Attenuated hepatosplanchnic uptake of lactate during intense exercise in humans

H. B. NIELSEN, J. O. CLEMMENSEN, C. SKAK, P. OTT, and N. H. SECHER.

Hepatosplanchnic O2 uptake increased from 67 ± 3 to 95 ± 13 ml/min, and the output of glucose increased from 1.1 ± 0.2 to 2.1 ± 0.3 mmol/min (P < 0.05). Even at the lowest hepatosplanchnic venous hemoglobin O2 saturation during exercise of 6%, the average concentration of glucose in arterial blood was maintained close to the resting level (5.2 ± 0.2 vs. 5.5 ± 0.2 mmol/l), whereas the difference between arterial and hepatic venous blood glucose increased to a maximum of 22 mmol/l. In arterial blood, the concentration of lactate increased from 1.1 ± 0.2 to 6.0 ± 1.0 mmol/l, and the hepatosplanchnic uptake of lactate was elevated from 0.4 ± 0.06 to 1.0 ± 0.05 mmol/min during exercise (P < 0.05). However, when the hepatosplanchnic venous hemoglobin O2 saturation became low, the arterial and hepatosplanchnic venous blood lactate difference approached zero. Even with a marked reduction in its blood flow, exercise did not challenge the ability of the liver to maintain blood glucose homeostasis. However, it appeared that the contribution of the Cori cycle decreased, and the accumulation of lactate in blood became influenced by the reduced hepatosplanchnic blood flow.

The progressive increase in blood lactate with exercise intensity is sometimes considered to be a reflection of anaerobic metabolism. However, muscle, even when working at a high intensity, may take up lactate (43). The blood lactate level is also influenced by the metabolism in other organs, including “resting” skeletal muscle (23), the heart (10), the brain (25), the kidneys (29), and notably the liver (42).

In response to low-intensity exercise, the hepatic extraction of lactate increases (2), despite a reduced blood flow (4, 41, 42). Yet a marked reduction in the hepatosplanchnic blood flow challenges the metabolic function of the liver (38). We hypothesized that the marked increase in blood lactate with intense exercise is influenced by a reduced uptake by the liver, even to an extent that it may affect gluconeogenesis. After an overnight fast, approximately one-third of the glucose production is by hepatic gluconeogenesis (24). On the other hand, the influence of exercise is controversial in humans, as hepatic gluconeogenesis has been reported both to increase (8) and to decrease (12). Friedlander et al. (14) suggested that the plasma clearance of lactate for the purpose of hepatic gluconeogenesis is reduced after training, indicating that a limited blood flow to liver affects its uptake of lactate. In the dog, the liver demonstrates a net release of lactate in response to exercise (15, 48). It is not known whether hepatic uptake of lactate is attenuated during intense exercise in humans or whether the liver releases lactate.

In healthy humans, we evaluated the concentration difference for lactate between arterial and hepatic venous blood and estimated the hepatosplanchnic blood flow and O2 uptake (V02) during exercise. We aimed for a work intensity that the subjects could maintain for ~30 min. Such a work rate was considered to elicit a significant accumulation of lactate in arterial blood and at the same time allow for an acceptable approximation to steady-state elimination of indocyanine green (ICG). To exclude an influence of exercise-induced arterial hypoxemia (13, 32) on hepatic metabolism, the evaluation was carried out with an inspired O2 fraction of both 0.21 and 0.30.

METHODS

Eight male subjects (Table 1) participated in the study after giving informed consent as approved by the Ethics Committee of Copenhagen (KF 01–276/97). None of the subjects had any diseases or injury 3 wk before the experiment, nor were they taking any medication. All subjects were studied in the resting state 10–12 h after an overnight fast. The subjects abstained from physical training, alcohol, and tobacco smoking on the day before the experiments, which began at 8:00 AM.

A catheter (1.0 mm ID; 20 gauge) was introduced into the brachial artery of the nondominant arm. A liver venous catheter (Cournand, 7 Fr) was introduced via the right median cubital vein and was guided with by the subject supine.

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Also con...calculated at each time point. In this case, the hepato-splanchnic...was expressed as the linear regression for the heart.

