Lactate kinetics at rest and during exercise in lambs with aortopulmonary shunts

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Department of Pediatric Cardiology, Beatrix Children’s Hospital, and Department of Thoracic Surgery, University of Groningen, and Groningen-Utrecht Institute for Drug Exploration, 9700 RB Groningen, The Netherlands

Beaumont-Krol, G. C. M., Willem G. Zijlstra, Jan Takens, Marieke C. Molenkamp, Koos J. Meuzelaar, Gioia B. Smid, and Jaap R. G. Kuipers. Lactate kinetics at rest and during exercise in lambs with aortopulmonary shunts. J. Appl. Physiol. 86(3): 832–839, 1999.—In a previous study [G. C. M. Beaumont-Krol, J. Takens, M. C. Molenkamp, G. B. Smid, J. J. Meuzelaar, W. G. Zijlstra, and J. R. G. Kuipers. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H1503–H1512, 1998], a lower systemic O2 supply was found in lambs with aortopulmonary left-to-right shunts. To determine whether the lower systemic O2 supply results in increased anaerobic metabolism, we used [1–13C]lactate to investigate lactate kinetics in eight 7-wk-old lambs with shunts and eight control lambs, at rest and during moderate exercise [treadmill; 50% of peak O2 consumption (V̇O2peak)]. The mean left-to-right shunt fraction in the shunt lambs was 55±3% of pulmonary blood flow. Arterial lactate concentrations and the rate of appearance (Ra) and disappearance (Rd) of lactate were similar in shunt and control lambs, both at rest (lactate: 1.201±0.76 vs. 1.214±1.51 µmol/l; Ra = Rd; 12.97±1.71 vs. 12.55±1.25 µmol·min−1·kg−1) and during a similar relative workload. We found a positive correlation between Ra and systemic blood flow [O2 supply, and V̇O2 in both groups of lambs. In conclusion, shunt lambs have similar lactate kinetics as do control lambs, both at rest and during moderate exercise at a similar fraction of their peak V̇O2, despite a lower systemic O2 supply.

CONGENITAL HEART DISEASE; lactate turnover rate; carbon-13-labeled substrates; metabolism; peak oxygen consumption

CONGENITAL HEART DISEASE, with a left-to-right shunt (such as a ventricular septal defect or a patent ductus arteriosus), results in volume overload of the left ventricle. Due to diversion of blood via the defect into the pulmonary arteries, the systemic blood flow may be compromised. Inadequate systemic blood flow has been described in preterm lambs with a patent ductus arteriosus and in rats with an arteriovenous fistula (9, 16). In previous studies, Gratama et al. (20) and Toorop et al. (36) demonstrated that in lambs, in a fed state and with a left-to-right shunt due to an aortopulmonary shunt, the left ventricular output at rest was much increased that their systemic blood flow did not differ significantly from that of control lambs. However, a lower systemic blood flow was found in shunt than in control lambs in a fasted state (4) or during exercise (20). A lower rate of systemic O2 supply was also found, consistent with the lower systemic blood flow. An impaired systemic O2 supply may lead to an O2 deficit in peripheral tissues, such as skeletal muscles, with a consequent increase in anaerobic metabolism. An increase in lactate production may then be expected.

In previous studies, Gratama et al. (18) did not find a difference in arterial lactate concentrations between shunt and control lambs. However, the arterial lactate concentration is the result of production and utilization, both of which can be increased while the arterial lactate concentration remains unchanged. The aim of this study, therefore, was to investigate, with the aid of 13C-labeled lactate, lactate production and utilization in conscious lambs with an aortopulmonary shunt and in control lambs, both at rest and during moderate exercise on a treadmill.

MATERIALS AND METHODS

We studied 16 lambs, of mixed breed, with documented dates of birth (7 wk old). Lambs were assigned to two groups: eight lambs with an aortopulmonary shunt and eight lambs without a shunt. Until the day of study, each lamb remained with its mother. Surgical preparation, catheter care, and antibiotic administration were performed as described previously (36). In the shunt lambs, a Goretex conduit (6 mm ID; W. L. Gore, Flagstaff, AZ) was sutured between the descending aorta and the main pulmonary artery. Catheters were inserted into the aorta, the pulmonary artery, the right ventricle (only in the shunt lambs), and the right and left atria. Precalibrated electromagnetic flow transducers (10–15 mm ID; Skalar Medical, Delft, The Netherlands) were placed around the ascending aorta just above the coronary arteries and around the pulmonary artery proximal to the conduit in the shunt lambs, and around the pulmonary artery only in the control lambs. The experiments were performed with the approval of the Ethics Committee on Animal Experiments of our university.

