

## CRITICAL CARE

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

D. Barthelmes<sup>1</sup>, S. M. Jakob<sup>1\*</sup>, S. Laitinen<sup>2</sup>, S. Rahikainen<sup>2</sup>, H. Ahonen<sup>2</sup> and J. Takala<sup>1</sup><sup>1</sup>Department of Intensive Care Medicine, Bern University Hospital and University of Bern, 3010 Bern, Switzerland<sup>2</sup>Department of Anaesthesiology, University Hospital Kuopio, 70210 Kuopio, Finland\* Corresponding author. E-mail: [stephan.jakob@insel.ch](mailto:stephan.jakob@insel.ch)

## 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  $\mu\text{mol kg}^{-1} \text{min}^{-1}$  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)  $\mu\text{mol kg}^{-1}$ ] than during central venous lactate infusion [4530 (3903–5514)  $\mu\text{mol kg}^{-1}$ ,  $P<0.05$ ]. At a similar hepatic lactate delivery ( $\sim 400 \mu\text{mol kg}^{-1} \text{min}^{-1}$ ), hepatic lactate uptake [mean and standard deviation (SD)] was higher during portal [118 (SD 55)  $\mu\text{mol kg}^{-1} \text{min}^{-1}$ ] than during central venous lactate infusion [44 (12)  $\mu\text{mol kg}^{-1} \text{min}^{-1}$ ,  $P<0.05$ ]. 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

Accepted for publication: 21 June 2010

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.<sup>1</sup>

Hepatic lactate uptake is a linear function of prehepatic lactate concentrations.<sup>2–5</sup> In sheep, the hepatic uptake during lactate infusion is a saturable process with second-order kinetics.<sup>6</sup> However, several factors modify this relationship, among them blood flow,<sup>7</sup> substrate availability (e.g. glucose),<sup>8</sup> pH,<sup>7 9</sup> and sepsis.<sup>10</sup> 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.<sup>11</sup>

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

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

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.<sup>1–24</sup> Briefly, animals were premedicated with i.m. atropine (0.05 mg kg<sup>-1</sup>) and azaperone (8 mg kg<sup>-1</sup>). Subsequently, thiopental (5–15 mg kg<sup>-1</sup>) was administered *via* a cannulated ear vein for tracheal intubation. Anaesthesia was maintained with thiopental (5 mg kg<sup>-1</sup> h<sup>-1</sup>) and fentanyl (30 µg kg<sup>-1</sup> h<sup>-1</sup>) until the end of the surgical procedure. After surgery and until the end of the experiment, anaesthesia was maintained using thiopental (5 mg kg<sup>-1</sup> h<sup>-1</sup>) and fentanyl (5 µg kg<sup>-1</sup> h<sup>-1</sup>). 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  $P_{a_{O_2}}$  levels above 13.3 kPa. Tidal volume was set to 10 ml kg<sup>-1</sup>.  $P_{a_{CO_2}}$  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<sup>-1</sup> 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<sup>-1</sup> h<sup>-1</sup>, 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

measurements using one dependent variable, one grouping factor (PV, CV, and controls), and one within-subject factor (time). In the case of non-normality, differences at baseline were tested using the Kruskal–Wallis test. Afterwards, changes over time were evaluated separately in each group using Friedman's test. The relationship between arterial lactate concentration and the various regional lactate exchanges was explored by linear regression analysis. Data are presented as mean and standard deviation (SD) or as median [95% confidence interval (CI)] as appropriate. Statistical significance was defined as  $P < 0.05$ .

## Results

At baseline (time0), variables were similar in all groups.

### Systemic haemodynamics

Cardiac output increased during lactate infusion in the PV and CV groups, without differences between groups (see Supplementary Table S1).

### Regional blood flow

Except for an increase in hepatic arterial blood flow in both lactate infusion groups, there were no differences between groups (see Supplementary Table S2).

### Blood gases and oxygen transport

Arterial pH and base excess increased in both lactate infusion groups ( $P < 0.05$ ), whereas arterial and mixed venous oxygen saturation decreased in these two groups (see Supplementary Table S3). Systemic oxygen consumption tended to decrease during lactate infusion in both groups (time–group interaction,  $P < 0.05$ ).

### Tonometry data

Gastric- and jejunal mucosal-arterial  $P_{CO_2}$  gradients decreased during the first 80–100 min in all groups (time effect for both  $P < 0.05$ ) without between-group differences (see Supplementary Table S4).

### Lactate concentrations and lactate deliveries

Data on regional lactate concentrations and lactate deliveries are presented in Figure 1 and Tables 1 and 2. All concentrations remained stable in the control group. Both CV and PV groups showed an increase in lactate concentration at all measured locations, with significant differences between them in the portal vein lactate concentrations at 80 min of lactate infusion and in the hepatic vein lactate concentrations at 80 min of lactate infusion. In both CV and PV groups, lactate deliveries increased steadily during the infusion phase and decreased afterwards, whereas the control group remained stable. A statistically significant difference between CV and PV was found for portal lactate delivery at 20, 60, and 80 min of lactate infusion (all  $P < 0.05$ ).

