during systemic inflammation, hence, are limited to its function as alkalizer to counteract metabolic acidosis.

**KEY WORDS:** lipopolysaccharide; sepsis; metabolism; acidosis; intestine; pyruvate.

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## INTRODUCTION

Sepsis/systemic inflammation alters energy metabolism and glucose homeostasis thereby leading to lactate accumulation, metabolic acidosis, and malglycemia [1]. Metabolic disorders indicate a serious prognosis for the patients and are associated with an increased mortality [2]. The experimental model of continuous lipopolysaccharide

(LPS) infusion used in the present study reflects most pathophysiological changes known from clinical sepsis [3].

Pyruvate plays a central role as a key intermediate in the metabolism of each cell. As the end product of glycolysis, it is either metabolized in the citrate cycle (under aerobic conditions) or becomes reduced to lactate (under anaerobic conditions) [2]. It is also the starting product of glyconeogenesis or is further processed to the amino acid alanine *via* transamination [2]. Supplied exogenously as sodium pyruvate, it exhibits protective effects in several animal models of ischemia-reperfusion injury, especially of the heart [4, 5], the brain [6, 7], and the intestines [8–10]. In animal models of hemorrhagic shock, favorable effects of sodium pyruvate have been demonstrated as well [11–15]. The protective action exerted by exogenous pyruvate is attributed to its anti-inflammatory [7, 16] or anti-oxidative action [14, 16] and, in particular, to its potential to improve mitochondrial energy supply, to regenerate NAD(P)H and to correct acidosis [2, 4, 13].

Numerous experimental studies reported that ethyl pyruvate—a derivative of pyruvate—is protective in various preclinical models of critical illnesses [17], such as sepsis and septic shock, too [18–21]. However, there is only one experimental study showing a beneficial effect of sodium pyruvate during systemic inflammation. Hamburger et al. used a rat model of LPS-induced shock and administered pyruvate in a prophylactic manner, which means before induction of endotoxemic shock [22]. In order to analyze a putative therapeutic role of pyruvate at a more progressed inflammatory stage, we applied, according to earlier studies [8, 9, 22], low-dosed infusions of sodium pyruvate 180 and 270 min after the onset of LPS infusion.

## MATERIALS AND METHODS

### Chemicals and Materials

Lipopolysaccharide (LPS; from *Escherichia coli*, serotype 0111:B4) and sodium pyruvate (PYR) were purchased from Sigma-Aldrich (St. Louis, USA). Isoflurane was obtained from AbbVie Deutschland (Ludwigshafen, Germany), ketamine 10% from Ceva (Düsseldorf, Germany), lidocaine (xylocaine 1%) from AstraZeneca (Wedel, Germany), medical oxygen from Air Liquide (Düsseldorf, Germany), Portex catheters (0.58 mm i.d./0.96 mm o.d.) from Smith Medical International (Grasbrunn, Germany), Ringer's solution from Fresenius Kabi (Bad Homburg, Germany), 2.0 ml self-filling arterial samplers containing 80 IU electrolyte-balanced heparin (PICO50) from Radiometer Medical (Brønshøj, Denmark), and sodium chloride solution (0.9%) from B. Braun (Melsungen, Germany).

### Animals

Male Wistar rats (460–520 g) were obtained from the central animal unit of the University Hospital Essen. They received human care according to the standards of the Federation of European Laboratory Animal Science Association (FELASA). The experimental procedure has been reviewed and approved by the local Animal Care and Use Committee with the permit number Az.: 84-02.04.2012.A205. Rats were kept under standardized conditions of temperature (22 ± 1 °C), humidity (55 ± 5%), and 12-h/12-h light/dark cycles (06:00 a.m. light on/06:00 p.m. light off, standard time) with free access to food (ssniff-Spezialdiäten, Soest, Germany) and water.

### Anesthesia, Analgesia, and Surgical Procedure

Rats were anesthetized with isoflurane and received ketamine and lidocaine for analgesia as described before [23]. Afterwards, catheters were inserted in femoral artery and vein and perfused with Ringer's solution to maintain the functionality of the catheters. At the end of the experiment, animals were sacrificed by cardiac incision under deep isoflurane anesthesia.