In the week before surgery and from 2 days after surgery, the lambs were familiarized with running on a motor-driven treadmill (Lauffergetest Jr. unior, Erich-J aeger, Hoechberg, Germany) during one short daily run. No training effect was pursued. The lambs ran freely on the treadmill without coercive measures. During the experiments, an external workload corresponding to 50% of the peak O2 consumption (V̇O2peak) was used. The V̇O2peak of each lamb was determined during a graded treadmill test 1 wk after surgery, as described previously (21). In brief, resting values were determined with the lamb freely standing on the treadmill. Systemic and pulmonary blood flows were measured with the electromagnetic flow transducers. At the same time, aortic,
pulmonary arterial, and left atrial pressures were measured. Furthermore, blood samples were withdrawn from the aortic and mixed venous catheters, i.e., from the pulmonary arterial catheter in the control lambs and the right ventricular catheter in the shunt lamb. O2 saturation was determined in both samples, and hemoglobin concentration was determined only in the sample from the aorta. After O2 consumption (V\textsubscript{O2}) had been calculated with the Fick formula, the lamb was subjected to a running speed of 3.5 km/h. After 3 min, the measurements were repeated and V\textsubscript{O2} was calculated again. Immediately after the blood samples had been collected, the workload was increased by setting the incline at 4%. After another 3 min, the measurements were repeated, and so on until the maximum incline of 15% was reached. Thereafter, the treadmill speed was increased by 0.5 km/h while the incline of 15% was maintained. The graded treadmill test in the shunt lambs was modified by starting at a running speed of 2.5 instead of 3.5 km/h. This modification was necessary because otherwise the speed and inclination corresponding to 50% of V\textsubscript{O2peak} could not be determined.

Experimental Protocol

Between days 10 and 14 after surgery, after an overnight fast of 18 h, the lambs were brought to the experimental room and put on the treadmill. After 2 h of habituation, during which the lambs stood quietly, the first measurements were performed, and blood samples were withdrawn. Systemic and pulmonary blood flow as well as aortic, pulmonary arterial, and left atrial pressures were measured every 10 min for 1 h.

To determine the lactate turnover rate, [1-\textsuperscript{13}C]lactate was administered according to the prime-dose, constant-rate infusion technique (34). Before the infusion of [1-\textsuperscript{13}C]lactate was started, blood samples were withdrawn from the aorta for determination of the lactate concentrations and the isotope ratio ([\textsuperscript{13}C]/[\textsuperscript{12}C] ratio) of lactate to determine the natural abundance of \textsuperscript{13}C in lactate. A priming dose of 15.6 mg/kg [1-\textsuperscript{13}C]lactate (99 atom% 13C; Tracer Technologies, Somerville, MA) was administered over 10 min into the right atrial catheter, followed by a constant-rate infusion (model 2620 pump; Harvard, Millis, MA) of 0.156 mg min\textsuperscript{-1} kg\textsuperscript{-1} [1-\textsuperscript{13}C]lactate (34, 39). During a steady state, two blood samples (at 30 and 40 min after the start of the infusion of the priming dose) were obtained from the aorta for determination of the lactate concentration and the isotope ratio of lactate. At the same time points, blood samples were withdrawn with a heparinized syringe from the aortic and mixed venous catheters. O2 saturation was determined in all samples. Hemoglobin concentration, pH, P\textsubscript{CO2}, P\textsubscript{O2}, and plasma HCO\textsubscript{3} concentration, as well as epinephrine and norepinephrine, were determined in the aortic sample. Immediately after the blood samples had been collected, the speed and inclination corresponding to 50% of V\textsubscript{O2peak} had been calculated with the Fick formula, the lamb was returned to the treadmill and the lamb was allowed to recover. After the last blood sample had been withdrawn, the treadmill was stopped and the lamb was allowed to recover.