Healthcare, Maurepas, France) positioned at the level of the and were connected to a pressure monitoring kit (Baxter...kept patent by continuous infusion of isotonic saline (3 ml/h)

from steady-state conditions (33); and Hct is the hematocrit.

\[
\frac{dCa}{dt}/H_1003 \quad r\text{med after maximal voluntary } V_e \text{ corresponding to } \sim 75\% \text{ of } V_{O_2\text{ max}} \text{ (Table 1).}
\]

The subjects were randomized to an in-spired } O_2 \text{ fraction of 0.21 or 0.30 in a double-blind fashion by using a crossover study design with } 1 \text{ h of recovery between trials. After each exercise session, perceived exertion was expressed according to a visual Borg scale (9).}

For description of hepatic blood flow, } O_2 \text{ uptake, and blood variables obtained from the hepatic vein, we used the term } "hepatosplanchnic" to indicate that blood from the hepatic vein also represents portal blood, whereas ICG is eliminated exclusively by the liver. For the assessment of hepatosplanchnic blood flow, a constant infusion of ICG (0.18 ± 0.02 } \mu \text{mol/l; Cardio-Green; Becton Dickinson, Cockeysville, MD}) was administered into an arm vein by a peristaltic roller pump (type 104; Ole Dih, Hvidovre, Denmark). A 45-min priming infusion secured a steady-state plasma concentration of ICG. Arterial and hepatic venous blood were collected simultaneously five times with a 3-min interval between samples. This procedure was performed in the last 15 min of the resting period and again in the last 15 min of exercise. Immediately on completion of the study, the samples were centrifuged, and plasma was frozen at −20°C. The ICG dye concentration was determined by high-performance liquid chromatography with a detection limit of 0.01 } \mu \text{mol/l (34).}

The estimated mean hepatosplanchnic blood flow at rest and during exercise was calculated as [IR − (V_{AOG} \cdot dCa/dt)]/[(Ca − Cv) \cdot [1/(1 − Hct)]], where IR is the infusion rate of ICG; Ca and Cv are the concentrations of ICG in the brachial artery and in the hepatic vein, respectively; dCa/dt is the Ca accumulation rate; V_{AOG} is the volume of distribution of ICG; dCa/dt \times V_{AOG} represents a correction for minor deviations from steady-state conditions (33); and Hct is the hematocrit. V_{AOG} was estimated as 0.05 \times body weight (kg), and dCa/dt \times V_{AOG} was expressed as the linear regression for the five samples (44). This correction factor was not used when blood flow was calculated at each time point. In this case, the hepatosplanchnic } V_{O_2} \text{ was calculated by using the Fick principle based on the } O_2 \text{ content. In the subject with the lowest hemoglobin } O_2 \text{ saturation obtained in the hepatic vein during cycling, determination of ICG failed. In two subjects, the hepatosplanchnic blood flow at rest was } \sim 3 \text{ l/min as found after a meal (36), and blood flows from these two subjects were excluded from the overall presentation because of suspicion of protocol violation. However, in both cases, the flow became reduced by 50\% during exercise associated with an increase in the hepatosplanchnic } V_{O_2}, \text{ i.e., these subjects showed the same pattern as found for the others.}

The subjects breathed through a two-way low-resistance T valve (model 2700; Hans Rudolph, Kansas City, MO) with humidified air delivered from a Douglas bag. The determinations of the flow rate and gas analysis were made continuously by using a cardipulmonary exercise test system (2001; Medical Graphics, St. Paul, MN). Measurements were made on-line with electrochemical } O_2 \text{ and } CO_2 \text{ infrared analyzers. After 5 min of rest to stabilize } V_e, \text{ the subject breathed ambient air and thereafter air with an inspired } O_2 \text{ fraction of either 0.21 or 0.30 for 5 min while being monitored in the exercise position. Measurements of } V_{O_2}, \text{ } V_e, \text{ the respiratory rate, expired } CO_2, \text{ respiratory exchange ratio, and end-tidal partial pressures for } O_2 \text{ and } CO_2 \text{ were averaged for every 30 s.}

Cardiac output was estimated by an impedance cardio- graph (CDM 3000 Hemodynamics Monitor, CardioDynamics International, San Diego, CA). Two disposable electrodes (Blue Sensor VL-00-S, MediCotest, Ølbytøkke, Denmark) were placed over the sternocleidomastoid muscle on each side. Also in the midaxillary line, a pair of electrodes was placed at the level of the umbilicus on both sides of the body. Cardiac output was calculated from pulsatile changes in thoracic electrical impedance (36, 47). Heart rate and mean arterial pressure were assessed invasively (Baxter), and results are expressed as the average, both at rest and during exercise.

