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CRITICAL CARE

Effect of site of lactate infusion on regional lactate exchange in pigs

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Key points

- This study addresses the uptake of lactate after central venous or portal infusion in pigs.
- Lactate metabolism is important for understanding the haemodynamics and regional blood flow of sepsis.
- Lactate infused into the portal vein is removed mainly by the liver, whereas central venous infusion results in less uptake by the liver.

Background. The rate of extra-hepatic lactate production and the route of influx of lactate to the liver may influence both hepatic and extra-hepatic lactate exchange. We assessed the dose–response of hepatic and extra-hepatic lactate exchange during portal and central venous lactate infusion.

Methods. Eighteen pigs randomly received either portal ($n=5$) or central venous ($n=7$) lactate infusion or saline ($n=6$). Sodium lactate was infused at 33, 66, 99, and 133 μmol kg^{-1} min^{-1} for 20 min each. Systemic and regional abdominal blood flows and plasma lactate were measured at 20 min intervals until 1 h post-infusion, and regional lactate exchange was calculated (area under lactate uptake–time curve).

Results. Total hepatic lactate uptake [median (95% confidence interval)] during the experimental protocol (140 min) was higher during portal [8198 (5487–12 798) μmol kg^{-1}] than during central venous lactate infusion [4530 (3903–5514) μmol kg^{-1}, $P<0.05$]. At a similar hepatic lactate delivery (~400 μmol kg^{-1} min^{-1}), hepatic lactate uptake [mean and standard deviation (SD)] was higher during portal [118 (SD 55) μmol kg^{-1} min^{-1}] than during central venous lactate infusion [44 (12) μmol kg^{-1} min^{-1}, $P<0.05$]. Time courses of arterial lactate concentrations and lactate uptake at other measured regions were similar in both groups.

Conclusions. Higher hepatic lactate uptake during portal compared with central venous lactate infusion at a similar total hepatic lactate influx underlines the role of portal vein lactate concentration in total hepatic lactate uptake capacity. Arterial lactate concentration does not depend on the site of lactate infusion. At higher arterial lactate concentrations, all regions participated in lactate uptake.

Keywords: cardiac output; hepato-splanchnic region; lactate uptake; regional blood flow; sodium lactate

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Hyperlactataemia as a result of insufficient tissue perfusion is frequently seen in critically ill patients and in patients undergoing emergency procedures. Although the measurement of blood lactate levels is widely used to assess the adequacy of tissue perfusion, the interpretation of elevated blood lactate levels is limited by several confounding factors, such as acute changes in acid–base balance, inter-organ substrate flux, peripheral and visceral tissue perfusion, and hepatic lactate uptake.

Lactate kinetics in the hepato-splanchnic region are difficult to assess in man because of lack of access to the portal vein for blood sampling, complex hepatic blood flow regulation, and a large reserve of the liver to extract lactate. For example, prolonged mesenteric ischaemia does not necessarily result in systemic hyperlactataemia due to increased hepatic lactate uptake and blood flow redistribution between superior mesenteric and coeliac trunk perfusion.[1]

Hepatic lactate uptake is a linear function of prehepatic lactate concentrations.[2–5] In sheep, the hepatic uptake during lactate infusion is a saturable process with second-order kinetics.[6] However, several factors modify this relationship, among them blood flow,[7] substrate availability (e.g. glucose),[8] pH,[7 9] and sepsis.[10] Interestingly, reduction in the size of healthy liver parenchyma does not lead to hyperlactataemia in patients after major hepatectomy, demonstrating large liver functional reserve with maintained lactate metabolism.[11]

The ability to metabolize lactate differs among various extra-hepatic organs.[12–17] The kidney removes 20–30% of an exogenous lactate load.[6 18–20] Muscle tissues are

responsible for the disposal of roughly one-fifth of the lactate load during sodium lactate infusion in healthy volunteers[21] and lactic acid infusion in dogs.[22] Lactate metabolism also occurs in the adipose tissue[23] and in portal drained viscera.[6] At arterial lactate concentrations >9 mmol litre^{-1}, peripheral tissues remove more lactate than the liver.[6]

The effect of the site of lactate infusion (or production) on local and remote organ lactate uptake, and the resulting systemic lactate appearance, has not been investigated. We hypothesized that (i) arterial lactate concentration determines the lactate exchange in extra-hepatic organs and (ii) at a similar total hepatic lactate influx, hepatic lactate uptake is enhanced when lactate is infused in the portal vein when compared with the central vein. According to this hypothesis, all organs will participate in lactate uptake when arterial lactate increases. Depending on their effective capability to metabolize lactate, the organs will however release some of the lactate load when arterial lactate concentrations decrease later. Moreover, a given lactate load should result in lower arterial lactate concentrations when originating from the splanchnic region when compared with other regions. Consequently, prehepatic lactate production would be more difficult to detect.