Measurements and Calculations

Systemic and pulmonary blood flows, heart rate, as well as aortic, pulmonary arterial, and left and right atrial pressures were measured with Gould P23 ID pressure transducers (Spectramed, Oxnard, CA) referenced to atmospheric pressure, with zero obtained with the pressure transducer at right atrial level (36). The precalibrated electromagnetic flow transducers were connected to Skalar MDL 400 flowmeters. All variables were recorded on an Elema Mingograf 800 in-put recorder (Siemens-Elema, Solna, Sweden). Systemic and pulmonary blood flows in shunt lambs were obtained from the pulmonary and the aortic flow transducers, respectively. Systemic blood flow of the control lambs was obtained from the pulmonary flow transducer. The aortic flow transducer was situatated distal to the origin of the coronary arteries. To obtain total left ventricular output in shunt lambs, coronary blood flow obtained with the microspheres was added to the aortic flow measured with the flow transducer (28). Effective

Table 1. Hemodynamic data, oxygen related-variables, and plasma catecholamine concentrations at rest and during maximal exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Shunt</th>
<th>Exercise</th>
<th>Shunt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>Control</td>
<td>142 ± 6</td>
<td>160 ± 7</td>
<td>282 ± 10†</td>
</tr>
<tr>
<td>Mean pressures, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>72 ± 3</td>
<td>57 ± 2*</td>
<td>74 ± 3</td>
<td>61 ± 3†</td>
</tr>
<tr>
<td>Pulmonary arterial</td>
<td>10 ± 2</td>
<td>16 ± 2*</td>
<td>10 ± 2</td>
<td>20 ± 4*</td>
</tr>
<tr>
<td>Left atrial</td>
<td>3 ± 1</td>
<td>10 ± 2*</td>
<td>1 ±†</td>
<td>10 ± 3*</td>
</tr>
<tr>
<td>Systemic blood flow, ml·min\textsuperscript{-1}·kg\textsuperscript{-1}</td>
<td>155 ± 8</td>
<td>125 ± 10*</td>
<td>330 ± 24†</td>
<td>273 ± 23†</td>
</tr>
<tr>
<td>Effective left ventricle stroke volume, ml/kg</td>
<td>1.11 ± 0.05</td>
<td>0.80 ± 0.07*</td>
<td>1.19 ± 0.11</td>
<td>1.10 ± 0.08†</td>
</tr>
<tr>
<td>Oxygen consumption, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>93 ± 1</td>
<td>92 ± 1</td>
<td>95 ± 1</td>
<td>92 ± 2</td>
</tr>
<tr>
<td>Mixed venous</td>
<td>52 ± 1</td>
<td>46 ± 3</td>
<td>28 ± 2†</td>
<td>24 ± 3†</td>
</tr>
<tr>
<td>Systemic oxygen supply, µmol·min\textsuperscript{-1}·kg\textsuperscript{-1}</td>
<td>743 ± 44</td>
<td>583 ± 53*</td>
<td>1,768 ± 128†</td>
<td>1,379 ± 124†</td>
</tr>
<tr>
<td>V\textsubscript{O2}, µmol·min\textsuperscript{-1}·kg\textsuperscript{-1}</td>
<td>336 ± 18</td>
<td>287 ± 22*</td>
<td>1,260 ± 88†</td>
<td>1,061 ± 93†</td>
</tr>
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<td>Epinephrine, nmol/l</td>
<td>1.6 ± 0.9</td>
<td>0.9 ± 0.3</td>
<td>16.3 ± 7.2†</td>
<td>7.4 ± 1.7†</td>
</tr>
<tr>
<td>Norepinephrine, nmol/l</td>
<td>9.0 ± 6.2</td>
<td>9.1 ± 3.5</td>
<td>17.0 ± 5.8</td>
<td>14.6 ± 3.3†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 control and 8 shunt lambs. V\textsubscript{O2}, oxygen consumption. †Shunt vs. control, P < 0.05; ‡rest vs. exercise, P < 0.05.
left ventricular stroke volume was calculated by dividing 
systemic blood flow by heart rate. O2 saturation was 
determined with an OSM2 hemoximeter (Radiometer, Copen-
haven, Denmark). Hemoglobin concentration was determined 
with the Haemocue method (B Hemoglobin Photometer; 
Haemocue, Helsingborg, Sweden). pHi, PCO2, PO2, and plasma 
HCO3 concentrations were determined with an ABL-2 blood-
gas analyzer (Radiometer).

