Peripheral chemoreflex activation and cardiac function during hypoxemia in near term fetal sheep without placental compromise

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Running head: Fetal chemoreflex and cardiac function in hypoxemia

Abstract

A drop in arterial oxygen content activates fetal chemoreflex including an increase in sympathetic activity leading to peripheral vasoconstriction and redistribution of blood flow to protect the brain, myocardium, and adrenal glands. By using a chronically instrumented fetal sheep model with intact placental circulation at near-term gestation, we investigated the relationship between peripheral chemoreflex activation induced by hypoxemia and central hemodynamics. A total of 17 Åland landrace sheep fetuses at 115-128/145 gestational days were instrumented. Carotid artery was catheterised in 10 fetuses and descending aorta in 7 fetuses. After a 4-day recovery, baseline measurements of fetal arterial blood pressures, blood gas values, and fetal cardiovascular hemodynamics by pulsed Doppler ultrasonography were obtained under isoflurane-anesthesia. Comparable data to baseline was collected 10 (acute hypoxemia) and 60 minutes (prolonged hypoxemia) after maternal hypo-oxygenation to saturation level of 70-80% was achieved. During prolonged hypoxemia, pH and base excess (BE) were lower, and lactate levels higher in the

descending aorta than in the carotid artery. During hypoxemia mean arterial blood pressure (MAP) in the descending aorta increased, while in the carotid artery MAP decreased. In addition, right pulmonary artery pulsatility index values increased, and the diastolic component in the aortic isthmus blood flow velocity waveform became more retrograde thus decreasing the aortic isthmus antegrade/retrograde blood flow (AoI Net Flow) ratio. Both fetal ventricular cardiac outputs were maintained even during prolonged hypoxemia when significant fetal metabolic acidemia developed. Fetal chemoreflex activation induced by hypoxemia decreased the perfusion pressure in the cerebral circulation. Fetal weight-indexed LVCO or AoI Net Flow-ratio did not correlate with a drop in carotid artery blood pressure.

New & Noteworthy

During fetal hypoxemia with intact placental circulation, peripheral chemoreflex was activated as demonstrated by an increase in the descending aorta blood pressure, pulmonary vasoconstriction and an increase in retrograde diastolic AoI blood flow, while both ventricular cardiac outputs remained stable. However, perfusion pressure in the cerebral circulation decreased. These changes were seen even during prolonged hypoxemia when significant metabolic acidosis developed. Weight-indexed LVCO or AoI Net Flow-ratio did not correlate with a drop in carotid artery blood pressure.

Keywords: physiology, blood flow, Doppler ultrasonography, aortic isthmus, hemodynamics

Introduction

Fetus is protected against hypoxemia by several mechanisms, such as high myocardial glycogen stores, increased oxygen affinity of fetal hemoglobin, near-maximal cardiac output, and the presence of fetal vascular shunts that optimize oxygen delivery to the vital organs (26, 37, 40). Fetal peripheral chemoreceptors respond rapidly to changes in arterial pO_2 and mediate the neural protective responses (10, 11, 16). The chemoreflex activation in the carotid body results in increased parasympathetic activity leading to initial fetal bradycardia. A simultaneous increase in sympathetic activity leads to peripheral vasoconstriction and the centralisation of blood flow (16, 23). When increased sympathetic activity is sustained, the parasympathetic effect is counteracted with a positive chronotropic effect and fetal bradycardia starts to recover (16). In addition, peripheral vasoconstriction increases blood pressure in the descending aorta leading to increased right ventricular afterload, which enhances shunting through the foramen ovale into the ascending aorta and cerebral circulation (15). Humoral agents are thereafter released which help to maintain the peripheral vasoconstriction and increase the heart rate even higher (16, 24). Hypoxemic vasodilatation of the fetal cerebrovascular bed is associated with the local release of vasoactive agents, such as adenosine and nitric oxide (7, 21). These responses may vary during pregnancy, because fetal autonomic nervous system and chemoreceptor sensitivity mature with advancing gestation (13, 22, 38, 42).

Hypoxemia in fetuses with intact placental circulation leads to alterations in central hemodynamics that can be detected by Doppler ultrasonography. The most important findings include an increase in pulmonary arterial vascular impedance (4, 30, 33) and the appearance of a retrograde diastolic blood flow component in the aortic isthmus blood flow velocity waveform (31). Furthermore, the right ventricular cardiac output may increase during fetal hypoxemia (31, 41).

We developed a fetal sheep model with intact placental circulatory physiology to investigate the relationship between peripheral chemoreflex activation induced by hypoxemia and fetal central hemodynamics. We hypothesized that hypoxemia-induced alterations in fetal cardiovascular hemodynamics reflect the activation of peripheral chemoreflex. From a clinical standpoint, it would be important, if we could find the moment when the fetal peripheral chemoreflex is unable to provide sufficient perfusion pressure and blood flow to the brain by non-invasive ultrasonography. Specifically, we wanted to examine 1) the changes in carotid artery and descending aorta blood pressures and blood gas values, 2) the alterations in fetal cardiovascular hemodynamics, and 3) the relationship between cardiovascular hemodynamics and fetal carotid artery and descending aorta blood pressures during hypoxemia.