### Total lactate uptake

During the whole experiment (140 min), the total hepatic lactate uptake was higher in PV [8198 (5487–12 798)  $\mu\text{mol kg}^{-1}$ ] compared with CV [4530 (3903–5514)  $\mu\text{mol kg}^{-1}$ ,  $P < 0.05$ ].

### Lactate exchange

Regional lactate exchanges are shown in Figure 2. During lactate infusion, three distinct patterns were present: in femoral and mesenteric regions, lactate exchange increased during infusion and returned to baseline immediately after lactate infusion was stopped. In these regions, there were no differences between the CV and PV groups. In the liver and kidney, lactate exchange continued to be positive after the infusion had been stopped, and returned only gradually to baseline during the subsequent 60 min. Hepatic lactate exchange (uptake) was significantly greater in PV when compared with CV. Pulmonary lactate exchange was highly variable and increased only after lactate infusion had been stopped.

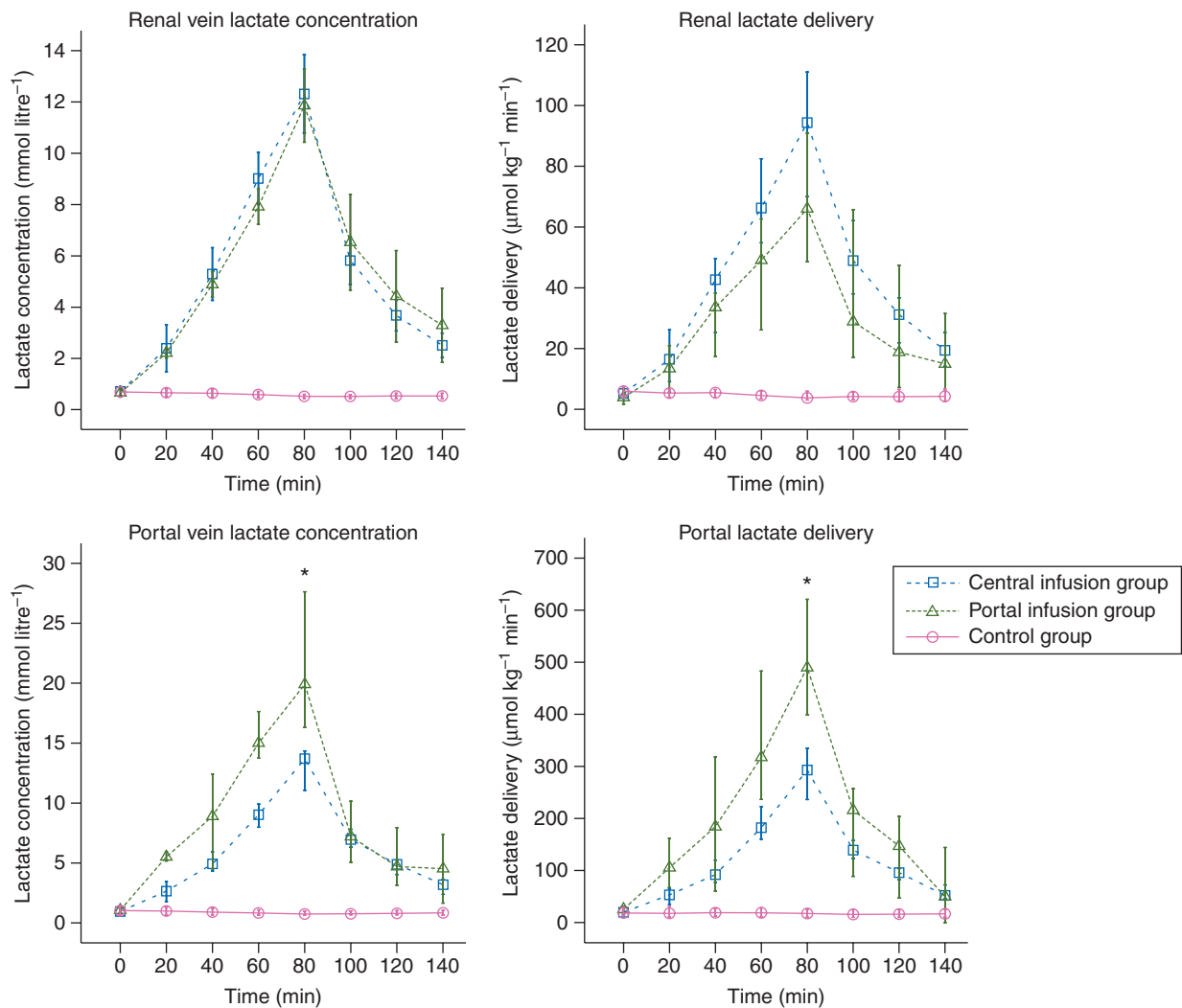
Hepatic lactate exchange in relation to delivery is shown in Figure 3. There were significant differences between the CV and the PV groups: during central vein infusion, hepatic lactate exchange reached a plateau at an infusion speed of 99  $\mu\text{mol kg}^{-1} \text{min}^{-1}$ . During portal vein infusion, hepatic lactate exchange continued to increase when 133  $\mu\text{mol kg}^{-1} \text{min}^{-1}$  was infused, and reached a maximum which was more than three times as high as during central vein lactate infusion. Moreover, when lactate infusion was stopped, hepatic lactate exchange decreased rapidly, and reached smaller values when compared with similar lactate delivery rates during lactate infusion.