### Experimental Groups

Experiments were performed with 8 rats per group (overall 32 rats). Lipopolysaccharide (LPS) was infused at a rate of 0.5 mg/kg × h over a period of 360 min to induce systemic inflammation in male Wistar rats. Sodium pyruvate (PYR; single dose 50 mg/kg × 15 min) was administered intravenously at $T = 180$ and $T = 270$ min after the beginning of the LPS infusion (Fig. 1).

The following experimental groups were compared:

- SHAM (sham control group): 0.9% sodium chloride solution
- PYR (pyruvate group): 0.9% sodium chloride solution, 50 mg PYR/kg × 15 min twice
- LPS (lipopolysaccharide group): 0.5 mg LPS/kg × h
- LPS + PYR (lipopolysaccharide plus pyruvate group): 0.5 mg LPS/kg h, 50 mg PYR/kg × 15 min twice

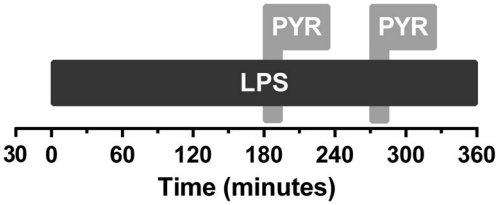


**Fig. 1.** Time scale of the administration of lipopolysaccharide (LPS) and sodium pyruvate (PYR). Catheters were inserted in femoral artery and vein before starting the LPS and PYR administration. Systemic inflammation was induced by an intravenous infusion of LPS (0.5 mg LPS/kg × h over 360 min). PYR was infused at $T = 180$ min and $T = 270$ min after starting the LPS infusion (2 × 50 mg PYR/kg × 15 min). Blood samples were taken from the femoral artery catheter directly before starting the induction of systemic inflammation (0 min) and any further hour (60, 120, 180, 240, 300, and 360 min).

### Assessment of Vital, Blood, and Plasma Parameters

Systemic blood pressure, heart rates, and breathing rates were determined in 10-min intervals. Core temperature was kept constant above 37 °C with an underlying heated operating table and by covering the rats with aluminum foil. Blood samples were taken from the femoral artery catheter immediately before starting the LPS infusion (0 min) and at any further hour (60, 120, 180, 240, 300, 360 min) using self-filling arterial samplers (containing 80 IU electrolyte-balanced heparin). Blood gases, acid-base parameters, electrolytes, and glucose and lactate concentrations were assessed with a blood gas analyzer equipped with additional electrodes (ABL 715, Radiometer, København, Denmark). Heparinized blood plasma was obtained from the blood samples by centrifugation. Concentration of cell-free hemoglobin was measured using the spectroscopic Soret band method [22]. Activities of lactate dehydrogenase (LDH), aminotransferases (ALAT, ASAT), and creatine kinase (CK-NAC) as well as creatinine concentration were determined with a fully automated clinical chemistry analyzer (Vitalab Selectra E, VWR International, Darmstadt, Germany). For each blood sampling (0.3 ml heparinized blood), rats were substituted with 0.3 ml of 0.9% sodium chloride solution.

### Statistics

The data are expressed as mean values ± standard error of the mean (SEM), and analyses were carried out