Materials and methods

The study protocol was approved by the National Animal Experiment Board of Finland (ESAVI/2387/04.10.07/2017). The animal care and experiments were performed in compliance with the national legislation (Finnish Government 2013; Parliament of Finland 2013) and the EU directive (The European Parliament and the Council of the European Union 2010).

A total of 17 Åland landrace sheep with time-dated singleton pregnancies were included in this study (Lammastila Sikka Talu, University of Turku, Rymättylä, Finland). The sheep were transported from the breeders to the Laboratory Animal Centre at the University of Oulu, Finland two weeks before the experiment. During this adaptation period, the sheep were group housed in two pens of 10.8 m^2 in area and during the experiment in individual pens of 3.6 m^2, with straw bedding. Adjacent sheep were able to be in contact with each other trought the windows between the pen walls, and no individual sheep was left alone in the animal room. The room temperature was 18 ± 2°C, ventilation rate 15 times per hour, and humidity 45 ± 5%. The light-dark cycle was 12 h-12 h, with the lights off at 18.00 h. The sheep were given tap water and hay *ad libitum*, and they

had a salt block in the pen. Individually rationed oat grains, turnip rape-based protein supplement (Farmarin rypsi; Hankkija-Maatalous Oy, Seinäjoki, Finland) and mineral and vitamin supplements (Lammas Hertta; Hankkija -Maatalous Oy) were given twice daily, and the rations were increased gradually towards the end of pregnancy. Supportive doses of calcium were given when needed (orally or intravenously). Animals were monitored several times daily by a veterinarian, animal technicians and the investigators for signs of pain, distress, injury, or disease. The focus was set to ensure the well-being of animals and to minimize pain and suffering (see methodological description below for details).

Surgery and Instrumentation

Fetal instrumentation was performed at 115-128 gestational days (term 145 days). The sheep were premedicated with ketamine (2mg/kg i.m.; Ketaminol vet; Intervet, Boxmeer, The Netherlands) and midazolam (0.2mg/kg i.m.; Midazolam Hameln; Hameln Pharmaceuticals, Hameln, Germany). Maternal left jugular vein was cannulated to obtain intravenous access and lactated Ringer solution was infused with a rate of 200ml/h. General anesthesia was induced with intravenous propofol (4–7 mg/kg; Propofol-Lipuro; Braun, Melsungen, Germany) and maintained with isoflurane (1.5–2.5%; Isofluran Baxter; Baxter S.A., Lessines, Belgium) in an oxygen–air mixture delivered via an endotracheal tube. Fentanyl (0.05–0.15 mg; Fentanyl-Hameln; Hamenln Pharma Plus, Hameln, Germany) was administered intravenously when required for pain relief based on maternal heart rate and arterial blood pressure changes during surgical stimuli.

A midline abdominal incision was made to access the uterus and the fetus through a hysterotomy. In case of a twin pregnancy, only one fetus was instrumented. In 10 fetuses, the head and upper body were delivered. Nonocclusive polyvinyl catheters were inserted into the carotid artery and internal jugular vein, with the catheter tips in the carotid artery and superior vena cava (SVC) pointing towards the heart. In 7 fetuses, the lower body was delivered, and a nonocclusive polyvinyl catheter

was inserted into the femoral artery with the catheter tip in the descending aorta pointing towards the heart. A three-lead 28-gauge silver-coated copper ECG wire (New England Wire Tech., Lisbon, NH, USA) was placed subcutaneously on the fetal chest. A separate polyvinyl catheter was placed in the amniotic cavity. Lost amniotic fluid was replaced with warm saline. Injection of penicillin G (1 million units; Geepenil; Orion Oyj, Espoo, Finland) was administered to the fetus. The surgical incisions were closed. All catheters were tunnelled subcutaneously and exteriorized through a small incision in the ewe's flank. Postoperative analgesia was provided with 100mg bubivacaine (Bubivacaine Accord 5mg/ml; Accord Healthcare B.V., Utrecht, Netherlands) injected locally into the surgical wounds and with transdermal fentanyl patches (Fentanyl ratiopharm; Ratiopharm, Ulm, Germany), at the dose rate of 2 μg /kg/h, applied to the ewe's antebrachium before surgery.