The relationships between arterial lactate concentration and regional lactate exchanges are shown in the Supplementary Figures S1–4. Significant correlations were found for all regions and all lactate infusion groups except the kidney during central venous lactate infusion.

## Discussion

The main finding of this study is a significantly higher hepatic lactate uptake during portal vein lactate infusion than during central vein infusion, even with similar total hepatic lactate delivery rates. Throughout the observation period, in addition to baseline lactate exchange, an amount equalling the total infused lactate was taken up in the liver in the PV group vs 50% in the CV group. In our model, maximal measured hepatic lactate uptake in the PV group was 127  $\mu\text{mol kg}^{-1} \text{min}^{-1}$ , which is higher than maximal hepatic lactate uptake during central vein infusion in sheep (95  $\mu\text{mol kg}^{-1} \text{min}^{-1}$ ).<sup>6</sup> Conceptually, the higher hepatic lactate uptake in the PV vs the CV group in our study can result from either higher hepatic blood flow or higher portal venous lactate concentrations.

It has been demonstrated that hepatic lactate metabolism is flow-dependent.<sup>25</sup> However, portal venous blood flows were similar in both groups in our study,



**Fig 1** Lactate levels and deliveries to the right kidney and the portal vein for pigs infused with lactate in the pulmonary artery or portal vein, or with saline. Lactate ( $2 \text{ mol litre}^{-1}$ ) and saline were infused in four consecutive steps (1, 2, 3, and  $4 \text{ ml kg}^{-1} \text{ h}^{-1}$ ) for 20 min each. Median and 95% CI. \*Difference between the two lactate infused groups ( $P < 0.05$ ).

and hepatic arterial flows were higher in the central infusion group, suggesting that the portal venous lactate concentration was the main determinant in the presence of normal liver blood flow. Portal lactate concentration is also an important determinant of hepatic lactate uptake in situations where increased hepatic lactate influx is the result of mesenteric ischaemia.<sup>1</sup> However, during mesenteric ischaemia, hepatic arterial blood flow increases; the so-called hepatic arterial buffer response.<sup>26</sup> Whether an increased hepatic arterial blood flow helps to extract lactate delivered by the portal route is not known.

At the highest lactate infusion rate, the liver remained the predominant site of lactate uptake: the hepatic, femoral, and mesenteric regions contributed 74%, 13%, and 5% (portal infusion) and 66%, 22%, and 7% (central

infusion), respectively, to total lactate uptake in the measured regions. This is in agreement with other studies measuring prehepatic lactate removal in sheep<sup>6</sup> and lactate uptake in the muscle tissue in healthy volunteers.<sup>21</sup> Since we did not infuse higher lactate concentrations, we are unable to confirm the findings of Naylor and colleagues<sup>6</sup> that extra-splanchnic tissues extract more lactate than the liver at higher lactate delivery rates. In patients, dogs, and rats, the kidney was shown to remove 20–30% of lactate load.<sup>6 18–20</sup> Since we measured the flow only in one of several kidney arteries, our renal lactate uptakes (5–8% of total lactate uptake in the measured regions) clearly underestimate the contribution of the kidneys to total lactate clearance.

Whereas lactate exchange decreased only gradually in the liver and kidney after the lactate infusion had been

**Table 1** Lactate concentrations in pigs infused with lactate (CV, central vein infusion group; PV, portal vein infusion group) or saline (control). Values are mean (SD) or median (95% CI). Statistically significant differences between CV and PV were detected only for the hepatic vein at the 80th minute

