Lower Arterial Glucose Concentrations in Lambs With Aortopulmonary Shunts After an 18-Hour Fast

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Spontaneously occurring hypoglycemia has been described in children with severe acute congestive heart failure. Hypoglycemia may be the result of an increase in glucose utilization in tissues, a decrease in glucose production, or a decrease in the dietary intake of nutrients. To determine whether hypoglycemia may also occur in congenital heart disease with volume overloading, we investigated glucose metabolism during and after an 18-hour fast in nine lambs with an aortopulmonary left-to-right shunt and nine control lambs. Plasma levels of hormones involved in the endocrine control of glucose metabolism were determined. The glucose production rate (rate of appearance [R_a]) was studied using [U-^{13}C]glucose. Gluconeogenesis through the Cori cycle was estimated by measuring glucose ^{13}C recycling. The arterial glucose concentration (3,409 ± 104 *v* 4,338 ± 172 μmol/L, $P < .001$) and R_a of glucose (16.97 ± 0.89 *v* 25.49 ± 4.28 μmol · min^{-1} · kg^{-1}, $P < .05$) were lower in shunt versus control lambs. There were no differences in hormone levels between control and shunt lambs. Fractional glucose ^{13}C recycling via the Cori cycle (6.9% ± 2.8% *v* 7.1% ± 2.5%) and gluconeogenesis from pyruvate and lactate (1.24 ± 0.58 *v* 1.95 ± 0.67 μmol · min^{-1} · kg^{-1}) were similar in both groups of lambs. The sum of glycogenolysis and gluconeogenesis from precursors other than pyruvate and lactate was lower in shunt versus control lambs (15.73 ± 1.07 *v* 23.54 ± 4.27 μmol · min^{-1} · kg^{-1}, $P < .05$). In conclusion, after an 18-hour fast, the arterial glucose concentration is lower in lambs with aortopulmonary shunts. This lower glucose concentration is associated with a decreased glucose production rate. In shunt lambs, glycogenolysis is decreased, while there is no difference in gluconeogenesis or hormonal control.

SPONTANEOUSLY occurring hypoglycemia has been described in adults with severe congestive heart failure.[1-3] Also, in children with acute congestive heart failure mostly due to congenital heart disease (CHD), hypoglycemia was found.[4-7] Hypoglycemia was ascribed to an extremely low glycogen content in the liver and/or hepatic insufficiency due to congestion or hypoperfusion of the liver. The decreased glycogen stores in the liver could be the result of an increase in glucose utilization in tissues, a decrease in glucose production, or a decrease in the dietary intake of nutrients. The decrease in dietary intake may be due to a poor clinical condition, and may be aggravated by a failure in the absorption of food due to edema of the small bowel.[4]

Hypoglycemia in children with CHD has not been thoroughly investigated, and has been studied only in cases of severe acute heart failure. However, hypoglycemia may occur more frequently, since the symptoms of hypoglycemia sometimes may not be recognized because they can mimic the symptoms of cardiac failure.[1,2] Unrecognized hypoglycemia may be deleterious in children with CHD, since it has been shown that even in newborn infants with normal hearts hypoglycemia per se leads to cardiac enlargement and failure.[5,8] Furthermore, neurological sequelae may occur.

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Analogous to the hypoglycemia described in severe acute heart failure, hypoglycemia may occur in CHD with moderate left-to-right shunts during reduced food intake or fasting. Due to the volume overload, pulmonary and systemic venous congestion occur, leading to symptoms such as shortness of breath and fatigue. Consequently, in infants, feeding difficulties with a diminished energy intake are often encountered.

To investigate whether hypoglycemia occurs in CHD with volume overload during fasting, glucose metabolism after an 18-hour fast was studied in lambs with an aortopulmonary left-to-right shunt and in control lambs. Furthermore, plasma levels of hormones involved in the endocrine control of glucose metabolism were determined. The glucose production rate (rate of appearance [Ra]) was studied with [U-^{13}C]glucose. Gluconeogenesis through the Cori cycle was studied by determination of glucose ^{13}C recycling.