Experimental protocol

Following a 4-day recovery period, general anesthesia was induced with a single bolus of propofol (4–7 mg/kg; Propofol-Lipuro; Braun, Melsungen, Germany) and maintained by isoflurane (1.5–2.5%; Isofluran Baxter; Baxter S.A., Lessines, Belgium) in an oxygen/air mixture. The depth of anesthesia was titrated to keep maternal heart rate and blood pressure within the normal physiologic range, while allowing for ultrasound examination without maternal discomfort. A 16-gauge polyurethane catheter was inserted into the maternal femoral artery in order to measure maternal arterial blood pressure and to obtain arterial blood gas samples. The ewe was placed supine with a right lateral tilt and allowed to stabilize for 30 minutes before the baseline measurements were taken. Thereafter, maternal hypo-oxygenation was induced in a re-breathing circuit to reach a maternal arterial oxygen saturation level of 70-80%. This was confirmed by an arterial blood gas sample. Ten minutes after the desired maternal oxygen saturation level was reached, the data for acute hypoxemia was collected. The data acquisition for prolonged hypoxemia was performed 60 minutes following the onset of hypoxemia.

Invasive monitoring

Fetal and maternal blood pressures were continuously monitored with disposable pressure transducers (DT-XX; Ohmeda, Hatfield, UK). Fetal blood pressures were referenced to intra-amniotic pressure. Maternal heart rate was obtained from the arterial pressure waveforms. Fetal ECG leads were connected to the ultrasound equipment to obtain fetal heart rate. Maternal and fetal blood gas values were analysed (correction to 39°C) at each study point using an Abbot i-Stat 1 arterial blood gas analyser (i-Stat, East Windsor, NJ, USA).

Ultrasonography

Vivid 7 Dimension ultrasound system (GE Vingmed Ultrasound, Horten, Norway) with a 10 MHz phased-array transducer was used to collect fetal cardiovascular hemodynamic parameters. The high-pass filter was set at minimum, and the angle of insonation was kept below 15 degrees. Three consecutive cardiac cycles were measured, and the mean values were used for analysis.

Fetal left (LVCO) and right (RVCO) ventricular cardiac outputs were calculated as previously described (35). Briefly, aortic and pulmonary valve diameters were measured, and their cross-sectional areas (CSA) were calculated. From the blood flow velocity waveforms of the aortic and pulmonary valves, time-velocity integrals (TVI) were measured and volumetric blood flows (Q) across the aortic (left ventricular cardiac output, LVCO) and pulmonary (right ventricular cardiac output, RVCO) valves were calculated (Q = CSA × TVI × fetal heart rate). The sum of LVCO and RVCO is the combined cardiac output (CCO). Fetal cardiac outputs were weight-indexed.

Blood flow velocity waveforms of the ductus arteriosus (DA), umbilical artery (UA), descending aorta (DAo), right pulmonary artery (RPA), pulmonary vein (Pulmvein), ductus venosus (DV) and inferior vena cava (IVC) were obtained to calculate their pulsatility index (PI) values as follows: (peak systolic velocity – end diastolic velocity) / time-averaged maximum velocity over the cardiac

cycle. Aortic isthmus blood flow velocity waveforms were recorded and the TVI ratio between antegrade and retrograde blood flow components was calculated (AoI Net Flow-ratio). Figure 1 demonstrates fetal sheep cardiovascular anatomy. To estimate volume blood flow in the placenta (Q_{plac}), umbilical venous (UV) volume blood flow was calculated as follows: 0.5 x UV maximum velocity (cm/s) x UV CSA (3). Placental vascular resistance (R_{plac}) was calculated by dividing descending aorta MAP by Q_{plac}. Both Q_{plac} and R_{plac} were weight-indexed (1). At each phase, the ultrasonographic data acquisition took about 15–20 minutes, and the data were collected in a random order by a single investigator. The ultrasonographic data were stored and analysed afterwards in a blind manner.

At the end of the experiment, the fetus and the ewe were killed with an i.v. overdose (100 mg/kg) of pentobarbital sodium (Mebunat vet; Orion Oyj, Espoo, Finland), and fetal weight was determined.

Statistical analysis

Data were analysed using SAS for windows (version 9.4; SAS Institute Inc., Cary, NC, USA). Summary measurements are presented as means and standard deviations (SD) unless otherwise stated. We used a repeated-measures mixed-model ANOVA for continuous outcomes to report the between-group differences at specific time points and within-group differences between different time points. Because fetal hypoxemia exposure was similar in both groups and ultrasonographic parameters of fetal hemodynamics did not differ significantly between the groups at any time point, we combined the ultrasononographic data from the two groups for statistical analyses. To test the correlation between the variables, Spearman's correlation coefficient (rho) was calculated. The strength of the association was considered for absolute values of rho 0.25-0.5 as weak, 0.5-0.75 as moderate, and 0.75-1 as strong correlation, while rho <0.25 was regarded as having no association. A two-tailed p-value of <0.05 was considered statistically significant. P-values should be treated with caution given the large number of statistical tests performed.

Results

Mean (SD) maternal weight was 54 (8) kg. Maternal blood pressure remained within normal physiologic range during the entire experiment. As expected, maternal pO_2 decreased significantly during hypoxemia (Table 1).