| Parameter   | Time    | Group         |               |                |                |               |                     |               |               | P-value (time) | P-value (time × group) |
|---|---------|---------------|---------------|----------------|----------------|---------------|---------------------|---------------|---------------|----------------|------------------------|
|   |         | Baseline      |               | Infusion phase |                |               | Post-infusion phase |               |               |                |                        |
|   |         | 0             | 20            | 40             | 60             | 80            | 100                 | 120           | 140           |                |                        |
| Lactate radial artery (mmol litre <sup>-1</sup> )       | CV      | 0.9 (0.3)     | 2.6 (1.0)     | 5.8 (0.8)      | 9.3 (1.1)      | 13.3 (1.8)    | 6.7 (1.0)           | 4.3 (0.6)     | 2.9 (0.5)     | <0.05          | <0.05                  |
|   | PV      | 0.8 (0.1)     | 2.6 (0.1)     | 5.4 (0.4)      | 8.6 (0.8)      | 13.4 (2.0)    | 7.6 (2.0)           | 5.3 (1.9)     | 4.1 (1.7)     |                |                        |
|   | Control | 0.9 (0.3)     | 0.8 (0.2)     | 0.8 (0.2)      | 0.7 (0.2)      | 0.7 (0.1)     | 0.7 (0.1)           | 0.7 (0.1)     | 0.7 (0.1)     | 0.7 (0.2)      |                        |
| Lactate femoral vein (mmol litre <sup>-1</sup> )        | CV      | 1.2 (0.3)     | 2.3 (0.7)     | 4.6 (0.8)      | 7.8 (0.9)      | 11.5 (1.6)    | 7.4 (1.1)           | 5.0 (0.6)     | 3.6 (0.5)     | <0.05          | <0.05                  |
|   | PV      | 1.0 (0.2)     | 2.2 (0.2)     | 4.3 (0.5)      | 7.1 (1.0)      | 11.3 (1.4)    | 8.3 (1.8)           | 6.2 (1.9)     | 4.8 (1.6)     |                |                        |
|   | Control | 1.1 (0.3)     | 1.0 (0.3)     | 1.0 (0.3)      | 1.0 (0.2)      | 0.9 (0.2)     | 0.9 (0.2)           | 0.9 (0.2)     | 1.0 (0.2)     |                |                        |
| Lactate hepatic vein (mmol litre <sup>-1</sup> )        | CV      | 0.3 (0.2–0.6) | 1.7 (0.8–2.3) | 3.8 (3.3–5.0)  | 6.9 (6.2–8.3)  | 11.7 (9.6–13) | 5.0 (4.4–5.9)       | 3.4 (2.6–3.7) | 1.9 (1.6–2.5) | <0.05          |                        |
|   | PV      | 0.5 (0.3–0.6) | 3.1 (1.8–3.8) | 6.9 (4.1–8.1)  | 10 (9–11)      | 16 (13–18)    | 5.7 (2.7–9.3)       | 3.4 (1.4–6.7) | 2.6 (0.8–5.4) | <0.05          |                        |
|   | Control | 0.4 (0.2–0.6) | 0.4 (0.2–0.6) | 0.4 (0.2–0.5)  | 0.3 (0.2–0.5)  | 0.3 (0.2–0.4) | 0.3 (0.2–0.4)       | 0.3 (0.2–0.4) | 0.3 (0.2–0.4) | 0.3 (0.2–0.4)  | NS                     |
| Lactate mesenteric vein (mmol litre <sup>-1</sup> )     | CV      | 1.0 (0.3)     | 2.7 (1.0)     | 5.5 (1.0)      | 9.0 (1.2)      | 12.7 (1.8)    | 6.7 (1.0)           | 4.5 (0.7)     | 3.1 (0.6)     | <0.05          | <0.05                  |
|   | PV      | 1.0 (0.2)     | 2.6 (0.3)     | 4.9 (0.9)      | 8.3 (1.0)      | 12.8 (2.0)    | 7.9 (2.4)           | 6.0 (2.3)     | 4.4 (1.8)     |                |                        |
|   | Control | 1.0 (0.3)     | 1.0 (0.3)     | 1.0 (0.3)      | 0.9 (0.2)      | 0.9 (0.2)     | 0.9 (0.2)           | 0.9 (0.2)     | 0.9 (0.2)     |                |                        |
| Mixed venous lactate (mmol litre <sup>-1</sup> )        | CV      | 0.7 (0.6–1.1) | 2.8 (1.8–3.6) | 5.7 (4.8–6.8)  | 9.1 (8.4–10.5) | 14 (12–15)    | 6.2 (5.8–7.2)       | 4.2 (3.6–4.9) | 2.9 (2.4–3.5) | <0.05          |                        |
|   | PV      | 0.8 (0.6–1.0) | 2.5 (2.3–2.7) | 5.3 (4.8–5.8)  | 8.5 (7.6–9.6)  | 12 (11–16)    | 7.1 (4.7–9.7)       | 4.8 (2.9–7.5) | 3.5 (1.9–5.9) | <0.05          |                        |
|   | Control | 0.9 (0.6–1.1) | 0.9 (0.6–1.0) | 0.7 (0.5–0.9)  | 0.7 (0.5–0.9)  | 0.6 (0.5–0.8) | 0.6 (0.5–0.8)       | 0.6 (0.5–0.8) | 0.7 (0.5–0.8) | NS             |                        |
| Systemic lactate appearance (mmol litre <sup>-1</sup> ) | CV      | 2.1 (0.9)     | 7.4 (3.2)     | 18.7 (5.3)     | 33.1 (5.4)     | 52.2 (9.8)    | 21.9 (5.4)          | 14.2 (3.9)    | 8.3 (5.2)     | <0.05          | <0.05                  |
|   | PV      | 2.2 (1.0)     | 6.7 (2.6)     | 15.8 (6.3)     | 28.7 (10.7)    | 51.1 (15.4)   | 22.9 (8.0)          | 14.7 (6.7)    | 10.4 (4.8)    |                |                        |
|   | Control | 2.5 (0.6)     | 2.4 (0.5)     | 2.2 (0.4)      | 2.0 (0.4)      | 1.8 (0.3)     | 1.8 (0.4)           | 1.9 (0.4)     | 1.9 (0.6)     |                |                        |