Paired samples of arterial and hepatosplanchnic venous blood were obtained at rest and after 18, 24, and 30 min of exercise by using heparinized syringes (Q550; Radiometer, Copenhagen, Denmark). Blood samples were kept on ice until analysis for blood-gas variables, acid-base status, and the glucose concentration by using an ABL apparatus (model 615; Radiometer). The concentration of lactate in plasma was determined by a YSI (model 2300; Yellow Springs Instruments). The blood } O_2 \text{ content was calculated as the sum of bound and dissolved } O_2.

Blood samples for assessment of plasma catecholamines were obtained at rest and during the last minute of exercise. Plasma was separated immediately and frozen. The catecholamine concentrations were determined by a single-isotope radioenzymatic method (6) by using high-performance liquid chromatography (Waters Chromatography Division, Millford, MA) with an average variability of 1% (31). The intrinsic hepatic clearance of a substance was } [hepatosplanchnic blood flow \cdot (1 − Hct)\cdot ln(Cv/Ca)], \text{ which is equivalent to the permeability-surface product and reflects the ability of the liver to extract a substance from plasma (27, 33). If the permeability of the membrane of the liver cell remains unchanged, the intrinsic clearance is a measure of the sinusoidal surface area (27, 33).}

Data are expressed as means with standard error of the mean. Comparisons among multiple samples were evaluated by the Friedman analysis of variance (SYSTAT). Significant effects were further evaluated by a Wilcoxon test by rank for locating significant paired differences. A } P \text{ value of } <0.05 \text{ was considered statistically significant.}

Table 1. Anthropometric data

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>} V_{O_2\text{max}}, l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>31</td>
<td>182</td>
<td>72</td>
<td>3.9</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>28</td>
<td>197</td>
<td>77</td>
<td>3.2</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>26</td>
<td>178</td>
<td>82</td>
<td>3.9</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>25</td>
<td>185</td>
<td>85</td>
<td>3.1</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>22</td>
<td>179</td>
<td>65</td>
<td>3.2</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>20</td>
<td>183</td>
<td>76</td>
<td>3.6</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>20</td>
<td>173</td>
<td>80</td>
<td>3.8</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>22</td>
<td>191</td>
<td>93</td>
<td>4.0</td>
</tr>
</tbody>
</table>

M, male; } V_{O_2\text{max}}, \text{ maximal } O_2 \text{ uptake.
RESULTS

\( V\dot{E} \) and circulation. Cycling resulted in elevated \( V\dot{E} \) associated with increased expired CO\(_2\) and \( V\dot{O}_2\) (Fig. 1) and changes in the end-tidal variables (Table 2). Thus the respiratory exchange ratio increased during exercise to establish a plateau (Fig. 1). Cardiac output, heart rate, and mean arterial pressure also increased (Table 2).

The estimated mean hepatosplanchnic blood flow decreased from a resting value of 1.6 ± 0.1 to 0.7 ± 0.1 l/min during exercise (\( P < 0.05 \)). Yet the hepatosplanchnic \( V\dot{O}_2\) was elevated from 67 ± 3 ml/min at rest to 93 ± 13 ml/min during exercise (\( P < 0.05 \)). When determined for each time point, it appeared that the hepatosplanchnic blood flow was lowest at the end of the exercise trial (Fig. 2).

The increase in the plasma concentrations of catecholamines was pronounced during cycling (Table 2). The hepatosplanchnic uptake of norepinephrine increased from 0.3 ± 0.9 to 5.0 ± 1.0 nmol/min, whereas the hepatosplanchnic uptake of epinephrine remained at the resting level during exercise (0.7 ± 0.2 nmol/min).