The gestational age on the day of the experiment was 119-132 days. The mean fetal weight was 2449 (342) g and did not differ significantly between fetuses that had their carotid artery or descending aorta catheterized (2408 (29) vs. 2508 (44)g, p=0.57). At baseline, fetal arterial pH and blood gas values were within the normal physiologic range and comparable between the carotid artery and the descending aorta (Table 2). During hypoxemia, fetal pO_2 decreased significantly from baseline values with no difference between the carotid artery and the descending aorta (Table 2). Fetal pH and base excess were lower and lactate values higher in the descending aorta than in the carotid artery during prolonged hypoxemia (Table 2).

Fetal carotid artery and descending aorta blood pressure values at different time points are presented in Figure 2. At baseline, fetal carotid artery and descending aorta blood pressures were comparable. During acute hypoxemia, carotid artery systolic (52 (7) vs. 42 (6) mmHg, p<0.001), mean (42 (7) vs. 33 (8) mmHg, p=0.001), and diastolic (31 (6) vs. 26 (6) mmHg, p=0.006) blood pressures decreased from baseline. During prolonged hypoxemia, carotid artery systolic and diastolic blood pressures did not change further. On the other hand, in the descending aorta, systolic (50 (5) vs. 62 (17) mmHg, p=0.025) and mean (39 (5) vs. 47 (12) mmHg, p=0.036) blood pressures increased from baseline during prolonged hypoxemia. There was a difference between the carotid artery and descending aorta blood pressures during both acute (systolic 42 (6) vs. 59 (8) mmHg, p<0.001, mean 33 (8) vs. 44 (12) mmHg, p=0.027, diastolic 26 (6) vs. 40 (13) mmHg, p=0.001) and prolonged (systolic 43 (6) vs. 62 (17) mmHg, p<0.001, diastolic 27 (7) vs. 40 (10) mmHg, p=0.003)

hypoxemia. Fetal heart rate was higher during prolonged hypoxemia compared to baseline (Table 3). Fetal systemic venous pressure did not change significantly during hypoxemia (Table 3).

Fetal weight-indexed cardiac outputs remained comparable to baseline during the experiment (Table 3). However, fetal RPA PI and Pulmvein PIV values increased significantly during hypoxemia (Figure 3, Table 4). In the AoI, hypoxemia increased the retrograde blood flow velocity waveform component leading to a significant decrease in the AoI Net Flow-ratio (Figure 3, Table 4). On the other hand, UA, DA and DAo PI values were not statistically significantly affected by fetal hypoxemia. In the fetal systemic venous circulation, IVC PIV values increased significantly during prolonged hypoxemia compared to baseline, while DV PIV values did not change (Figure 3, Table 4). There was a trend towards a decrease in weight-indexed Q_{plac} and an increase in $R_{plac.}$ However, these changes did not reach statistical significance (Table 3).

At baseline, RPA PI showed a strong negative correlation with weight-indexed LVCO (rho = -0.82, p = 0.023) (Figure 4) and moderate negative correlation with AoI Net Flow-ratio (rho = -0.51, p = 0.007). During prolonged hypoxemia, AoI Net Flow-ratio correlated moderately positively with weight-indexed Q_{plac} (rho = 0.51, p = 0.036). In addition, there were strong positive correlations between descending aorta systolic (rho = 0.93, p = 0.003), mean (rho = 0.90, p = 0.006) (Figure 4), and diastolic (rho = 0.79, p = 0.036) blood pressures and weight-indexed Q_{plac} during prolonged hypoxemia. Furthermore, weight-indexed LVCO showed strong positive correlations with descending aorta systolic (rho = 0.89, p = 0.036) and mean (rho = 0.76, p = 0.041) blood pressure during prolonged hypoxemia. RPA PI had a strong negative correlation with descending aorta systolic blood pressure during prolonged hypoxemia (rho = -0.79, p = 0.036). On the other hand, AoI Net Flow-ratio (rho = 0.02-0.29; p>0.05) and weight-indexed LVCO (rho = 0.05-0.41; p>0.05) did not show any statistically significant correlation with carotid artery blood pressures at baseline or during hypoxemia. Hypoxemia-induced decrease in the carotid artery blood pressure did not

differ between fetuses with antegrade (>1) and retrograde (<1) AoI Net Flow-ratio (data not shown).