**Table 2** Lactate delivery in pigs infused with lactate (CV, central vein infusion group; PV, portal vein infusion group) or saline (control). Values are mean (sd) or median (95% CI)

| Parameter   | Time    | Group         | Infusion phase |               |               |               | Post-infusion phase |               |               |               | P-value (time) | P-value (time × group) |
|---|---------|---------------|----------------|---------------|---------------|---------------|---------------------|---------------|---------------|---------------|----------------|------------------------|
|   |         |               | 0              | 20            | 40            | 60            | 80                  | 100           | 120           | 140           |                |                        |
| Femoral lactate delivery ( $\mu\text{mol kg}^{-1} \text{min}^{-1}$ )          | CV      | 2.8 (1.6)     | 11.9 (9.4)     | 26.1 (17.3)   | 48.3 (27.7)   | 63.2 (40.8)   | 18.6 (7.7)          | 13.4 (4.9)    | 9.5 (3.8)     | <0.05         | <0.05          |                        |
|   | PV      | 3.3 (1.3)     | 10.8 (5.3)     | 26.1 (14.6)   | 43.6 (24.8)   | 79.8 (40.0)   | 33.2 (17.0)         | 20.8 (10.3)   | 16.6 (10.1)   | <0.05         | <0.05          |                        |
|   | Control | 2.58 (0.78)   | 2.47 (0.91)    | 2.50 (0.64)   | 2.17 (0.81)   | 1.97 (0.85)   | 1.98 (0.90)         | 1.9 (0.9)     | 1.9 (1.0)     | 1.9 (1.0)     | <0.05          | <0.05                  |
| Hepatic arterial lactate delivery ( $\mu\text{mol kg}^{-1} \text{min}^{-1}$ ) | CV      | 0.9 (0.6–2.0) | 5.5 (3.2–6.2)  | 14 (10–25)    | 33 (17–61)    | 76 (47–117)   | 41 (21–56)          | 26 (14–31)    | 14 (6–24)     | <0.05         | <0.05          |                        |
|   | PV      | 1.1 (0.4–2.8) | 8.0 (4.7–9.8)  | 18 (14–26)    | 40 (32–51)    | 73 (51–103)   | 41 (24–59)          | 30 (12–44)    | 22 (9.8–28)   | <0.05         | <0.05          |                        |
|   | Control | 1.5 (0.7–2.9) | 1.7 (0.6–3.2)  | 2.0 (0.7–3.2) | 1.8 (0.6–3.4) | 2.3 (0.9–3.6) | 2.0 (1.0–3.4)       | 1.9 (1.1–3.4) | 1.9 (0.9–3.6) | 1.9 (0.9–3.6) | NS             | NS                     |
| Mesenteric lactate delivery ( $\mu\text{mol kg}^{-1} \text{min}^{-1}$ )       | CV      | 8.6 (2.5)     | 28 (12)        | 65 (18)       | 113 (29)      | 162 (42)      | 69 (16)             | 47 (11)       | 33 (12)       | <0.05         | <0.05          |                        |
|   | PV      | 11 (3.4)      | 34 (6.3)       | 74 (15)       | 127 (25)      | 209 (39)      | 107 (35)            | 75 (34)       | 54 (25)       | <0.05         | <0.05          |                        |
|   | Control | 12 (4.8)      | 13 (4.1)       | 11.7 (3.2)    | 11.1 (3.5)    | 10 (3.5)      | 10 (3.4)            | 11 (3.9)      | 10 (3.2)      | <0.05         | <0.05          |                        |
| Pulmonary lactate delivery ( $\mu\text{mol kg}^{-1} \text{min}^{-1}$ )        | CV      | 53 (19)       | 208 (80)       | 494 (95)      | 899 (129)     | 1390 (97)     | 566 (81)            | 374 (66)      | 220 (122)     | <0.05         | <0.05          |                        |
|   | PV      | 63 (21)       | 194 (45)       | 472 (148)     | 867 (254)     | 1536 (429)    | 686 (286)           | 448 (211)     | 314 (159)     | <0.05         | <0.05          |                        |
|   | Control | 68 (14)       | 67 (18)        | 61 (12)       | 58 (15)       | 51 (11)       | 51 (14)             | 52 (13)       | 52 (15)       | <0.05         | <0.05          |                        |