Blood-gas variables. The arterial CO\(_2\) pressure increased, and the hepatic venous CO\(_2\) partial pressure was even higher than in arterial blood (Table 2). The arterial O\(_2\) partial pressure did not change from the resting level. Also, the arterial hemoglobin O\(_2\) saturation was not affected by exercise, whereas hematocrit and, therefore, the arterial O\(_2\) content increased. During cycling, the hemoglobin O\(_2\) saturation in hepatic venous blood decreased and reached a lowest level of 6% in one subject. Furthermore, pH values of arterial and hepatic venous blood were reduced. The average O\(_2\) concentration difference between arterial and hepatic venous blood increased from 40 ± 3 ml/l at rest to 142 ± 13 ml/l during exercise.

Substrates. The glucose level obtained in the hepatic vein increased markedly during exercise, with no significant change in the average glucose concentration in arterial blood (Table 2). Yet after 24 min of exercise, the glucose level in arterial blood became lower than at rest (Fig. 3). The hepatic venous and the arterial blood glucose concentration difference increased during exercise and reached a maximum of 22 nmol/l when the hemoglobin O\(_2\) saturation in the hepatic vein became low (Fig. 4). The hepatosplanchnic glucose release increased from a resting level of 1.1 ± 0.05 to 2.1 ± 0.26 mmol/min (\( P < 0.05 \)).

The concentration of lactate in blood increased in response to exercise (Fig. 4). Yet the hepatosplanchnic uptake of lactate increased from 0.4 ± 0.06 to 1.0 ± 0.05 mmol/min during exercise (\( P < 0.05 \)). With a decrease in hepatic venous O\(_2\) saturation to a minimum of 6–10%, the arteriohepatic venous difference for lactate approached zero (Fig. 4). In one subject, the concentration of lactate obtained from the hepatic vein was higher than in arterial blood.

Intrinsic clearance. The hepatic intrinsic clearance of catecholamines was not significantly affected by exercise. The intrinsic clearance of ICG declined from 2,592 ± 175 to 774 ± 33 ml/min and that of lactate was reduced from 27.4 ± 4.1 to 10.2 ± 3.5 l/min (\( P < 0.05 \)).

Inspired O\(_2\) fraction of 0.30. Perceived exertion decreased from 18 (15–19) in normoxia to 16 (13–17) (median and range) during exercise in hyperoxia (\( P < 0.05 \)).

Fig. 1. Pulmonary O\(_2\) uptake (\( V\dot{O}_2; \text{top left} \)), pulmonary CO\(_2\) output (\( V\dot{CO}_2; \text{bottom left} \)), respiratory exchange ratio (RER; \text{top right} \), and pulmonary ventilation (\( V\dot{E}; \text{bottom right} \)) at rest and in response to 30 min of cycling with an inspired O\(_2\) fraction of 0.21. Values are means ± SE.
0.05). Respiratory variables were not affected by an increased inspired O₂ fraction, whereas the arterial O₂ pressure was higher than during control exercise (Table 2). The acid-base status, the concentrations of hemoglobin and the plasma catecholamines, and the concentration of glucose were not affected by hyperoxia. Although the concentration of lactate tended to be lower, it did not reach statistical significance. Both

![Fig. 2. Hepatosplanchnic blood flow at rest and during submaximal ergometer cycling with an inspired O₂ fraction of 0.21 or 0.30. Each exercise period is 30 min, and the blood flows are measured in the last 15 min separated by 3 min. A resting period separates the 2 trials. Values are means ± SE. Small symbols represent the individual values, and the large solid symbols are the average for the 5 subjects with a "normal" resting hepatic blood flow. *Different from rest, P < 0.05.