MATERIALS AND METHODS

With approval of the Ethical Committee on Animal Experiments of the Faculty of Medical Sciences, Groningen, The Netherlands, 18 7-week-old lambs of mixed breed with documented dates of birth were studied. They were assigned to two groups: nine with an aortopulmonary shunt and nine without a shunt. Surgical preparation at the age of 4 weeks, catheter care, and antibiotic administration were performed as described previously.[9-11] In the shunt lambs, a Goretex conduit (ID 6 mm; W.L. Gore, Flagstaff, AZ) was sutured between the descending aorta and the main pulmonary artery. Catheters were inserted into the aorta, pulmonary artery, right ventricle (only in shunt lambs), and right and left atrium. Precalibrated electromagnetic flow transducers (ID 10 to 15 mm; Skalar Medical, Delft, The Netherlands) were placed in the shunt lambs around the ascending aorta just above the coronary arteries and around the pulmonary artery proximal to the conduit, and in the control lambs only around the pulmonary artery. Until the day of study, each lamb remained with its mother and fed ad libitum by breast and with hay.

Experimental Protocols

After an 18-hour fast, the lambs were weighed and brought to the experiment room. We chose a long fasting period because lambs are

ruminants, and it therefore takes more time for lambs to reach a fasted state. Throughout the experiment, only water was allowed to the lambs. Systemic and pulmonary blood flow and aortic, pulmonary arterial, and left-atrial pressure were measured every 15 minutes for 1 hour. Blood flow to the myocardium was determined with one of four (^{141}Ce, ^{113}Sn, ^{103}Ru, and ^{95}Nb; NEN-Trac, Du Pont, Biotechnology Systems, Wilmington, DE) radionuclide-labeled microspheres (15 μm diameter) as previously described.[9,12] The microspheres were randomly chosen in each lamb. They were previously shown to produce the same results.[9,12,13] Blood samples were drawn from the aorta for determination of the glucose concentration. Because a lower arterial glucose concentration was found in the first three shunt lambs compared with the control lambs, the last six lambs from each group were studied additionally during the entire preceding night. In these lambs, the experiments started at 4 PM and lasted until the next morning at 11 AM. Every 2 hours, blood samples were drawn from the aorta to determine the hematocrit and substrate concentrations (glucose, pyruvate, lactate, β-hydroxybutyrate [BOB], acetoacetate, free fatty acids [FFAs], and total and free glycerol). Every 4 hours, blood samples were drawn from the aorta to determine hormone levels (adrenaline, noradrenaline, cortisol, glucagon, and insulin).

To determine the glucose production rate (R_a) and glucose recycling, [U-^{13}C]glucose was administered according to the priming-dose/constant-rate infusion technique[14] in all lambs after the 18-hour fast (between 10 and 11 AM). Before the start of [U-^{13}C]glucose infusion, blood samples were drawn from the aorta for determination of substrate concentrations and the isotope ratio (^{13}C/^{12}C) of glucose to determine the natural abundance of ^{13}C in glucose. A priming dose of 7.3 mg · kg^{-1} [U-^{13}C]glucose (99 atom % ^{13}C; Isotec, Miamisburg, OH) was administered over 10 minutes into the right atrial catheter, followed by a constant-rate infusion (model 2620; Harvard Pump, Millis, MA) of 0.073 mg · min^{-1} · kg^{-1} [U-^{13}C]glucose.[15] During a steady state, three blood samples (30, 45, and 60 minutes after starting infusion of the priming dose) were obtained from the aorta for determination of the glucose isotope ratio, blood gases, hemoglobin, and hematocrit. Blood samples from the aortic and mixed-venous catheters, ie, the right ventricular catheter in shunt lambs and the pulmonary arterial catheter in control lambs, were drawn every 15 minutes with a heparinized syringe for determination of oxygen saturation. Immediately after the last blood sample, radionuclide-labeled microspheres were injected into the left atrium while a reference sample was drawn for 1.25 minutes at a rate of 6 mL/min with a Harvard pump from the aortic catheter into a preweighed heparinized syringe.[12]