**Table 1.** Effects of Sodium Pyruvate (PYR) on Vital, Blood And Plasma Parameters[a] During Systemic Inflammation

| Parameters | Sham 360 min | 0 min | PYR 360 min | LPS 360 min | LPS + PYR 360 min |
|---|---|---|---|---|---|
| Systemic blood pressure (mmHg) | 89 ± 3 | 93 ± 6 | 90 ± 4 | 89 ± 12 n.s. vs. Sham | 77 ± 11 n.s. vs. LPS |
| Heart rate ($min^{-1}$) | 327 ± 13 | 276 ± 9 | 327 ± 10 | 384 ± 13 P = 0.0085 vs. Sham | 387 ± 10 n.s. vs. LPS |
| Breathing rate ($min^{-1}$) | 45 ± 4 | 53 ± 2 | 38 ± 3 | 51 ± 6 n.s. vs. Sham | 47 ± 5 n.s. vs. LPS |
| Body temperature (°C) | 38 ± 0 | 37 ± 0 | 38 ± 0 | 38 ± 0 n.s. vs. Sham | 38 ± 0 n.s. vs. LPS |
| pH | 7.275 ± 0.021 | 7.277 ± 0.019 | 7.267 ± 0.040 | 7.135 ± 0.084 n.s. vs. Sham | 7.272 ± 0.028 n.s. vs. LPS |
| $pCO_2$ (mmHg) | 49 ± 2 | 47 ± 1 | 46 ± 3 | 40 ± 4 P = 0.0181 vs. Sham | 40 ± 3 n.s. vs. LPS |
| Base excess (mmol/L) | − 4.6 ± 0.3 | − 4.0 ± 0.8 | −2.4 ± 1.1 | −11.1 ± 1.0 P = 0.0098 vs. Sham | −5.5 ± 2.6 P = 0.0230 vs. LPS |
| $HCO_3$ (mmol/L) | 20.0 ± 0.4 | 20.6 ± 0.5 | 21.8 ± 0.9 | 15.0 ± 1.0 P = 0.0226 vs. Sham | 17.7 ± 0.8 n.s. vs. LPS |
| $K^+$ (mmol/L) | 5.0 ± 0.1 | 4.9 ± 0.1 | 4.9 ± 0.2 | 5.5 ± 0.2 n.s. vs. Sham | 5.2 ± 0.1 n.s. vs. LPS |
| $Na^+$ (mmol/L) | 140 ± 0 | 141 ± 0 | 140 ± 1 | 142 ± 1 n.s. vs. Sham | 142 ± 1 n.s. vs. LPS |
| $Cl^-$ (mmol/L) | 114 ± 1 | 114 ± 1 | 111 ± 1 | 119 ± 1 P = 0.0136 vs. Sham | 111 ± 1 P < 0.0001 vs. LPS |
| $Ca^{2+}$ (mmol/L) | 1.46 ± 0.03 | 1.55 ± 0.01 | 1.44 ± 0.02 | 1.30 ± 0.03 P = 0.0003 vs. Sham | 1.26 ± 0.02 n.s. vs. LPS |
| ALT (U/L) | 76 ± 19 | 49 ± 13 | 114 ± 44 | 449 ± 69 P = 0.0001 vs. Sham | 376 ± 67 n.s. vs. LPS |
| AST (U/ L) | 90 ± 13 | 68 ± 9 | 242 ± 91 | 827 ± 147 P = 0.0003 vs. Sham | 857 ± 151 n.s. vs. LPS |
| LDH (U/L) | 164 ± 26 | 163 ± 22 | 393 ± 167 | 2300 ± 430 P < 0.0001 vs. Sham | 2246 ± 270 n.s. vs. LPS |
| CK-NAC (U/L) | 219 ± 70 | 300 ± 69 | 174 ± 32 | 982 ± 163 P = 0.0035 vs. Sham | 1233 ± 241 n.s. vs. LPS |
| Creatinine (mg/dl) | 0.83 ± 0.08 | 0.71 ± 0.14 | 0.68 ± 0.07 | 1.56 ± 0.20 P = 0.0102 vs. Sham | 1.27 ± 0.27 n.s. vs. LPS |
| Glucose (mg/dL) | 146 ± 10 | 137 ± 5 | 154 ± 9 | 31 ± 7 P < 0.0001 vs. Sham | 25 ± 6 n.s. vs. LPS |
| Lactate (mmol/L) | 1.1 ± 0.1 | 1.1 ± 0.1 | 1.2 ± 0.1 | 2.9 ± 0.4 P < 0.0001 vs. Sham | 3.1 ± 0.2 n.s. vs. LPS |
| Cell-free hemoglobin (μmol/L) | 8.9 ± 1.1 | 12.7 ± 2.3 | 8.7 ± 1.5 | 33.4 ± 4.9 P < 0.0001 vs. Sham | 28.2 ± 3.7 n.s. vs. LPS |

[a] Vital parameters, blood gases, electrolytes, plasma enzyme activities as well as the plasma concentration of creatinine, glucose, lactate, and cell-free hemoglobin of the groups SHAM (n = 8), PYR (n = 8), LPS (n = 8), and LPS + PYR (n = 8) are shown (mean values ± SEM) either before the beginning of the LPS infusion (baseline, T = 0 min) or at T = 360 min. Baseline values of the sham group were not significantly different from those of the other groups. Lipopolysaccharide was infused at a rate of 0.5 mg LPS/kg × h over a period of 360 min to induce systemic inflammation in male Wistar rats. Sodium pyruvate (PYR; single dose: 50 mg/kg × 15 min) was administered intravenously at 180 and 270 min after the beginning of the LPS infusion