Table 2. Effects of inspired O₂ fraction of 0.21 and 0.30 at rest and during cycling

<table>
<thead>
<tr>
<th></th>
<th>21% O₂</th>
<th>30% O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Work</td>
</tr>
<tr>
<td>Vₜ, l/min</td>
<td>10 ± 1</td>
<td>72 ± 8*</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>13 ± 2</td>
<td>37 ± 4*</td>
</tr>
<tr>
<td>PETCO₂, Torr</td>
<td>38 ± 1</td>
<td>41 ± 1</td>
</tr>
<tr>
<td>PAO₂, Torr</td>
<td>41 ± 1</td>
<td>37 ± 8*</td>
</tr>
<tr>
<td>PVCO₂, Torr</td>
<td>45 ± 1</td>
<td>53 ± 3*</td>
</tr>
<tr>
<td>PVCO₂, Torr</td>
<td>42 ± 1</td>
<td>24 ± 3*</td>
</tr>
</tbody>
</table>
| pH (a)              | 7.42 ± 0.01 | 7.38 ± 0.01 | 7.41 ± 0.01 | 7.39 ± 0.01*
| pH (v)              | 7.40 ± 0.01 | 7.32 ± 0.01*| 7.40 ± 0.01 | 7.34 ± 0.01*|
| BE (a), mmol/l      | 2.3 ± 0.3 | 2.5 ± 1.2*| 1.8 ± 0.4 | 0.3 ± 0.6*|
| BE (v), mmol/l      | 2.8 ± 0.4 | 0.8 ± 0.9*| 2.6 ± 0.5 | 2.4 ± 0.6|
| HCO₃⁻ (a), mmol/l   | 0.1 10.2 | 0.4 23 | 0.5 18 | 0.9 26*
| HCO₃⁻ (v), mmol/l   | 0.4 24 | 24 ± 0.5 | 26 ± 0.4 | 24 ± 0.5*|
| SaO₂, %             | 97.4 ± 0.2 | 96.9 ± 0.1* | 98.4 ± 0.1 | 98.4 ± 0.1|
| SvO₂, %             | 77.4 ± 1.6 | 37.4 ± 6.0* | 80.3 ± 2.5 | 45.8 ± 6.3*†|
| HB (a), mmol/l      | 9.3 ± 0.1 | 10.2 ± 0.1* | 9.3 ± 0.1 | 10.1 ± 0.1*|
| HB (v), mmol/l      | 9.5 ± 0.1 | 10.1 ± 0.1* | 9.3 ± 0.1 | 10.0 ± 0.1*|
| Hct (a), %          | 46.5 ± 0.6 | 50.3 ± 0.3* | 46.0 ± 0.9 | 49.6 ± 0.8*|
| Hct (v), %          | 46.4 ± 1.1 | 49.7 ± 0.5* | 46.1 ± 0.8 | 49.3 ± 0.9*|
| CaO₂, ml/l          | 207 ± 22 224 ± 2* | 209 ± 4 227 ± 3†|
| CvO₂, ml/l          | 167 ± 4 185 ± 14* | 171 ± 7 104 ± 15†|
| VO₂, l/min          | 0.3 ± 0.0 | 2.6 ± 0.1* | 0.4 ± 0.0 | 2.6 ± 0.1*|
| HR, beats/min       | 70 ± 4 180 ± 3* | 75 ± 5 175 ± 6*|
| Cardiac output,l/min| 6.6 ± 0.4 | 19 ± 1* | 7.0 ± 0.5 | 18 ± 1*|
| MAP, mmHg           | 93 ± 4 111 ± 3* | 92 ± 0 106 ± 3*|
| Glucose (a), mmol/l | 5.45 ± 0.15 | 5.15 ± 0.23 | 5.30 ± 0.1 | 4.67 ± 0.1|
| Glucose (v), mmol/l | 6.10 ± 0.14 | 9.42 ± 1.19* | 6.0 ± 0.19 | 8.81 ± 1.25*|
| Lactate (a), mmol/l | 1.14 ± 0.14 | 5.97 ± 1.00* | 1.0 ± 0.1 | 4.21 ± 0.48*|
| Lactate (v), mmol/l | 0.84 ± 0.21 | 4.96 ± 1.0* | 0.7 ± 0.2 | 3.23 ± 0.49*|
| Norepi (a), mmol/l  | 1.3 ± 0.1 | 11.9 ± 3.1* | 10.7 ± 2.2*|
| Norepi (v), mmol/l  | 1.4 ± 0.4 | 5.0 ± 1.0* | 4.6 ± 1.2*|
| Epi (a), mmol/l     | 1.0 ± 0.6 | 1.9 ± 0.4* | 1.6 ± 0.3*|
| Epi (v), mmol/l     | 0.2 ± 0.3 | 0.9 ± 0.3* | 0.7 ± 0.4*|