Measurements

Systemic and pulmonary blood flow, heart rate, and aortic, pulmonary arterial, and left- and right-atrial pressure were measured as previously described with Gould P23 ID pressure transducers (Spectramed, Oxnard, CA) referenced to atmospheric pressure with zero obtained with the pressure transducer at the right-atrial level.[9] The precalibrated electromagnetic flow transducers were connected to Skalar MDL 400 flowmeters. All variables were recorded on an Elema Mingograf 800 ink-jet recorder (Siemens-Elema, Solna, Sweden). Systemic and pulmonary blood flow rates in shunt lambs were obtained from the pulmonary and aortic flow transducers, respectively; systemic blood flow in control lambs was obtained from the pulmonary flow transducer. The position of the aortic flow transducer was distal to the origin of the coronary arteries. To obtain total left-ventricular output in shunt lambs, the coronary blood flow obtained with the microspheres was added to the aortic flow measured with the flow transducer.[15] The pH, P_{CO_2}, P_{O_2}, and plasma HCO_3^- concentration were determined with an ABL-2 blood gas analyzer (Radiometer, Copenhagen, Denmark) The hemoglobin concentration was determined with the Haemocue method (B Hemoglobin Photometer; Haemocue, Helsingborg, Sweden), and the hematocrit was determined with the microcapillary method. Oxygen saturation was determined with an OSM2 hemoximeter (Radiometer).

Immediately after sampling, the blood samples were mixed with sodium fluoride to stop glycolysis and kept in ice. For the determination of glucose, pyruvate, lactate, BOB, and acetoacetate, part of the blood was deproteinized with cold 18% perchloric acid (2:1 vol/vol) and centrifuged. The protein-free supernatant was removed and neutralized with a potassium hydroxide/morpholinopropane sulfonic acid mixture. Glucose, pyruvate, lactate, BOB, acetoacetate, FFA, and total and free glycerol levels were determined in duplicate by enzymatic methods.[16,17]

Plasma noradrenaline and adrenaline concentrations were determined by high-performance liquid chromatography with electrochemical detection.[18] After sample collection, the blood was centrifuged at 4°C. The thrombocyte-poor plasma was fortified with the antioxidant glutathione and stored at −20°C pending determination. The cortisol level was measured by radioimmunoassay (RIA) on unextracted serum. The antigen was labeled with tritium, and separation of antibody-bound label from "free" label was achieved by active-charcoal suspension at 0°C. The RIA series was incubated at 60°C for 30 minutes. The antisera were raised in rabbits to a conjugate of bovine serum albumin with cortisol-3-(*O*-carboxymethyl)oxime-21-acetate. The glucagon level was measured by RIA using a kit for pancreatic glucagon (Novo, Copenhagen, Denmark). Total plasma insulin levels were measured by RIA using a Pharmacia Kit (Pharmacia Diagnostics, Uppsala, Sweden).

For determination of the isotope ratio of glucose, the plasma was deproteinized with ethanol for 30 minutes at 4°C. After centrifugation, the supernatant was removed and dried under nitrogen. Pyridine/acetic anhydride (1:2 vol/vol) was added, and this mixture was allowed to react for at least 24 hours at room temperature to form the pentaacetate derivative.[15] The samples were dried under nitrogen and dissolved in 100 μL hexane. The isotope ratio was determined by gas chromatography/mass spectrometry. A Hewlett-Packard model 5890 gas chromatograph (Hewlett-Packard, Palo Alto, CA) was interfaced to a VG Trio-2 quadrupole mass spectrometer (Fisons Instruments, Manchester, UK). The mass spectrometer was used in the chemical ionization mode. Single-ion monitoring was performed at *m/z* 408, 409, 410, 411, and 414, corresponding to M + 0, M + 1, M + 2, M + 3, and M + 6. Standards containing 0.0%, 1.5%, 3.0%, and 4.5% D-[U-^{13}C]glucose were prepared by diluting natural D-glucose with D-[U-^{13}C]glucose to obtain a calibration graph of isotope ratio versus molar fraction (r = .998, slope = 1.031). The molar fraction (F) of [U-^{13}C]glucose in the blood samples was calculated from this calibration graph.

Calculations

Left-to-right shunt flow was obtained by subtracting systemic from pulmonary blood flow. The left-to-right shunt fraction was calculated by dividing left-to-right shunt flow by pulmonary blood flow. The blood oxygen concentration was calculated as the product of oxygen saturation, hemoglobin concentration, and a hemoglobin oxygen-binding capacity of 1.36 mL/g.[19] Systemic oxygen supply was calculated as the product of arterial oxygen concentration and systemic blood flow. Whole-body oxygen consumption (V_{O_2}) was calculated by multiplying the arterial–mixed-venous oxygen concentration difference by systemic blood flow.