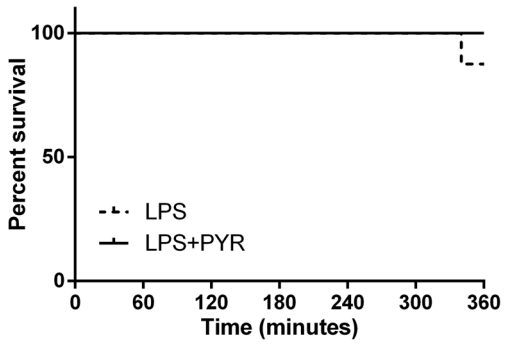


**Fig. 2.** Effect of sodium pyruvate (PYR) on survival during systemic inflammation. Lipopolysaccharide (LPS) was infused at a rate of 0.5 mg/kg × h over a period of 360 min to induce systemic inflammation in male Wistar rats. Sodium pyruvate (PYR; single dose 50 mg/kg × 15 min) was administered intravenously at 180 and 270 min after the beginning of the LPS infusion. Shown are $n = 8$ rats per group.

using GraphPad Prism 6 (Graph Pad Prism Software Onc, San Diego, USA). Comparison among multiple groups was performed using one-way analysis of variance for all independent continuous variables (vital, blood and plasma parameters, parameters of thromboelastometry as well as macroscopic small intestinal changes) followed by a Dunnet *post hoc* test. Differences in acid-base parameters over time within each group were determined by repeated-measures one-way ANOVA. An *a priori* alpha error $p$ of less than 0.05 was considered statistically significant (95% confidence interval).

The survival rate of each group was calculated at the end of the study ($T = 360$ min). Survival curves were analyzed by the Kaplan-Meier method.

## RESULTS

In absence of lipopolysaccharide (LPS), the application of sodium pyruvate (PYR) did not alter any of the selected parameters (Table 1). All rats without receiving any LPS survived the whole experimental period of