Discussion

This fetal sheep study was designed to investigate how fetal chemoreflex activation induced by hypoxemia is reflected in fetal central hemodynamics at near term gestation with intact placental circulation. Hypoxemia activated fetal chemoreflex as shown by an increase in the descending aorta blood pressure and a decrease in the carotid artery blood pressure. Increased descending aorta blood pressure most likely reflects hypoxemia-induced peripheral vasoconstriction as shown by Giussani et al. (16). Fetal heart rate increased during prolonged hypoxemia indicating increased sympathetic activation. Under hypoxemia, fetal blood gas values measured from the carotid artery and descending aorta demonstrated a divergent pattern. In the descending aorta, pH and BE decreased, and lactate values increased significantly more than in the carotid artery, demonstrating the importance of fetal circulatory shunts, i.e., ductus venosus and foramen ovale, to protect the brain by allowing the oxygenated blood from the placenta to enter cerebral circulation. In the fetal central hemodynamics, hypoxemia induced vasoconstriction in the pulmonary circulation as demonstrated by an increase in right pulmonary artery PI values, and a decrease in the AoI Net Flow-ratio. We found no correlation between weight-indexed LVCO or AoI Net Flow-ratio and fetal carotid artery blood pressure.

Aortic isthmus is an important watershed area in the fetal arterial circulation that reflects the balance between upper (brain) and lower body (placenta) resistances (14, 31, 32). The physiologic importance of aortic isthmus has been studied in acute fetal sheep experiments, in which placental vascular resistance has been increased by limiting umbilical venous return to the fetus (8). A 50 % reduction in the umbilical venous blood flow was associated with a retrograde diastolic flow through the aortic isthmus (8). When the umbilical venous flow reduction reached about 75 %, the

net forward flow through the aortic isthmus approached zero. At the same time, fetal descending aorta blood pressure was maintained and fetal hypercapnia without hypoxemia developed. In a similar experiment, carotid artery blood pressure and volume blood flow were maintained during a progressive reduction in the umbilical venous blood flow, while pO_2 decreased and pCO_2 increased significantly. The authors found that the delivery of oxygen to the brain is preserved despite a significant drop in arterial oxygen content as long as the net flow through the aortic isthmus is antegrade (14). The restriction of umbilical venous return led to a significant drop in both left and right ventricular cardiac outputs (14). In the present study, we found a similar change in the aortic isthmus blood flow profile with intact placental circulation and unchanged fetal cardiac outputs. We found no significant correlation between the AoI Net Flow-ratio and carotid artery or descending aorta blood pressures during hypoxemia. In addition, weight-indexed LVCO did not correlate with carotid artery blood pressure under hypoxemia. In addition, the blood pressure changes in the carotid artery induced by hypoxemia were comparable between fetuses with antegrade (ratio >1) and retrograde (ratio <1) aortic isthmus net blood flow. Furthermore, we have shown previously that in fetal sheep with complete occlusion of the ascending aorta, carotid artery blood pressure decreased dramatically demonstrating that the aortic isthmus failed to redirect blood flow from the ductus arteriosus and descending aorta to the aortic arch (20). Our findings suggest that the AoI Net Flow-ratio or LVCO are not related to changes in fetal cerebral perfusion pressure and therefore cannot be used as surrogates of perfusion pressure in the fetal brain.

Fetal hypoxemia led to vasoconstriction in pulmonary arterial bed, as indicated by an increase in the RPA PI values. In addition, pulmonary vein PIV values increased, most likely reflecting a significant reduction in the volume blood flow in the lung circulation, while another explanation could be a rise in the left atrial pressure. We found significant negative correlations between the RPA PI values and the AoI Net Flow-ratio and weight-indexed LVCO at baseline. In other words, a drop in the lung volume blood flow would lead to a decrease in the LVCO and an increase in the

retrograde component in the aortic isthmus blood flow pattern. We have shown that foramen ovale has a limited capacity to increase its volume blood flow (18, 29). These findings suggest that fetal pulmonary blood flow has an important role in the regulation of left ventricular output and hemodynamics in the aortic isthmus.

Both fetal ventricular cardiac outputs were maintained even during prolonged hypoxemia when significant fetal metabolic acidemia had developed. Our findings are in agreement with previous studies showing that during acute hypoxemia fetal cardiac outputs remain unchanged or RVCO can even increase (32, 41). Cohn et al. (10) studied circulatory responses to hypoxemia and acidemia in fetal sheep at near-term gestation by using nuclide-labeled microspheres and their results suggested that in fetuses who developed acidemia, cardiac output fell significantly. In the present study, fetal metabolic acidemia was even more severe than in the study by Cohn et al. (10). Different methodology to measure fetal cardiac output could at least partially explain this discrepancy in the results. On the other hand, our results are in agreement with studies demonstrating stable ventricular cardiac outputs in sheep fetuses with metabolic acidemia and placental embolization (2) as well as increased placental vascular resistance caused by Angiotensin II (25). Furthermore, human fetuses with placental insufficiency and growth restriction have comparable weight-indexed cardiac outputs to control fetuses, while the proportion of cardiac output directed to the placenta is reduced, indicating enhanced recirculation of umbilical blood in the fetal body (27, 32, 36). In the present study, the weight-indexed placental volume blood flow and vascular resistance, and UA PI values did not change statistically significantly during hypoxemia. For calculation of placental vascular resistance, we could only include those fetuses with descending aorta blood pressure, because the carotid artery blood pressure response to hypoxemia was different. Under hypoxemia, the AoI Net Flow-ratio and descending aorta blood pressures correlated positively with the weight-indexed placental blood flow. Our findings are in agreement with earlier studies demonstrating the relationship between aortic isthmus hemodynamics and placental volume blood flow (14), as well

as unchanged UA PI values during hypoxemia (31). The strong positive correlations between descending aorta blood pressures and placental volume blood flow demonstrate the importance of perfusion pressure in the maintenance of placental volume blood flow, because the umbilicoplacental circulation has no significant autoregulative capacity (5).