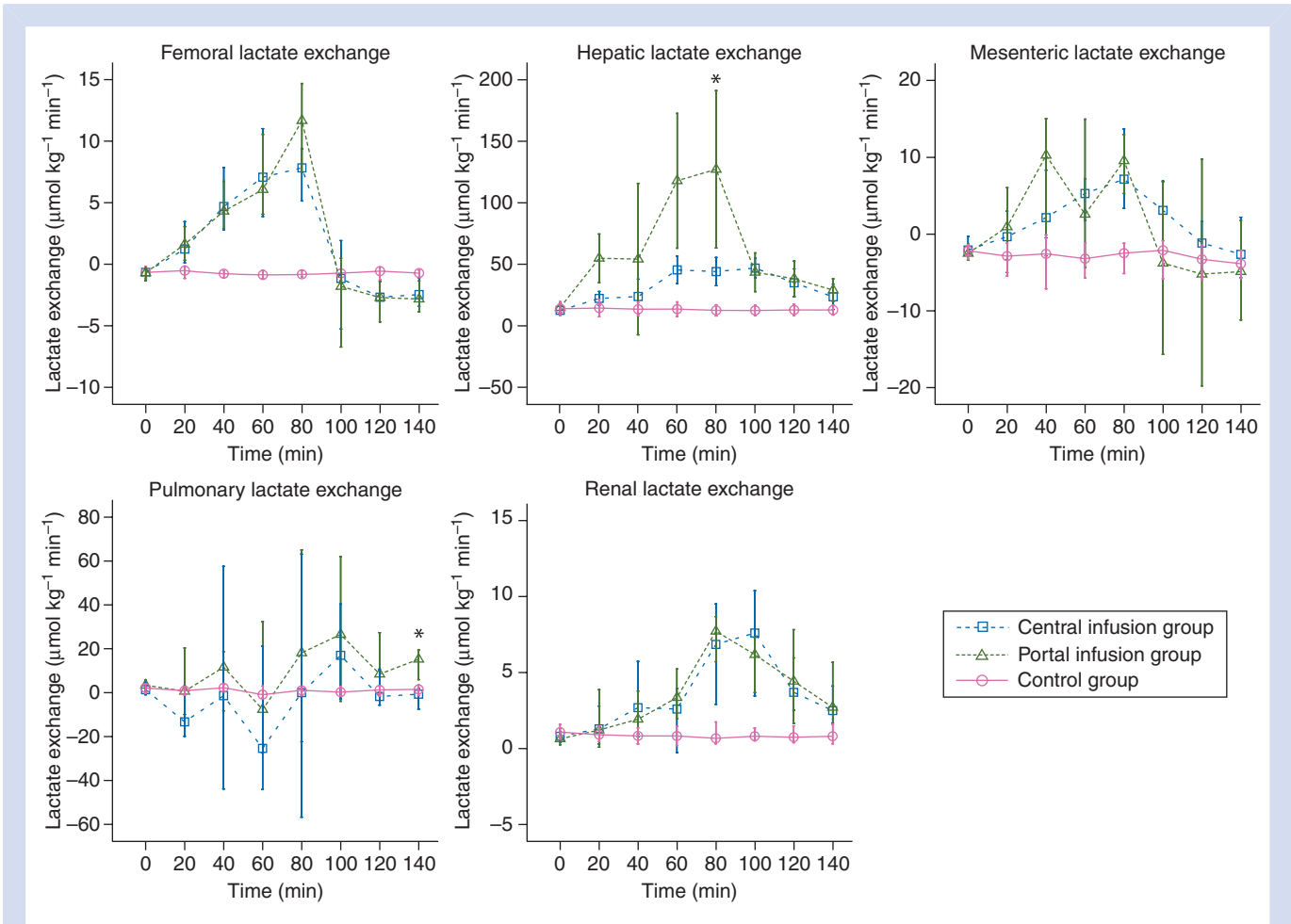
stopped, transient lactate uptake during lactate infusion in mesenteric and femoral regions turned to net lactate release very quickly. This is likely to reflect partial storage of lactate and later release, rather than active metabolism in these regions. The post-infusion changes in the mesenteric region did not differ significantly among the three groups examined. One possibility is a higher 'lactate storage' capacity of the mesenteric when compared with the femoral region, with later onset of lactate release. Since blood sampling was stopped at 140 min, we have no data to support this hypothesis.

At the highest lactate infusion rate, total apparent tissue lactate uptake (the sum of uptakes in the measured regions) was much higher in the PV group ( $173 \mu\text{mol kg}^{-1} \text{min}^{-1}$ ) when compared with the CV group ( $68 \mu\text{mol kg}^{-1} \text{min}^{-1}$ ). Consequently, a significant part of the lactate infused into the central vein must have been removed by other, unmeasured tissues (e.g. brain, heart, and other skeletal muscles). Our estimate on lung lactate exchange should be interpreted with caution: the mixed venous–arterial lactate gradient is small, even during central venous infusion. Hence, small measurement errors may induce large variations in calculated lactate uptake, and up to five serial samples may be necessary for a reliable estimate of lung lactate exchange.<sup>27</sup> This was not done in the present study, both for technical reasons and due to the blood volume needed for the analyses.