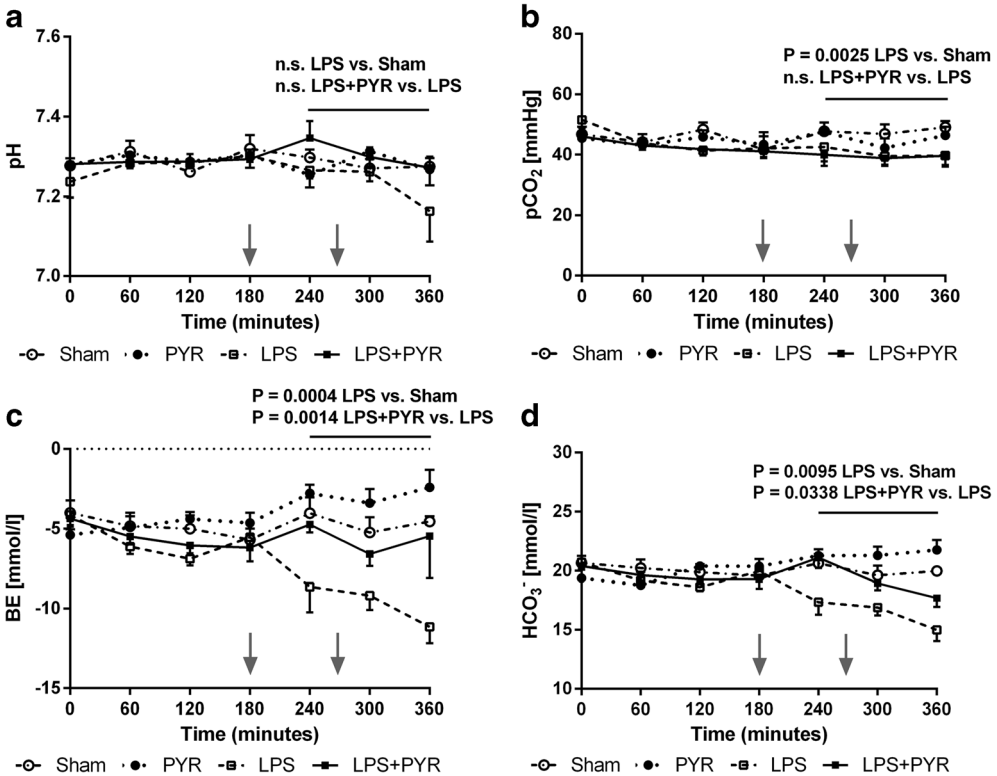


**Fig. 3.** Effect of sodium pyruvate on pH (**a**), carbon dioxide partial pressure (**b**), base excess (BE, **c**), and bicarbonate concentration ($HCO_3^-$, **d**) during systemic inflammation. Lipopolysaccharide (LPS) was infused at a rate of 0.5 mg/kg × h over a period of 360 min to induce systemic inflammation in male Wistar rats. Sodium pyruvate (PYR; single dose 50 mg/kg × 15 min) was administered intravenously at 180 and 270 min after the beginning of the LPS infusion (gray arrows).

360 min. Mortality rate was 12.5% following continuous infusion of LPS (1/8). In rats additionally treated with sodium pyruvate (LPS + PYR), the mortality rate was 0% (0/8). The difference was not significant (Fig. 2).

Continuous infusion of LPS led to tachycardia, affected the electrolyte homeostasis (hypocalcemia and hyperchloremia; Table 1) and energy metabolism (lactate formation, metabolic acidosis with compensatory hyperventilation; early hyperglycemia and finally hypoglycemia; Table 1; Figs. 3 and 4). LPS caused severe organ and tissue injury (increases in plasma concentration of creatinine; increases in activities of transaminases, lactate dehydrogenase and creatine kinase; small intestinal microvascular stasis; Tables 1 and 2) and led to massive hemolysis (increased levels of cell-free hemoglobin; Table 1). Rats treated with LPS also showed significant alterations in blood coagulation (increases in clotting time, decreases in strength and firmness of the clot; Table 3).

The additional infusion of PYR significantly improved the LPS-induced changes in acid-base status (normalization of arterial pH, base excess, and bicarbonate concentration; Table 1; Fig. 3). The LPS-related lactate accumulation was not affected by PYR (Table 1; Fig. 4). Except the acid-base status and the plasma chloride concentration (amelioration of hyperchloremia; Table 1), the additional infusion of PYR did not significantly improve the LPS-dependent changes to systemic parameters (Table 1). Regarding the plasma concentration of cell-free hemoglobin, PYR slightly reduced hemolysis during systemic inflammation, though not significantly (Table 1). The LPS-induced hypoglycemia was not improved by PYR (Fig. 4). PYR neither affected the LPS-induced small intestinal injury (Table 2) nor reduced LPS-dependent alterations in parameters of thromboelastometry (Table 3).

## DISCUSSION

Protective effects by exogenous sodium pyruvate already have been described in various experimental models of injury, among others during intestinal ischemia-reperfusion injury [8–10], hemorrhagic shock [11–15], and septic shock [22]. However, the latter study only showed a prophylactic effect of sodium pyruvate during septic shock [22]. An article on the clinical investigation of sodium pyruvate during septic shock recently has been retracted [24].

To our knowledge, a purely therapeutic effect of sodium pyruvate has not yet been investigated during systemic inflammation. In the present study, sodium pyruvate was administered at a stage when systemic inflammation induced by lipopolysaccharide (LPS) infusion was full-blown and first symptoms became manifest. At time point $T = 180$ min, selected for the first sodium pyruvate treatment (referring to earlier studies [23]), among others plasma glucose level, concentration of cell-free hemoglobin and lactate dehydrogenase activity are clearly altered in LPS group rats compared to the control group. Sodium pyruvate, in the present study, ameliorated metabolic acidosis during systemic inflammation as indicated by less acidotic arterial pH as well as higher base excess and bicarbonate concentration. However, except for the acid-base status and a normalization of plasma chloride, the additional infusion of sodium pyruvate after LPS treatment prevented neither hypoglycemia and lactate formation nor organ and tissue injuries, hemolysis, and alterations in blood coagulation.