The glucose production rate, R_a (micromoles per minute per kilogram), was calculated as

$$R_a = \left(\frac{F_I}{F_{AO}} - 1 \right) \cdot I,$$

where F_I is the molar fraction of [U-^{13}C]glucose in the infusate, F_{AO} is the molar fraction of [U-^{13}C]glucose in the aorta at steady state, and I is the rate of tracer infusion (micromoles per minute per kilogram). Since the arterial glucose concentration did not change throughout the experiment, the glucose R_a was equal to the glucose disappearance rate

(R_d). The metabolic clearance rate ([MCR] milliliters per minute per kilogram) was calculated by dividing the R_d by the plasma glucose concentration.

The gluconeogenic pathway through pyruvate and lactate (Cori cycle) was estimated from the fractional glucose ^{13}C recycling[20]:

$$\text{fractional glucose } ^{13}C \text{ recycling} = \frac{3 \cdot F_{13_{C_3}} + 2 \cdot F_{13_{C_2}} + F_{13_{C_1}}}{6 \cdot F_{13_{C_6}} + 3 \cdot F_{13_{C_3}} + 2 \cdot F_{13_{C_2}} + F_{13_{C_1}}}.$$

Gluconeogenesis via the Cori cycle was then calculated as the product of fractional glucose ^{13}C recycling and R_a. The sum of glycogenolysis and gluconeogenesis from other precursors such as glycerol and amino acids was estimated by subtracting the gluconeogenesis via the Cori cycle from the R_a.

Statistical Analysis

The data are expressed as the mean ± SEM. To compare hemodynamic variables between shunt and control lambs, a Student two-tailed *t* test for unpaired samples was used. To compare substrate and hormone concentrations between the fed state (4 PM) and fasted state (other time points) and between shunt and control lambs, a repeated-measures ANOVA was performed. This was followed by a Wilcoxon signed-rank test for unpaired, or paired data, respectively. Linear regression analysis was performed using a statistical computer program (NCSS, Kaysville, UT). A *P* value of .05 or less was considered statistically significant.

RESULTS

Hemodynamic Data

On the day of study, there were no statistically significant differences in age (45 ± 1 *v* 47 ± 2 days) between shunt and control lambs. Weight tended to be lower in shunt lambs (12.5 ± 0.8 *v* 14.0 ± 0.6 kg, $P = .15$). The left-to-right shunt was 54% ± 4% of the left-ventricular output. The left-to-right shunt led to significant hemodynamic and oxygen consumption–related differences between shunt and control lambs (Table 1).

Table 1. Hemodynamic Data and Oxygen Consumption–Related Variables

Variable	Control	Shunt
Heart rate (bpm)	136 ± 10	144 ± 8
Mean blood pressure (mm Hg)		
Aortic	74 ± 3	61 ± 4*
Pulmonary arterial	11 ± 1	17 ± 3*
Left atrial	3 ± 1	12 ± 3*
Right atrial	2 ± 1	7 ± 2
Blood flow (mL · min^{-1} · kg^{-1})		
Systemic	138 ± 7	115 ± 6*
Pulmonary	138 ± 7	254 ± 16*
Arterial parameters		
pH	7.37 ± 0.02	7.38 ± 0.01
P_{CO_2} (kPa)	4.6 ± 0.1	5.0 ± 0.1*
P_{O_2} (kPa)	13.5 ± 0.6	12.1 ± 0.5
HCO_3^- (mmol/L)	19.3 ± 0.8	21.3 ± 0.6*
Stroke volume (mL/kg)		
Left ventricular	1.04 ± 0.07	1.79 ± 0.13*
Systemic oxygen supply (μmol · min^{-1} · kg^{-1})	637 ± 47	487 ± 33*
V_{O_2} (μmol · min^{-1} · kg^{-1})	269 ± 19	226 ± 7*

NOTE. Data are the means ± SEM; n = 9 for both groups of lambs.
*$P < .05$, shunt *v* control.