We found an increase in the pulsatility of IVC blood flow velocity waveform during prolonged hypoxemia, the most likely explanation being augmented atrial contraction, because fetal systemic venous pressure did not increase during hypoxemia (19). On the other hand, DV PIV values did not change significantly during the experiment. Fetal oxygen tension is known to be an important regulator of DV tonus and caliber; fetal hypoxemia dilates DV to increase the DV blood flow shunting from the placenta (28). Therefore, these hypoxemia-related changes in the DV hemodynamics could mask the effect of augmented atrial contraction.

During prolonged hypoxemia, descending aorta pH and base excess values were significantly lower, and lactate levels higher than in the carotid artery. Since blood gas values in the carotid artery represent the blood that is mainly coming from the placenta, and descending aorta blood gas values represent the blood coming from the IVC and SVC, the differences we observed demonstrate the ability of intact placenta to remove lactate from the fetal circulation and also the physiologic importance of the fetal shunts, mainly DV and foramen ovale, to provide blood from the placenta to critical fetal organs.

Even though we did not directly measure the cerebral volume blood flow, we can estimate that it increased during hypoxemia because of unchanged left ventricular output and increased retrograde aortic isthmus flow during diastole. In addition, Fouron et al. (14) demonstrated a slight increase in the carotid artery volume blood flow during umbilical venous constriction, even though left ventricular output decreased significantly. In near term fetal sheep, it has been estimated that about 2.6% of the combined cardiac output is directed to the brain, while SVC blood return represents

about 25% of the combined cardiac output (38). We can roughly estimate that in fetal sheep SVC volume blood flow equals the volume blood flow in the brachiocephalic artery. The brachiocephalic artery is a single blood vessel arising from the aortic arch supplying the upper body and brain. Therefore, by redirecting blood flow from the upper body towards the brain by means of peripheral vasoconstriction and cerebral vasodilatation, fetus could markedly increase brain blood flow without any change in the volume blood flow of the brachiocephalic artery.

Our findings are clinically important. The hypoxemia induced fetal chemoreflex activation led to a reduction in the perfusion pressure of the cerebral circulation. It has been shown that neuronal damage is more associated with hypotension than the degree of hypoxia in near-term fetal sheep (17). However, hypoxemia related alterations in the fetal central hemodynamics or LVCO were not associated with the reduction in the perfusion pressure of the brain which, therefore, most likely reflected decreased cerebrovascular resistance. On the other hand, our results are in agreement with previous studies demonstrating that non-invasive Doppler ultrasound could be used to identify hypoxemic fetuses at near term gestation by monitoring fetal branch pulmonary artery and aortic isthmus hemodynamics.

This study has some limitations. The surgery could cause a significant stress to the fetus. However, the postoperative period should be long enough for the recovery of fetal myocardial function and circulatory physiology (12). Furthermore, fetal blood gas values and blood pressures were within the normal physiological range at baseline indicating sufficient recovery (12). The experiments were performed under general anaesthesia that could influence fetal cardiovascular responses to hypoxemia. However, studies have shown that at reasonable anesthetic depth, and without myocardial or peripheral cardiovascular disease, the newborn lamb can coordinate neural, endocrine, and local tissue responses to increase cardiovascular performance in response to hypoxemia (9). In an ideal study design, both carotid artery and descending aorta blood pressures would have been measured simultaneously from the same fetus. This approach would have

significantly increased the risk for fetal loss due to more extensive instrumentation. Validation studies in fetal sheep have shown that invasive and Doppler echocardiographic volume blood flow calculations correlate well (39). The intraobserver variabilities of Doppler ultrasonographic parameters of fetal sheep cardiovascular hemodynamics are comparable to those found in human fetuses during the second half of pregnancy (6, 34).

We conclude that hypoxemia increased descending aorta blood pressures and decreased carotid artery blood pressures, indicating the activation of the fetal chemoreflex. During hypoxemia, descending aorta pH decreased, and lactate values increased more than the corresponding values in the carotid artery, demonstrating the importance of fetal circulatory shunts, i.e., ductus venosus and foramen ovale, to protect the brain. Hypoxemia induced vasoconstriction in the fetal pulmonary circulation and decreased the AoI Net Flow-ratio. However, fetal weight-indexed LVCO or AoI Net Flow-ratio did not correlate with carotid artery blood pressures, suggesting that these parameters do not reflect the cerebral perfusion pressure.