Immediately after they were withdrawn, the blood samples 
were mixed with sodium fluoride to stop glycolysis and were 
then put in ice. For the determination of the concentration of 
lactate, a part of the blood was deproteinized with cold 18%
perchloric acid (2.5, vol/vol) and centrifuged. The protein-free 
supernatant was removed and neutralized with a potassium 
hydroxide-morpholinopropanesulfonic acid mixture. Lactate 
was determined in duplicate by an enzymatic method (5).

For the determination of the isotope ratio of lactate, fatty 
aacids were removed from the plasma by extraction with 
chloroform. The lactate was then extracted with diethyl 
ether-ethyl acetate and dried under nitrogen. [1-13C]lactate 
was determined in duplicate by an enzymatic method (5).

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aacids were removed from the plasma by extraction with 
chloroform. The lactate was then extracted with diethyl 
ether-ethyl acetate and dried under nitrogen. [1-13C]lactate 
was determined in duplicate by an enzymatic method (5).

Table 2. Hemodynamic data, blood gases, and oxygen saturation at rest and during moderate exercise (50% of Vo2peak).

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Rest</th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
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<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>Con</td>
<td>128±9</td>
<td>191±11†</td>
<td>212±9†</td>
<td>222±9†</td>
</tr>
<tr>
<td></td>
<td>Shunt</td>
<td>147±9</td>
<td>176±10†</td>
<td>188±11†</td>
<td>197±11†</td>
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<tr>
<td>Mean pressures, mmHg</td>
<td>Aortic</td>
<td>Con</td>
<td>74±4</td>
<td>71±5</td>
<td>70±3</td>
</tr>
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<td>Shunt</td>
<td>67±4</td>
<td>60±3</td>
<td>60±3</td>
</tr>
<tr>
<td></td>
<td>Pulmonary arterial</td>
<td>Con</td>
<td>10±1</td>
<td>13±2</td>
<td>13±2†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shunt</td>
<td>20±3*</td>
<td>17±3</td>
<td>18±2</td>
</tr>
<tr>
<td></td>
<td>Left atrial</td>
<td>Con</td>
<td>3±1</td>
<td>2±1</td>
<td>2±1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shunt</td>
<td>12±3*</td>
<td>10±4</td>
<td>9±3</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>Con</td>
<td>7.39±0.01</td>
<td>7.40±0.02†</td>
<td>7.40±0.02†</td>
<td>7.42±0.01†</td>
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<tr>
<td></td>
<td>Shunt</td>
<td>7.39±0.01</td>
<td>7.39±0.02</td>
<td>7.39±0.02</td>
<td>7.39±0.02</td>
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<tr>
<td></td>
<td>Pulmonary arterial</td>
<td>Con</td>
<td>5.0±0.2</td>
<td>4.7±0.2†</td>
<td>4.6±0.2†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shunt</td>
<td>5.0±0.0</td>
<td>5.0±0.2</td>
<td>4.8±0.2</td>
</tr>
<tr>
<td></td>
<td>PO2, kPa</td>
<td>Con</td>
<td>14.7±0.5</td>
<td>15.5±0.9</td>
<td>14.4±0.7</td>
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<tr>
<td></td>
<td></td>
<td>Shunt</td>
<td>14.5±0.7</td>
<td>14.0±0.6</td>
<td>14.1±0.5</td>
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<tr>
<td></td>
<td>HCO3, mmol/l</td>
<td>Con</td>
<td>21.0±0.8</td>
<td>20.8±0.8</td>
<td>20.5±1.0</td>
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<td></td>
<td></td>
<td>Shunt</td>
<td>21.6±0.8</td>
<td>21.1±0.8</td>
<td>21.0±0.9</td>
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<tr>
<td>Oxygen saturation,</td>
<td>Aortic</td>
<td>Con</td>
<td>94±1</td>
<td>95±1</td>
<td>95±0†</td>
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<tr>
<td></td>
<td></td>
<td>Shunt</td>
<td>94±1</td>
<td>94±1</td>
<td>94±1</td>
</tr>
<tr>
<td></td>
<td>Mixed venous</td>
<td>Con</td>
<td>51±1</td>
<td>36±2†</td>
<td>38±2†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shunt</td>
<td>49±3</td>
<td>39±3†</td>
<td>38±3†</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin, g/l</td>
<td>Con</td>
<td>81±2</td>
<td>84±3</td>
<td>84±2</td>
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<td></td>
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<td>Shunt</td>
<td>84±2</td>
<td>83±2</td>
<td>82±1</td>
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</table>

Values are means ± SE; n = 8 control (Con) and 8 shunt lambs. Vo2peak = peak Vo2. *Shunt vs. control, P < 0.05; †rest vs. exercise, P < 0.05.
by means of a single-injection dilution technique with deuterium oxide (\(^2\text{H}_2\text{O}\)), was 780 and 809 ml/kg for control and shunt lambs, respectively (19).