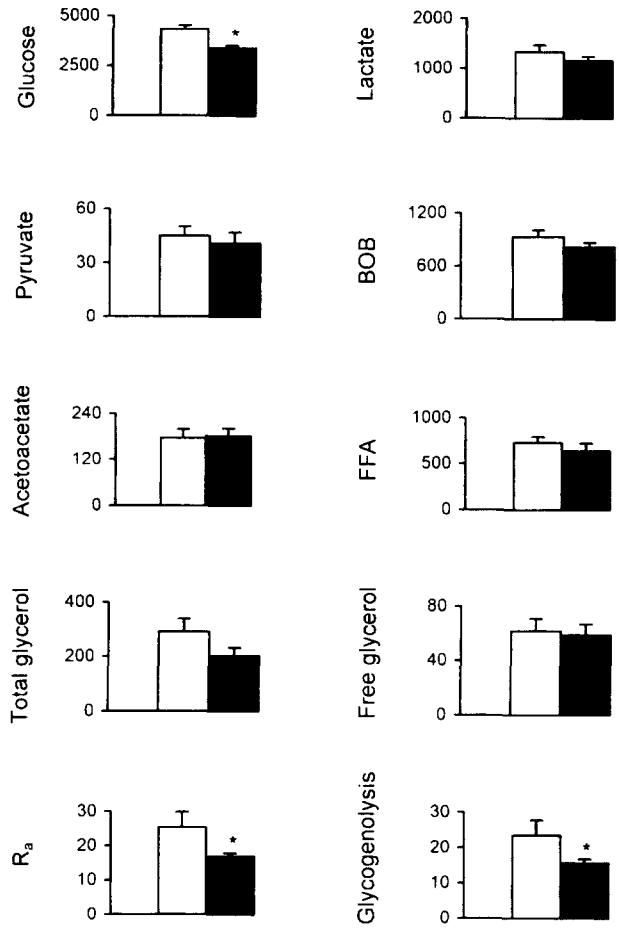

Fig 1. Arterial substrate concentrations (μmol/L), R_a (μmol · min^{-1} · kg^{-1}), and glycogenolysis (sum of glycogenolysis and gluconeogenesis from precursors other than pyruvate and lactate, μmol · min^{-1} · kg^{-1}) in control (□, n = 9) and shunt (■, n = 9) lambs after an 18-hour fast. Data are the means ± SEM. *$P < .001$.

Substrates

After an 18-hour fast, arterial glucose concentrations were lower in shunt versus control lambs (3,409 ± 104 *v* 4,338 ± 172 μmol/L, $P < .001$). There was no statistically significant difference for concentrations of the other substrates (Fig 1). The arterial glucose concentration was lower when the pulmonary blood flow, left-ventricular stroke volume, or left-atrial pressure were higher. There was no correlation between the arterial glucose concentration and heart rate (Fig 2). We found no correlation between arterial glucose concentration and the glucose production rate ($r = .40$, $P = .18$). In the last six lambs of each group, which were studied during the entire preceding night, there was an increase in acetoacetate and BOB and a decrease in glucose in both groups (Fig 3).

Hormone Levels

There were no differences in hormone levels between control and shunt lambs. Insulin levels decreased due to fasting in both