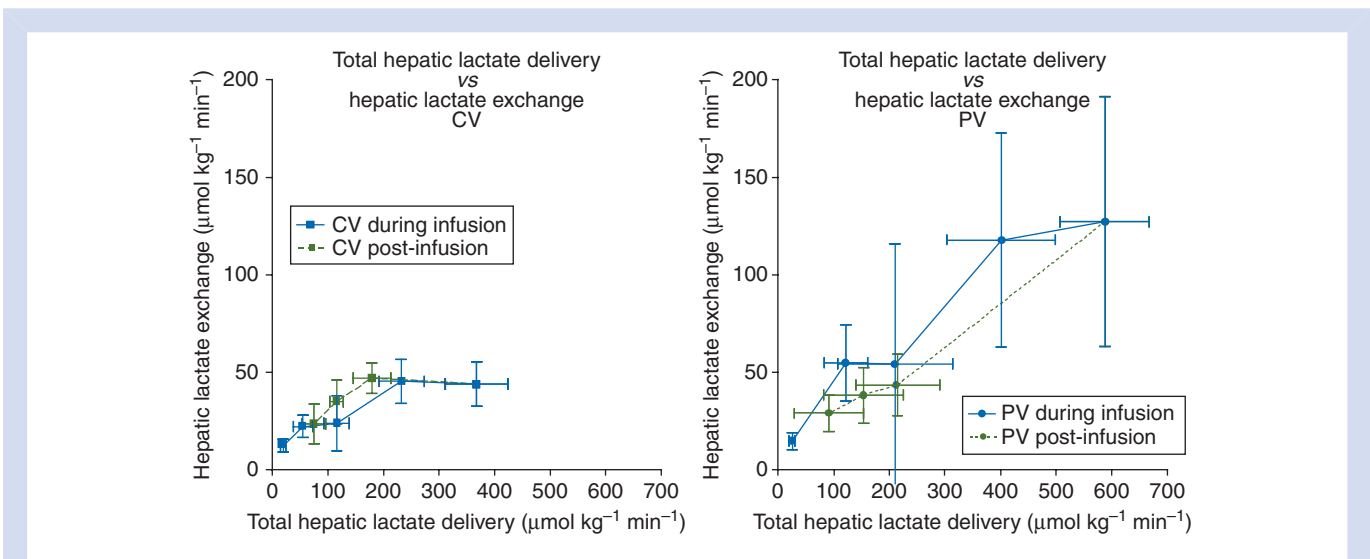
We interpret the increasing systemic oxygen consumption during lactate infusion as the consequence of increased lactate metabolism, and the decreasing arterial oxygen saturation as a consequence of increasing systemic oxygen extraction and intra-pulmonary shunt.<sup>28</sup>

This study has limitations. First, lactate was infused and not produced by tissue hypoxia. Accordingly, effects of changes in systemic and regional blood flows, acidosis, and/or inflammation on regional lactate metabolism were not taken into account.<sup>7–10</sup> Nevertheless, effects of regional lactate exchange during mesenteric ischaemia<sup>1</sup> and systemic hypoperfusion<sup>25</sup> have been addressed. Secondly, since no tracers were used, the relationship between lactate uptake, storage, metabolism, and release, and the extent to which all of these processes occurred in the various tissues, cannot be addressed.

In summary, this study demonstrates that portal vein lactate concentration is an important determinant of hepatic lactate uptake. However, time course and magnitude of increases in arterial plasma lactate concentrations as a result of regional lactate infusion are not dependent on the site of lactate infusion. Besides several organs such as the liver or the kidney that contribute to lactate extraction, other parts of the body, such as the mesenteric region or the legs, may also have an important function in removing lactate from the blood. Our data suggest that in these regions, the arterial lactate concentration is the main determinant of tissue lactate uptake. If lactate is infused into a central vein, extra-hepatic tissues extract more lactate than the liver.



**Fig 2** Femoral, hepatic, mesenteric, pulmonary, and renal lactate exchange in pigs infused with lactate in the pulmonary artery or portal vein, or with saline (circle). Lactate ( $2 \text{ mol litre}^{-1}$ ) and saline were infused in four consecutive steps (1, 2, 3, and 4  $\text{ml kg}^{-1} \text{h}^{-1}$ ) for 20 min each. Median and 95% CI. \*Difference between the two lactate infused groups ( $P < 0.05$ ).



**Fig 3** Total hepatic lactate exchange vs hepatic lactate delivery in pigs infused with lactate in the pulmonary artery (CV) or portal vein (PV) during and after infusion. Mean (1 SD). The difference in lactate exchange between CV and PV was significantly different ( $P < 0.05$ ).

## Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

## Conflict of interest

The Department of Intensive Care Medicine has, or has had in the past, research contracts with Abbott Nutrition International, B. Braun Medical AG, CSEM SA, Edwards Lifesciences Services GmbH, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG, and Orion Corporation; and research & development/consulting contracts with Edwards Lifesciences SA and Maquet Critical Care AB. The money is/was paid into a departmental fund; no author receives/received individual fees. The past contract with Edwards Lifesciences is unrelated to and did not influence the current study.