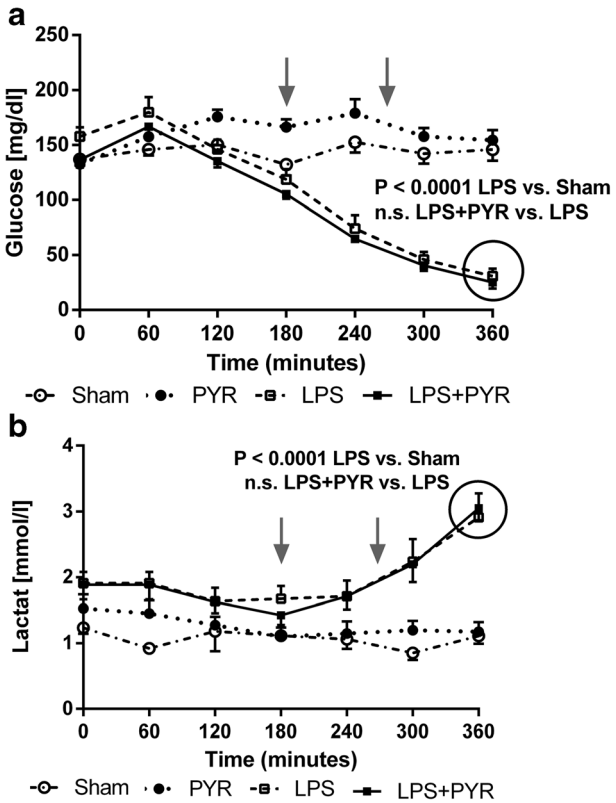


**Fig. 4.** Effect of sodium pyruvate on plasma glucose (**a**) and lactate (**b**) level during systemic inflammation. Lipopolysaccharide (LPS) was infused at a rate of 0.5 mg/kg × h over a period of 360 min to induce systemic inflammation in male Wistar rats. Sodium pyruvate (PYR; single dose 50 mg/kg × 15 min) was administered intravenously at 180 and 270 min after the beginning of the LPS infusion (gray arrows).

**Table 2.** Effect of Sodium Pyruvate (PYR) on Small Intestinal Macroscopic Changes[a] During Systemic Inflammation

| Parameters | SHAM 360 min | PYR 360 min | LPS 360 min | LPS + PYR 360 min |
|---|---|---|---|---|
| Macroscopic score | 0.2 ± 0.1 | 0.6 ± 0.2 | 5.7 ± 1.6 $^{P = 0.0049 \text{ vs. Sham}}$ | 7.4 ± 1.7 $^{\text{n.s. vs. LPS}}$ |

[a] The macroscopic score of the rat small intestine of the groups SHAM (n = 8), PYR (n = 8), LPS (n = 8), and LPS + PYR (n = 8) are shown for time point T = 360 min. Lipopolysaccharide was infused at a rate of 0.5 mg LPS/kg × h over a period of 360 min to induce systemic inflammation in male Wistar rats. Sodium pyruvate (PYR; single dose 50 mg/kg × 15 min) was administered intravenously at 180 and 270 min after the beginning of the LPS infusion

Pyruvate recently was promised as "alkalizer to counteract hypoxic lactic acidosis" [2]. As a metabolizable anion, metabolism of exogenous pyruvate would contribute to a consumption of protons ($H^+$) and, thus, to systemic alkalinization [9]: Aerobic metabolization of pyruvate to carbon dioxide and water would consume an equal-molar [$H^+$], anaerobic metabolization to lactate would consume an equal-molar [$H^+$], and the rebuilding to glucose during gluconeogenesis would consume double-molar [$H^+$] [2, 9]. Since the blood glucose level did not increase after the pyruvate infusion during systemic inflammation in the present study, a metabolization of pyruvate back to glucose (gluconeogenesis) is rather unlikely. A reduction of pyruvate to lactate also seems improbable, because lactate concentrations are comparable in LPS group rats treated and untreated with sodium pyruvate. Accordingly, exogenous sodium pyruvate appears to be metabolized to carbon dioxide and water, which subsequently result in systemic alkalinization. This is in line with own previous reports on pyruvate infusion during intestinal ischemia-reperfusion injury [8, 9].