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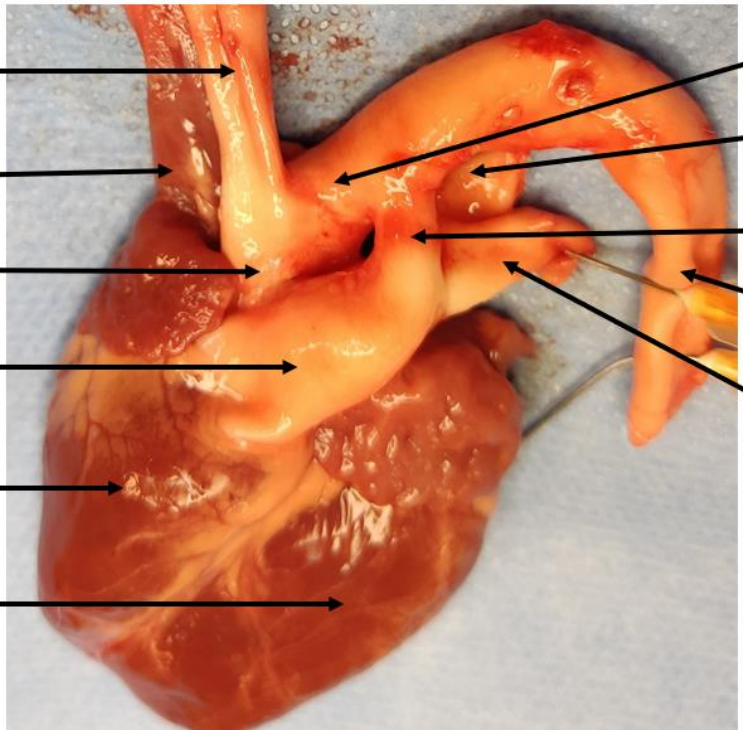
Figure legends:

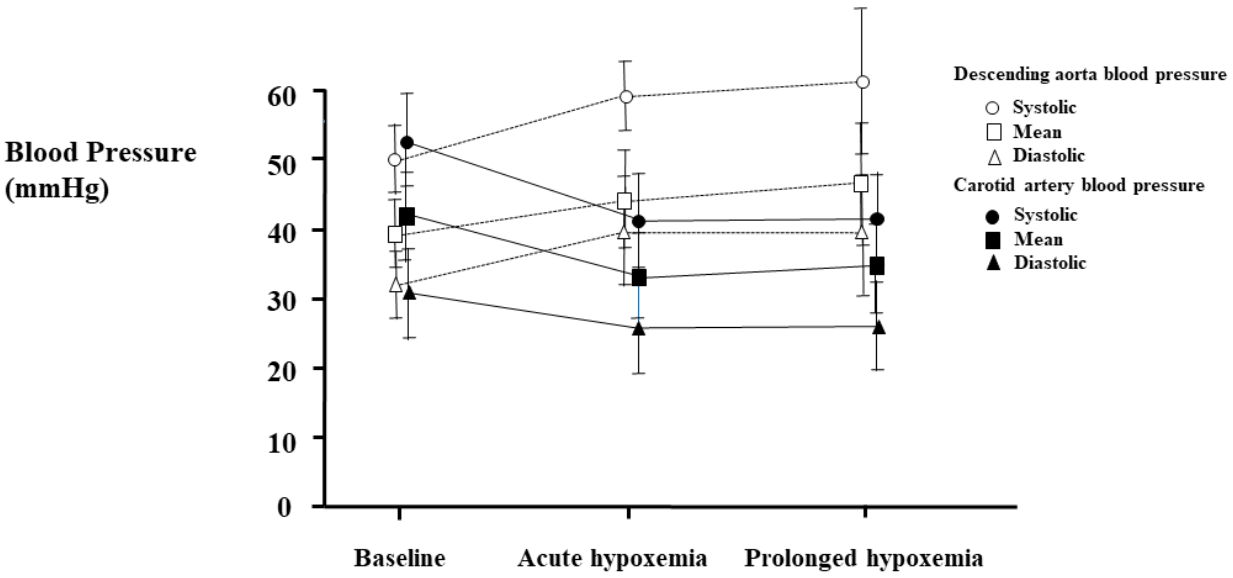
Figure 1. Anatomy of fetal sheep heart and central blood vessels.