Cao is the mean concentration of lactate (in micromoles per milliliter) of the consecutive aortic samples, 

\[ D_F \alpha \text{ is the difference in } F \text{ of } [1-13C] \text{lactate of the consecutive aortic samples, } \Delta t \text{ is the time (in minutes) between the two samples, and } F \alpha \text{ is the mean molar fraction of } [1-13C] \text{lactate of the consecutive aortic samples.} \]

\[ R_d \text{ then follows from} \]

\[ R_d = R_\alpha - \frac{\Delta C_{\beta\alpha}}{\Delta t} \]

where \(\Delta C_{\beta\alpha}\) is the difference in concentration of lactate in the consecutive aortic samples. The metabolic clearance rate (MCR, in milliliters per minute per kilogram) was calculated by dividing \(R_d\) by the blood lactate concentration.

Statistical Analysis

Data are expressed as means ± SE. To compare the hemodynamic variables between shunt and control lambs, Student’s two-tailed t-test for unpaired samples was used. To compare the hemodynamic and lactate-related variables at rest with those at the various time periods during exercise, repeated-measures ANOVA was performed. Subsequently, this was followed by Student’s two-tailed t-test for paired samples. To compare the plasma concentrations of epinephrine and norepinephrine between shunt and control lambs at
rest, a Wilcoxon signed-rank test was used. To compare the plasma concentrations of epinephrine and norepinephrine at rest with those at the various time periods during exercise, a Wilcoxon signed-rank test for matched pairs was performed. Linear regression analysis was performed with the aid of a statistical computer program (NCSS, Kaysville, UT). A P value < 0.05 was considered statistically significant.

RESULTS

Hemodynamic Data

\( \dot{V}O_2 \)peak experiment. The maximal absolute external workload achieved by the shunt lambs was significantly lower than that of control lambs (speed, 3.6 ± 0.1 vs. 3.9 ± 0.1 km/h, respectively; \( P < 0.05 \); inclination, 12 ± 1 vs. 15 ± 0 %, respectively; \( P < 0.001 \)). Hemodynamic data, \( O_2 \)-related variables, and plasma catecholamine concentrations at rest and during maximal exercise (\( \dot{V}O_2 \)peak) are shown in Table 1. Systemic blood flow, systemic \( O_2 \) supply, and \( \dot{V}O_2 \) at rest were lower in shunt than in control lambs. \( \dot{V}O_2 \)peak tended to be lower in the shunt than in the control lambs. There was no significant difference in plasma epinephrine and norepinephrine concentrations between the two groups of lambs, either at rest or during maximal exercise.

Moderate exercise (50% of \( \dot{V}O_2 \)peak). On the day of the study, there were no statistically significant differences between the control and the shunt lambs in age (45 ± 1 vs. 44 ± 1 days, respectively) and weight (13.4 ± 0.8 vs. 12.6 ± 0.6 kg, respectively). Blood gases were normal in both groups of lambs (Table 2). During moderate exercise, the relative workload was similar in control and shunt lambs (Fig. 1G). The absolute external workload, however, was lower in shunt than in control lambs (speed, 2.9 ± 0.1 vs. 3.4 ± 0.1 km/h, respectively; \( P < 0.01 \); 0% inclination in both groups of lambs). The mean left-to-right shunt fraction in the shunt lambs was 55 ± 3% of pulmonary blood flow at rest and decreased to 52 ± 3 (\( P < 0.05 \)), 46 ± 3, and 42 ± 4% of pulmonary blood flow at 10, 20, and 30 min of moderate exercise. The left-to-right shunt led to significant hemodynamic and \( \dot{V}O_2 \)-related differences between shunt and control lambs (Table 2, Fig. 1). The hemodynamic response to exercise was similar in shunt and control lambs, and most of the differences between the two groups at rest persisted during exercise (Table 2, Fig. 1). Systemic blood flow, systemic \( O_2 \) supply, and \( \dot{V}O_2 \) were lower in shunt than in control lambs, both at rest and during moderate exercise (Fig. 1, B-D). There was no difference in arterial \( O_2 \) saturation or arteriovenous \( O_2 \) concentration difference between shunt and control lambs either at rest (2,012 ± 116 vs. 2,193 ± 131 µmol/l, respectively) or during exercise. There was no difference in plasma epinephrine or norepinephrine concentrations between shunt and control lambs. In both groups of lambs, plasma epinephrine and norepinephrine concentrations increased during exercise compared with resting levels (Fig. 1, E and F).