## References

- Jakob SM, Merasto-Minkkinen M, Tenhunen JJ, Heino A, Alhava E, Takala J. Prevention of systemic hyperlactatemia during splanchnic ischemia. *Shock* 2000; **14**: 123–7
- Sestoft L, Marshall MO. Hepatic lactate uptake is enhanced by low pH at low lactate concentrations in perfused rat liver. *Clin Sci (Lond)* 1986; **70**: 19–22
- Felipe A, Remesar X, Pastor-Anglada M. L-lactate uptake by rat liver. Effect of food deprivation and substrate availability. *Biochem J* 1991; **273**: 195–8
- Reilly PE, Chandrasena LG. Glucose lactate interrelations in sheep. *Am J Physiol* 1978; **235**: E487–92
- Annison EF, Lindsay DB, White RR. Metabolic interrelations of glucose and lactate in sheep. *Biochem J* 1963; **88**: 243–8
- Naylor JM, Kronfeld DS, Freeman DE, Richardson D. Hepatic and extrahepatic lactate metabolism in sheep: effects of lactate loading and pH. *Am J Physiol* 1984; **247**: E747–55
- Sestoft L, Marshall MO. Regulation of lactate uptake and lactate production in liver from 48-h-starved rats: effects of pH, flow and glucose concentration. *Clin Sci (Lond)* 1988; **74**: 403–6
- Sestoft L, Bartels PD, Folke M. Pathophysiology of metabolic acidosis: effect of low pH on the hepatic uptake of lactate, pyruvate and alanine. *Clin Physiol* 1982; **2**: 51–8
- Lloyd MH, Iles RA, Simpson BR, Strunin JM, Layton JM, Cohen RD. The effect of simulated metabolic acidosis on intracellular pH and lactate metabolism in the isolated perfused rat liver. *Clin Sci Mol Med* 1973; **45**: 543–9
- Chrusch C, Bautista E, Jacobs HK, et al. Blood pH level modulates organ metabolism of lactate in septic shock in dogs. *J Crit Care* 2002; **17**: 188–202
- Chiolero R, Tappy L, Gillet M, et al. Effect of major hepatectomy on glucose and lactate metabolism. *Ann Surg* 1999; **229**: 505–13
- Levy MN. Uptake of lactate and pyruvate by intact kidney of the dog. *Am J Physiol* 1962; **202**: 302–8
- Van Hall G, Jensen-Urstad M, Rosdahl H, Holmberg HC, Saltin B, Calbet JA. Leg and arm lactate and substrate kinetics during exercise. *Am J Physiol Endocrinol Metab* 2003; **284**: E193–205
- Gladden LB. Net lactate uptake during progressive steady-level contractions in canine skeletal muscle. *J Appl Physiol* 1991; **71**: 514–20
- Cohen JJ, Randall EW. Alkalosis and renal para-aminohippurate transport in dog: relation to lactate uptake. *Am J Physiol* 1964; **206**: 383–90
- Wolfe RR, Hochachka PW, Trelstad RL, Burke JF. Lactate oxidation in perfused rat lung. *Am J Physiol* 1979; **236**: E276–82
- Rhoades RA, Shaw ME, Eskew ML, Wali S. Lactate metabolism in perfused rat lung. *Am J Physiol* 1978; **235**: E619–23
- Mizock BA, Falk JL. Lactic acidosis in critical illness. *Crit Care Med* 1992; **20**: 80–93
- Leal-Pinto E, Park HC, King F, MacLeod M, Pitts RF. Metabolism of lactate by the intact functioning kidney of the dog. *Am J Physiol* 1973; **224**: 1463–7
- Yudkin J, Cohen RD. The contribution of the kidney to the removal of a lactic acid load under normal and acidotic conditions in the conscious rat. *Clin Sci Mol Med* 1975; **48**: 121–31
- Ferrannini E, Natali A, Brandi LS, et al. Metabolic and thermogenic effects of lactate infusion in humans. *Am J Physiol* 1993; **265**: E504–12
- Gladden LB, Yates JW. Lactic acid infusion in dogs: effects of varying infusate pH. *J Appl Physiol* 1983; **54**: 1254–60
- Prior RL. Effect of level of feed intake on lactate and acetate metabolism and lipogenesis in vivo in sheep. *J Nutr* 1978; **108**: 926–35
- Jakob SM, Tenhunen JJ, Heino A, Pradl R, Alhava E, Takala J. Splanchnic vasoregulation during mesenteric ischemia and reperfusion in pigs. *Shock* 2002; **18**: 142–7
- Jakob SM, Tenhunen JJ, Laitinen S, Heino A, Alhava E, Takala J. Effects of systemic arterial hypoperfusion on splanchnic hemodynamics and hepatic arterial buffer response in pigs. *Am J Physiol Gastrointest Liver Physiol* 2001; **280**: G819–G827
- Lautt WW, Legare DJ, d'Almeida MS. Adenosine as putative regulator of hepatic arterial flow (the buffer response). *Am J Physiol* 1985; **248**: H331–8
- De Backer D, Creteur J, Zhang H, Norrenberg M, Vincent JL. Lactate production by the lungs in acute lung injury. *Am J Respir Crit Care Med* 1997; **156**: 1099–104
- Takala J. Hypoxemia due to increased venous admixture: influence of cardiac output on oxygenation. *Intensive Care Med* 2007; **33**: 908–11