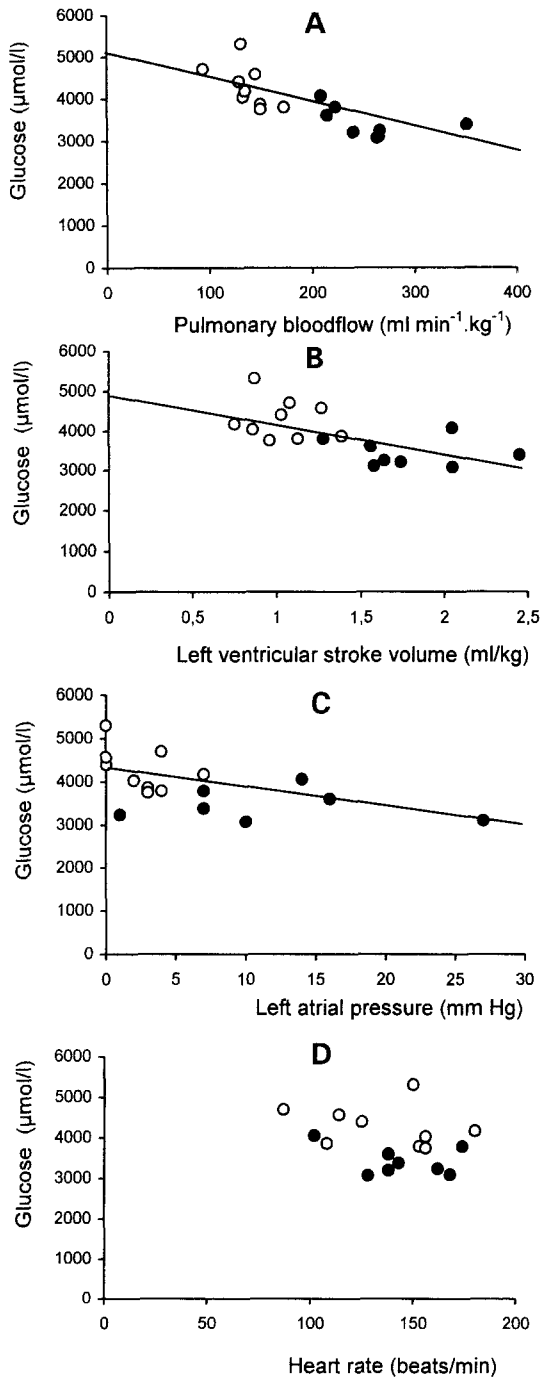

Fig 2. Correlation between arterial glucose concentration (µmol/L) and hemodynamic parameters. (A) Pulmonary blood flow: y = 5,000 − 6.2×, $r = -.73$, $P < .001$. (B) Left ventricular stroke volume: y = 4,887 − 748×, $r = -.62$, $P < .01$. (C) Left atrial pressure: y = 4,200 − 40×, $r = -.54$, $P < .05$. (D) Heart rate, NS. (○) Control, n = 9; (●) shunt, n = 9.

groups, whereas the other hormones did not change due to fasting.

Glucose Production, Gluconeogenesis, and Glycogenolysis

Steady-state conditions for the isotope ratio of glucose were reached. The R_a (or R_d) was lower in shunt versus control lambs (16.97 ± 0.89 *v* 25.49 ± 4.28 µmol · min^{-1} · kg^{-1}, $P < .05$). The MCR was similar in both groups (4.86 ± 0.20 *v* 6.05 ± 0.97 mL · min^{-1} · kg^{-1}). Fractional glucose ^{13}C recycling via the Cori cycle (6.9% ± 2.8% *v* 7.1% ± 2.5%) and gluconeogenesis from pyruvate and lactate (1.24 ± 0.58 *v* 1.95 ± 0.67 µmol · min^{-1} · kg^{-1}) were similar in both groups of lambs. The sum of glycogenolysis and gluconeogenesis from precursors other than pyruvate and lactate was lower in shunt versus control lambs (15.73 ± 1.07 *v* 23.54 ± 4.27 µmol · min^{-1} · kg^{-1}, $P < .05$).

DISCUSSION

The results show that after an 18-hour fast, arterial glucose was lower in lambs with an aortopulmonary shunt versus control lambs, although a hypoglycemic level was not reached. However, there was a distinct relationship between the arterial glucose concentration, on one hand, and pulmonary blood flow or left-ventricular stroke volume or left-atrial pressure, on the other hand, suggesting that in the case of a more severely compromised systemic circulation, hypoglycemia might occur.

The lower arterial glucose concentration is the result of either greater glucose utilization or a decreased rate of production. An increase in glucose utilization in shunt lambs may be associated with their higher energy demand for cardiac and respiratory performance, but our data do not support the notion that glucose utilization is indeed increased. In another study,[21] we demonstrated that the mean myocardial glucose uptake in shunt lambs was 21.72 µmol · min^{-1} · 100 g^{-1}, which accounts for only 3.6% of glucose utilization by the whole body. Furthermore, although myocardial oxygen consumption was higher in shunt versus control lambs, as described previously,[9,10] whole-body oxygen consumption was lower in shunt versus control lambs (Table 1). Glucose clearance from the blood was similar in both groups, and glucose disappearance (R_d) was even decreased in shunt lambs compared with control lambs. Therefore, a decrease in glucose production is the probable cause of the lower arterial glucose concentration in shunt lambs. A similar relationship between hypoglycemia and the glucose production rate has been found in small-for-gestational-age newborn babies and animals.[22-25]