Using different models of injury, our collaboration never found an improvement of the elevated lactate level by applying low-dosed sodium pyruvate infusion (50–100 mg/kg) during intestinal ischemia-reperfusion [8, 9] or septic shock [22], no matter if the administration of sodium pyruvate occurred before or after the insult. Thus, even a prophylactic administration of sodium pyruvate had no influence on the plasma lactate level [22]. However, during both sepsis/septic shock and ischemia-reperfusion injury, sodium pyruvate ameliorates metabolic acidosis [8, 9, 22]. During severe hemorrhagic shock (25–30 mmHg; Waack et al. 2018, unpublished data), however, resuscitation with Ringer's sodium pyruvate (100 mg/kg) was without any effect on acid-base status. In that model of severe hemorrhagic shock, we found a reduction of the lactate level not just following resuscitation with Ringer's sodium pyruvate during severe hemorrhagic shock but also with Ringer's malate and Ringer's solution. We therefore concluded that the improvement of lactate in these experiments is more a consequence of a restored perfusion rather than a direct effect of sodium pyruvate (Waack et al. 2018, unpublished data).

It is, hence, important to clarify that exogenous sodium pyruvate is an "alkalizer to correct metabolic acidosis" in course of critical illnesses. Exogenous sodium pyruvate, however, is not capable to reduce the elevated lactate level following pathogenic insults. The above review article [2] promising pyruvate as therapeutic in "lactic acidosis correction," however, relies among others on a report comparing Ringer's sodium pyruvate with Ringer's lactate with no fluid resuscitation in a rat model of moderate hemorrhagic shock (40 mmHg) [13]. The authors found that resuscitation with sodium pyruvate resulted in lower lactate level compared to resuscitation with lactate or no resuscitation and concluded that pyruvate corrects lactic acidosis [13].

Furthermore, there is one experimental study using a LPS model demonstrating that ethyl pyruvate

**Table 3.** Effect of Sodium Pyruvate (PYR) on Parameters of Thromboelastometry (NATEM)[a] During Systemic Inflammation

| Parameters | SHAM 360 min | PYR 360 min | LPS 360 min | LPS + PYR 360 min |
|---|---|---|---|---|
| CFT (s) | 63 ± 5 | 59 ± 4 | 239 ± 58 $^{P = 0.0124 \text{ vs. Sham}}$ | 338 ± 100 $^{\text{n.s. vs. LPS}}$ |
| AUC (mm*100) | 7117 ± 211 | 7235 ± 122 | 4361 ± 261 $^{P < 0.0001 \text{ vs. Sham}}$ | 3572 ± 490 $^{\text{n.s. vs. LPS}}$ |

[a] The clot formation time (CFT) and the area under the curve (AUC—quantifies strength and firmness of clot) of the groups SHAM ($n = 8$), PYR ($n = 8$), LPS ($n = 8$), and LPS + PYR ($n = 8$) are shown for time point $T = 360$ min. Lipopolysaccharide was infused at a rate of 0.5 mg LPS/kg × h over a period of 360 min to induce systemic inflammation in male Wistar rats. Sodium pyruvate (PYR; single dose: 50 mg/kg × 15 min) was administered intravenously at 180 and 270 min after the beginning of the LPS infusion

(administered 1 h after LPS initiation) prevented from disseminated intravascular coagulation [25]. In the present study, however, we did not observe any effect of sodium pyruvate on coagulation parameters, neither LPS-induced alterations in coagulation time nor changes in clot quality have been affected by sodium pyruvate. Although ethyl pyruvate is quite distinct from sodium pyruvate, of course, administration of sodium pyruvate in a more prophylactic manner may be an effective maneuver to prevent from disseminated intravascular coagulation.

Moreover, although a protection of erythrocytes by sodium pyruvate has already been described in *in vitro* studies [2], in our animal model, any protective influence of sodium pyruvate on LPS-induced hemolysis was missing.

## CONCLUSION

The therapeutic effect of sodium pyruvate during sepsis/systemic inflammation is limited to its function as alkalizer to correct metabolic acidosis. A benefit on survival was missing with the present study design. Further studies are necessary to test the efficacy of sodium pyruvate resuscitation in hemorrhagic and septic shock with the note that the experimental groups to be compared are aptly chosen.

## ACKNOWLEDGMENTS

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