Lactate Kinetics

\( \dot{V}O_2 \)peak experiment. The arterial lactate concentrations at rest and during exercise at each level of a similar absolute external workload were much the same in shunt and control lambs (Fig. 2). The lactate concentration at \( \dot{V}O_2 \)peak was lower in shunt than in control lambs.

Moderate exercise (50% of \( \dot{V}O_2 \)peak). The arterial lactate concentrations at rest and during moderate exercise were similar in control and shunt lambs (Fig. 3). In both groups of lambs, there was an increase in arterial lactate concentration during exercise in comparison with resting levels. Lactate \( R_a \) and \( R_d \) did not differ between shunt and control lambs, either at rest (12.97 ± 3.836 LACTATE KINETICS AT REST AND EXERCISE IN LAMBS WITH SHUNTS

Fig. 3. A: arterial lactate concentration (○), rate of appearance (\( R_a \); □), and rate of disappearance (\( R_d \); ○) in control lambs \( n = 8 \) at rest and during exercise at 50% \( \dot{V}O_2 \)peak. B: arterial lactate concentration (●), \( R_a \) (■), and \( R_d \) (●) in shunt lambs \( n = 8 \) at rest and during exercise at 50% \( \dot{V}O_2 \)peak. Data are means ± SE. $Rest vs. exercise, P < 0.05.
1.71 vs. 12.55 ± 1.25 µmol·min⁻¹·kg⁻¹, respectively) or during exercise at a similar relative workload (Fig. 3). $R_d$ was always lower than $R_a$ during exercise, which is consistent with the increase in arterial lactate concentration. MCR of lactate was similar in shunt and control lambs, both at rest (11.35 ± 0.95 vs. 10.94 ± 1.09 µmol·min⁻¹·kg⁻¹, respectively) and during exercise.

The $R_a$ of lactate increased in both groups of lambs when the $V_{O_2}$, the systemic blood flow, or the systemic O₂ supply was higher (Fig. 4).

**DISCUSSION**

We found that the arterial lactate concentration and the lactate production rate were similar in shunt and control lambs, both at rest and during exercise on a treadmill at a similar relative workload of 50% of their $V_{O_2peak}$. Also, the $R_d$ and the MCR of lactate were similar in both groups of lambs. Hence, the shunt lambs have similar lactate kinetics as do the control lambs but at a lower level of absolute external workload. In both groups of lambs, the arterial concentration of lactate increased during exercise, compared with resting levels, due to a larger increase in the $R_a$ than in the $R_d$. Despite a lower systemic $O_2$ supply in the shunt lambs compared with that in the control lambs, both at rest and in a more pronounced manner during exercise, the lactate production rate in shunt lambs was not higher than in control lambs. At rest, the shunt lambs have apparently adapted themselves to the lower systemic $O_2$ supply by consuming less $O_2$; this is in agreement with a metabolism that is turned down. The lower systemic $V_{O_2}$ in the shunt lambs may be caused by less growth or by restrictions of external work. A similar relationship between a low systemic blood flow and $O_2$ supply, and a limited use of skeletal muscles, has been described in humans and in beagles for situations such as immobilization, bed rest, or senescence (6, 23).

We found a direct relationship between systemic $V_{O_2}$ and lactate production in both groups of lambs; this is in agreement with earlier studies in dogs (27), rats (13), and humans (31). Lactate production was higher when more work was done and more energy was expended. Shunt and control lambs have equal lactate production and $R_d$ at rest and during exercise at a similar fraction of the exercise capacity (Fig. 3). However, from the direct relationship between lactate production and systemic $V_{O_2}$, it may be speculated that, at a similar absolute external workload, the lactate production rate will be higher in shunt than in control lambs. A higher lactate production in the shunt lambs may be the result of a different state of fitness, since it is known that, in human beings with different levels of training, lactate kinetics are similar when exercising at a similar relative workload but are indeed different when exercising at a similar absolute external workload (12).