The decrease in the R_a may have been caused by a decrease in gluconeogenesis and/or a decrease in glycogenolysis. By determining glucose ^{13}C recycling, we estimated the amount of lactate (pyruvate) that is converted back to glucose via the Cori cycle. Although this amount does not comprise total gluconeogenesis, it is the greater part of it. Gluconeogenesis estimated by glucose ^{13}C recycling was similar in shunt and control lambs. This is in agreement with the observation that neither the arterial concentration of pyruvate and lactate nor the regulatory hormone levels were different between the two groups of lambs.

When we subtract from the glucose R_a the gluconeogenesis via the Cori cycle, we obtain the sum of glycogenolysis and

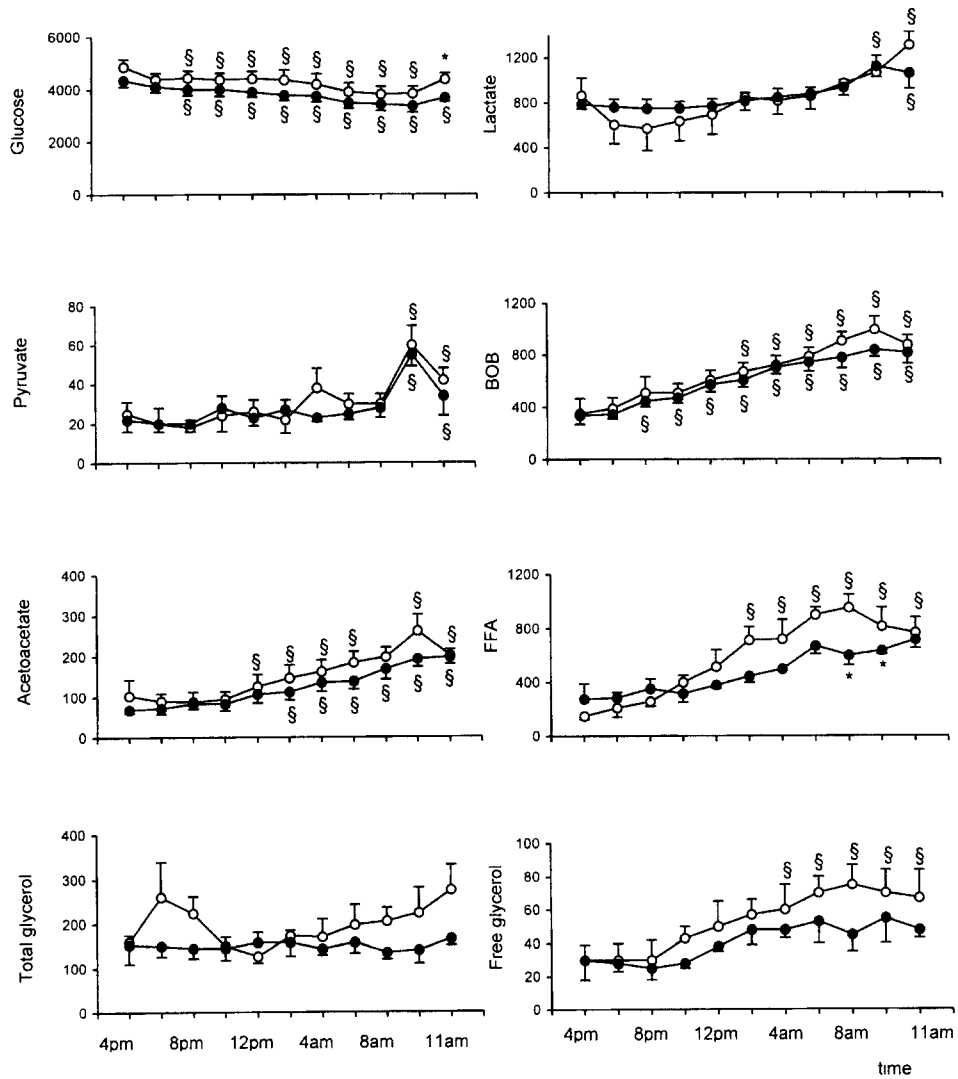

Fig 3. Arterial substrate concentrations (μmol/L) in control (○, n = 6) and shunt (●, n = 6) lambs during the 18-hour fast. Data are the mean ± SEM. *$P < .05$, control *v* shunt. §$P < .05$, fasted *v* fed state.