Values are means ± SE at rest and during exercise (blood variables represent the average of values obtained either in normoxia or hyperoxia). Vₜ, pulmonary ventilation; RR, respiratory rate; PETCO₂, end-tidal PO₂; PaCO₂, arterial PO₂; PaCO₂, arterial PO₂; PaO₂, arterial PO₂; PaCO₂, arterial PO₂; PvO₂, venous PO₂; PcO₂, venous PO₂; Vo₂, pulmonary O₂ uptake; VECO₂, pulmonary CO₂ output; BE, base excess; SaO₂, arterial O₂ saturation of Hb; SvO₂, venous O₂ saturation of Hb; a, arterial; v, venous; Hct, hematocrit; CaO₂, arterial O₂ content; CvO₂, venous O₂ content; HR, heart rate; MAP, mean arterial pressure; Norepi, norepinephrine; Epi, epinephrine. *Significantly different from rest, P < 0.05. †Significantly different from 21% O₂, P < 0.05.

DISCUSSION

The present study demonstrates that, despite a marked reduction in the hepatosplanchnic blood flow during exercise in humans, the liver maintained its metabolic functions, as indicated by an increased hepatosplanchnic venous-arterial glucose difference and an almost constant level of glucose in arterial blood. However, when the hepatosplanchnic blood flow reached a minimum and was associated with a reduction in hepatic venous O₂ saturation to 6%, the contribution of the Cori cycle to glucose production appeared to collapse. Thus an exercise intensity associated with a reduction in the hepatosplanchnic uptake of lactate would contribute to the accumulation of lactate in arterial blood.
A reduced uptake of lactate challenges the assumption that the increased blood lactate level during exercise reflects anaerobic metabolism in working skeletal muscle. With a moderate reduction of hepatosplanchnic blood flow, the concentration difference between arterial and hepatosplanchnic venous lactate increased to ~1.5 mmol/l and was associated with an arterial concentration close to 4 mmol/l, i.e., identical to the definition of the so-called “anaerobic threshold” (5). When this level is surpassed, the concentration difference between arterial and hepatosplanchnic venous lactate was close to zero. Thus intense exercise approaches the physiology described during hemorrhage (38), for which a marked blood loss is associated with enhanced lactate production, both by the liver and the kidneys (38).

**Hepatosplanchnic blood flow and \( \dot{V}_O_2 \) during exercise.** We observed a >50% reduction in hepatosplanchnic blood flow concomitant with an increase in hepatosplanchnic \( \dot{V}_O_2 \) by 36%. Others have documented this magnitude of exercise-induced reduction in hepatosplanchnic blood flow, although indirect techniques were used (40). With a bolus injection of ICG and measurements of the systemic ICG concentrations, Rowell et al. (41) and Clausen and Trap-Jensen (11) reported that exercise reduces the fractional clearances of ICG to between 19 and 93% of the resting value, even in nonfasting subjects. With a similar technique to calculate hepatosplanchnic blood flow, Kjaer et al. (28) report a reduction from 0.8 to 0.4 l/min during exercise in fasting subjects. Although the relative changes correspond to the present results, the absolute values seem to be underestimated. The bolus technique is based on the assumption that the hepatic extraction of ICG is 1.00 (33), but the hepatic extraction could be as low as 60–70% (20, 27). Thus with the use of constant infusion of ICG and blood sampling from the artery and the hepatic vein, the resting hepatosplanchnic blood flow has been estimated to be 1.1–1.7 l/min (2–4, 7, 11, 36, 39). By using this technique during exercise, the reduction of hepatosplanchnic blood flow is up to 50% (3, 4, 7, 11), even after a meal (36).
With the use of constant infusion of ICG, Rowell et al. (42) also estimated hepatosplanchnic blood flow and \( \dot{V}O_2 \) during exercise. It was demonstrated that the hepatosplanchnic \( \dot{V}O_2 \) increased from 74 ml/min at the initial stage of moderate exercise to 93 ml/min at the end of exercise (1 h, \(-60\% \dot{V}O_2_{\text{max}} \)), but baseline values were not presented. With a more prolonged exercise protocol, the hepatosplanchnic \( \dot{V}O_2 \) increased to 120% of the resting level, whereas the hepatosplanchnic blood flow remained constant (2). These results appear to be in agreement with the present data, supporting the observation that the liver is able to enhance its \( \dot{V}O_2 \), despite a reduction in blood flow.