A reduced systemic $O_2$ supply and a higher lactate production by skeletal muscles has been observed in human beings with congestive heart failure in comparison with healthy men when exercising at a similar absolute external workload (1, 8, 14, 30). The reduced
systemic $O_2$ supply and the expected higher lactate production in shunt lambs, when they exercise at a similar absolute external workload, may have been caused by the inability of the heart to perfuse skeletal muscles adequately or by abnormalities in the skeletal muscles themselves. In a previous study, Gratama et al. (20) did indeed find a decreased blood flow to skeletal muscles in shunt compared with control lambs during exercise at 80% of their $V_{O2peak}$. This is in agreement with the lower skeletal muscle blood flow as described in rats, with an arteriovenous fistula, during exhaustive exercise on a treadmill (16) and in patients with congestive heart failure (38). Abnormalities in the skeletal muscles themselves were found in human beings with congestive heart failure, who have reduced exercise capacity (30, 37), depletion of oxidative enzymes (8, 14), fibrosis (2), and myofibrillar breakdown (8, 14), probably as a result of a limited use of skeletal muscles.

One should consider whether the maximal exercise capacity was achieved in both groups of lambs while they exercised at a different $V_{O2peak}$ protocol. Some determinants of maximal exercise point to a similar maximal exercise level, whereas others suggest that the exercise at $V_{O2peak}$ might have been lower in the shunt than in the control lambs. The heart rates at $V_{O2peak}$ in the shunt lambs were lower than in the control lambs, although not statistically significant different from the results described by Gratama et al. (21) in a study in which both control and shunt lambs exercised at a similar $V_{O2peak}$ protocol. Furthermore, in both our groups of lambs, the maximal heart rates during $V_{O2peak}$ were even higher than the heart rates achieved during infusion with 0.1 $\mu$g·min$^{-1}$·kg$^{-1}$ isoproterenol, which are a good approximation of the heart rate at maximal exercise (22). The similar mixed venous $O_2$ saturations in the shunt and control lambs give evidence that the shunt lambs did exercise until exhaustion. On the other hand, the arterial lactate concentrations and the plasma concentrations of epinephrine and norepinephrine tended to be lower in the shunt than in the control lambs. Therefore, we cannot rule out the possibility that the shunt lambs had exercised at a lower level than the control lambs, both during the maximal and the moderate exercise tests. A difference in the moderate-exercise experiments between shunt and control lambs might have occurred to the extent that the shunt lambs were exercising at somewhat <50% of $V_{O2peak}$ and the control lambs were exercising at somewhat >50% of $V_{O2peak}$.

We found a decreased exercise capacity in shunt lambs compared with control lambs, as has also been shown in previous studies (21). In children with congenital heart defects, a decreased exercise capacity has also been described (11, 15, 17). A decreased exercise capacity may be caused by a lower systemic blood flow, a lower $O_2$ transport capacity to the muscles, and/or a lower arteriovenous $O_2$ concentration difference over the skeletal muscles. We found a similar arteriovenous $O_2$ concentration difference, but we did indeed find a lower systemic blood flow in shunt lambs compared with control lambs and, as a consequence, a lower systemic $O_2$ supply.

Whether the decreased exercise capacity in shunt lambs can be improved by physical training remains to be investigated. Physical training leads to cardiovascular adaptations with an increase in maximal $V_{O2}$, stroke volume, and systemic blood flow (6, 7). Furthermore, endurance training may produce major adaptations in skeletal muscles (25). These adaptations to training in skeletal muscles result in an increased oxidative capacity and a lower lactate production during exercise of any given intensity (25). In patients with congestive heart failure, bicycle training has been shown to improve exercise tolerance and to decrease their complaints (10, 35).

In conclusion, we have found that lambs with an aortopulmonary shunt have the same lactate kinetics as control lambs at rest and during moderate exercise performed at a similar fraction of their $V_{O2peak}$, despite a lower systemic $O_2$ supply. We speculate that the shunt lambs have adapted themselves to the decreased systemic $O_2$ supply through consuming less $O_2$ by limiting the performance of external work.

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