gluconeogenesis from substrates other than pyruvate and lactate. The contribution of other substrates like glycerol and amino acids under the present circumstances will be slight, since during fasting glycogenolysis accounts for the major part of the glucose production rate.[26] The value thus obtained was lower in shunt versus control lambs, indicating that in shunt lambs glycogenolysis was decreased. This may be due to a change in hormonal control or to diminished glycogen stores. The concentrations of glucagon and insulin were not different between the two groups of lambs. Therefore, we assume that the glycogen content in the liver of shunt lambs is lower. This is in agreement with the lower glycogen content found in liver biopsies of adults and children with hypoglycemia associated with CHD.[4,6] The lower glycogen stores in shunt lambs may be the result of a higher energy demand of the myocardium and respiratory muscles. Less of the daily energy intake, which often is insufficient due to shortness of breath and fatigue, remains for the growth of the lambs and supplementation of energy stores. The lower weight found in the shunt lambs is in agreement with less growth. Moreover, it should be taken into account that the extracellular volume of shunt lambs is 11% higher than that of control lambs.[27] Although not statistically significant, the weight gain of shunt lambs was lower than that of control lambs (37 ± 17 *v* 53 ± 30 g/d). Both the lower weight and the lower weight gain of the shunt lambs suggest undernutrition as a possible cause of lower glycogen stores. Growth retardation due to noncardiac causes, as in small-for-gestational-age children and animals, may lead to hypoglycemia due to reduced or even absent hepatic glycogen stores.[22,28,29]

To prove that undernutrition is indeed the cause of the lower glucose production via lower glycogen stores, a study will be necessary in which the energy intake of shunt lambs is measured and, subsequently, the glucose metabolism of these shunt lambs is compared with that of normally fed control lambs and control lambs fed with a diet providing a similar energy intake as in the shunt lambs.

Hypoglycemia per se due to fasting may be deleterious for maintaining an adequate cardiac output in CHD, since even in normal hearts hypoglycemia may lead to heart failure.[5,8] Fasting leads to hyperketonemia, which results in a decreased contractility of the myocardium.[30,31] In our study, systemic blood flow, mean aortic pressure, and whole-body oxygen consumption were lower in shunt versus control lambs. In previous studies from our laboratory, aortic systolic pressure, systemic blood flow, and whole-body oxygen consumption were not different in shunt and control lambs in the fed state.[10]

The lower arterial glucose concentrations found in lambs with aortopulmonary shunts may have implications for children with CHD. Feeding difficulties due to shortness of breath and fatigue are often encountered in children with CHD with a left-to-right shunt, and may place them in a state of insufficient energy intake. When these children subsequently need surgery, a situation for which a prolonged fasting period is required, a decrease in the glucose concentration or even hypoglycemia may occur. The glucose concentration may even be lower in children than in our lambs, because the lambs still had some straw in their stomach after an 18-hour fast, which could have contributed to the glucose production. A low glucose concentration may be of clinical importance not only because of the neurologic sequelae, which may occur after unrecognized hypoglycemia, but also because it is known that even in newborn infants with normal hearts hypoglycemia is deleterious, with cardiac enlargement and failure as a result.[5,8] In particular, in newborn infants with CHD, aggravation of heart failure immediately before surgery might increase the risk of hemodynamic deterioration during and after surgery. In adults, even myocardial infarction secondary to hypoglycemia has been described.[32] We therefore recommend that children with CHD be carefully monitored for the presence of hypoglycemia.

In conclusion, we have demonstrated that after an 18-hour fast, arterial glucose concentrations are lower in lambs with aortopulmonary shunts than in control lambs. This lower glucose concentration was associated with a decreased glucose production rate. Glycogenolysis was decreased in shunt lambs compared with control lambs, while there was no difference in gluconeogenesis. There was no difference in hormonal control. Therefore, we assume that the limited glycogen stores in shunt lambs were more readily depleted than those in control lambs.

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