Methods

The study was performed in accordance with the National Institutes of Health guidelines for the care and use of experimental animals and with the approval of the Institutional Animal Care and Use Committee of the University of Kuopio, Finland. The experimental setup has been described previously in detail.[1 24] Briefly, animals were premedicated with i.m. atropine (0.05 mg kg^{-1}) and azaperone (8 mg kg^{-1}). Subsequently, thiopental (5–15 mg kg^{-1}) was administered *via* a cannulated ear vein for tracheal intubation. Anaesthesia was maintained with thiopental (5 mg kg^{-1} h^{-1}) and fentanyl (30 μg kg^{-1} h^{-1}) until the end of the surgical procedure. After surgery and until the end of the experiment, anaesthesia was maintained using thiopental (5 mg kg^{-1} h^{-1}) and fentanyl (5 μg kg^{-1} h^{-1}). This anaesthesia regimen was sufficient to suppress any movements and reactions of physiological parameters to surgery and post-surgical manipulations and no neuromuscular blocking agents were used. All animals were ventilated by a volume-controlled ventilator without PEEP. $F_{I_{O_2}}$ was adjusted to keep Pa_{O_2} levels above 13.3 kPa. Tidal volume was set to 10 ml kg^{-1}. Pa_{CO_2} was kept between 4.5 and 5.5 kPa by adjusting minute ventilation. Monitoring and animal preparation are described fully in the Supplementary material. Briefly, anaesthetized animals underwent laparotomy and ultrasound transit-time flow probes (Transonic Systems Inc., Ithaca, NY, USA) were placed around the coeliac trunk, superior mesenteric, common hepatic, right kidney and femoral arteries, and portal vein, and catheters for blood sampling were inserted into the hepatic, mesenteric, right kidney, femoral, and distal portal veins, and for lactate infusion into proximal portal vein.

Experimental protocol

Eighteen female pigs [36 (5) kg body weight] were deprived of food, but not water, for 12 h before the experiment. After surgery, haemodynamics were allowed to stabilize for 60 min. Animals were randomly allocated to three groups: portal vein infusion group (PV), central vein infusion group (CV), and normal saline infusion group (control). One experiment was repeated due to technical problems with the portal vein transit-time flow probe in an animal from the PV group. By mistake, in the repeated experiment, lactate infusion was administered *via* the central vein catheter. This resulted ultimately in an uneven number of animals in the three experimental groups: PV, n=5; CV, n=7; and control, n=6.

During a period of 80 min, the animals in the CV and PV groups received infusions of 2 mol litre^{-1} sodium lactate into the central vein and distal portal veins, respectively, and 0.9% saline in the respective other vessel, whereas all animals in the control group received 0.9% saline in both vessels equally. Sodium lactate was infused in a stepwise manner at rates of 1, 2, 3, and 4 ml kg^{-1} h^{-1}, with each infusion lasting 20 min. Saline infusions were administered at the same rates. At baseline (time0), and after each 20 min step (time20 to time140), systemic and regional blood flows were measured, and blood samples were drawn from radial and pulmonary arteries and from femoral, renal, mesenteric, proximal portal, and hepatic veins for blood gas analysis and determination of haemoglobin and plasma lactate concentrations. The measurements were continued at 20 min intervals for 1 h after the last step of lactate infusion. At the end of the experiment, the animals were killed with an i.v. overdose of magnesium. Haemodynamic monitoring is described in the Supplementary material.

Regional blood flow, blood gas, haemoglobin, and lactate measurements

Ultrasound transit-time flow probes were calibrated *in vitro* before recording of the signals (Flowmeters T108 and T208, Transonic Systems Inc.). Blood samples for the measurement of haemoglobin, blood gas analysis, and lactate were analysed immediately after withdrawal. Haemoglobin concentrations and oxygen saturations were measured with an analyzer designed for porcine blood (OSM 3, Radiometer, Copenhagen, Denmark). Blood gases were analysed at 37°C in a blood gas analyzer (ABL 500, Radiometer). An amperometric enzyme sensor method (YSI 2300 Stat Plus®, YSI Inc., Yellow Springs, OH, USA) was utilized to measure plasma lactate. Calculations for regional lactate exchanges are given in the Supplementary material.

Statistics

Detailed statistics are described in the Supplementary material. Briefly, differences between groups for normally distributed variables (Kolmogorov–Smirnov test) were assessed by analysis of variance (ANOVA) for repeated