An increase in hepatosplanchnic \( \dot{V}O_2 \) is suggested to arise from the glycogenolytic and gluconeogenic activities of the liver. With the use of stable isotopes during a fast, 30–66% of the hepatic glucose production is related to gluconeogenesis (24). The twofold increase in total production of glucose (7) is also related to enhanced gluconeogenesis during exercise (8). This was achieved at an exercise intensity associated with a concentration of lactate in arterial blood of \(-4 \text{ mmol/l} \) (8). At that level, the present data correspond to those of Bergman et al. (8) as the liver increases its uptake of lactate, presumably as part of the Cori cycle. However, with a further reduction in the hepatosplanchnic blood flow, the Cori cycle appears to be attenuated, supporting findings by Coggan et al. (12).

The present observations are based on the concentration difference for lactate between arterial and hepatic venous blood, and we do not have any further evidence for gluconeogenesis in the liver. One consideration is that a low blood flow to splanchnic organs reduces pH in the tissue, probably because of enhanced anaerobic metabolism (26). Another consideration is that enhanced glycogenolysis may lead to formation of lactate. However, as in the present study, Bergeron et al. (7) found that the level of glucose remained stable almost throughout the experiment. However, after 24 min of exercise, arterial blood glucose was reduced to 4.8 mmol/l, indicating that the metabolic function of the liver can be challenged by strenuous exercise.

Whether sympathetic nervous activity is of importance for attenuation of hepatic gluconeogenesis and an upregulation of glycogenolysis is not known. The hepatic artery is provided with both \( \alpha- \) (22) and \( \beta- \) receptors (21). With a high concentration of epinephrine, the hepatic production of glucose increases, partly because of an increased supply of gluconeogenic substrates (alanine) and partly related to a direct action on the liver cells (45). On the other hand, exercise with \( \beta- \) receptor blockade results in diminished hepatic uptake of gluconeogenic precursors, decreased lactate uptake, and increased glucose output (3). Gleeson (17) suggested that interleukins released from the working muscles during exercise are important for glucose production in the liver.

Hepatic sinusoidal collapse. With a reduction in hepatosplanchnic blood flow, the available number of hepatic sinusoids may decrease. In the cat, “derecruit- ment” of the hepatic sinusoids takes place when the hepatic blood flow is reduced to a similar extent as during exercise (19). In fact, norepinephrine reduces the blood volume of the liver (40) and also the plasma volume in the hepatic sinusoids may be affected (20). With a 30 and 40% blood loss during hemorrhage in the pig, hepatic norepinephrine uptake decreases, suggestive of a partial sinusoidal collapse (38). A reduced intrinsic hepatic clearance of ICG found during exercise in the present study suggests that the active sinusoidal area is reduced in response to exercise in humans.

Hyperoxia. During submaximal exercise, hyperoxia does not affect \( \dot{V}O_2 \) (1, 37, 46), but a lowered concentration of lactate in arterial blood appears to be a consistent finding (18, 30, 46). The enhanced exercise performance with hyperoxia (35, 37, 46) is related to a higher oxidation rate for pyruvate, limiting the accumulation of lactate (30). From the present data, a reduced level of lactate in blood during exercise with hyperoxia is not related to an enhanced hepatic uptake of lactate.

We found that the liver enhanced its \( \dot{V}O_2 \), although blood supply was reduced by \(-50\% \) during exercise. The hepatosplanchnic exchange of lactate, glucose, and catecholamines did not become flow dependent, even in the face of a reduction of the sinusoidal surface area. Despite the reduction in hepatosplanchnic blood flow during exercise, the liver is able to upregulate its metabolic function, yet the Cori cycle appears to decrease its importance for blood glucose homeostasis.

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