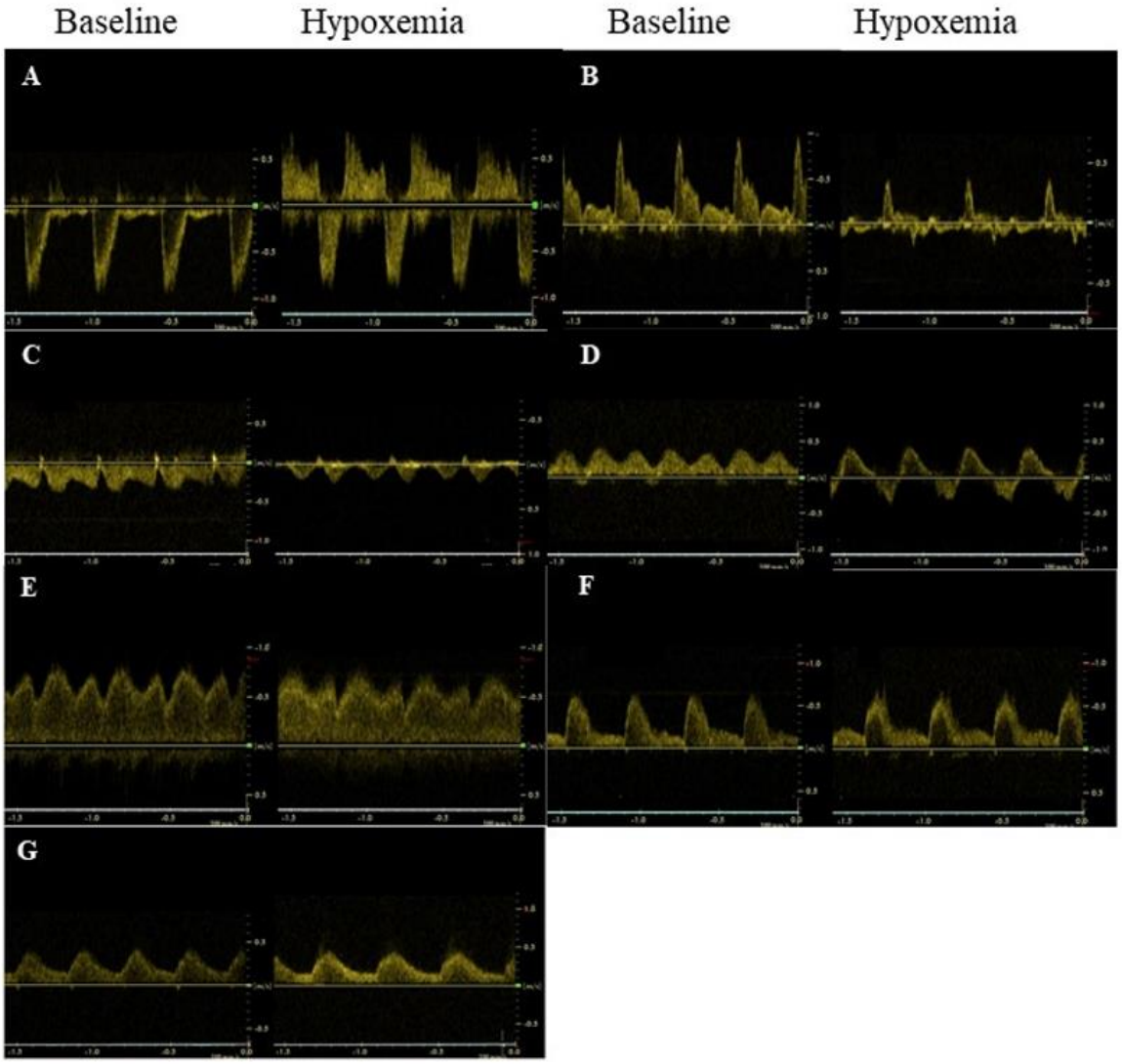
Figure 2. Fetal systolic, mean, and diastolic blood pressures in the carotid artery (n=10) and the descending aorta (n=7) during the experiment. Symbols represent mean values and vertical bars represent one standard deviation.

Figure 3. Blood flow velocity waveforms of A) aortic isthmus, B) right pulmonary artery, C) pulmonary vein, D) inferior vena cava, E) ductus venosus, F) descending aorta and G) umbilical artery at baseline and during hypoxemia.

Figure 4. Correlations between a) weight-indexed left ventricular cardiac output (LVCO) and right pulmonary artery pulsatility index (RPA PI) values at baseline, and b) descending aorta mean arterial pressure (MAP) and weight-indexed placental volume blood flow (Qplac / kg) during prolonged hypoxemia.


Brachiocephalic artery
Superior vena cava
Ascending aorta
Main pulmonary artery
Right ventricle
Left ventricle
Aortic isthmus
Right pulmonary artery
Ductus arteriosus
Descending aorta
Left pulmonary artery


Blood Pressure (mmHg)
60
50
40
30
20
10
0
Baseline
Acute hypoxemia
Prolonged hypoxemia
Descending aorta blood pressure
Systolic
Mean
Diastolic
Carotid artery blood pressure
Systolic
Mean
Diastolic


Baseline
Hypoxemia
Baseline
Hypoxemia
A
B
C
D
E
F
G

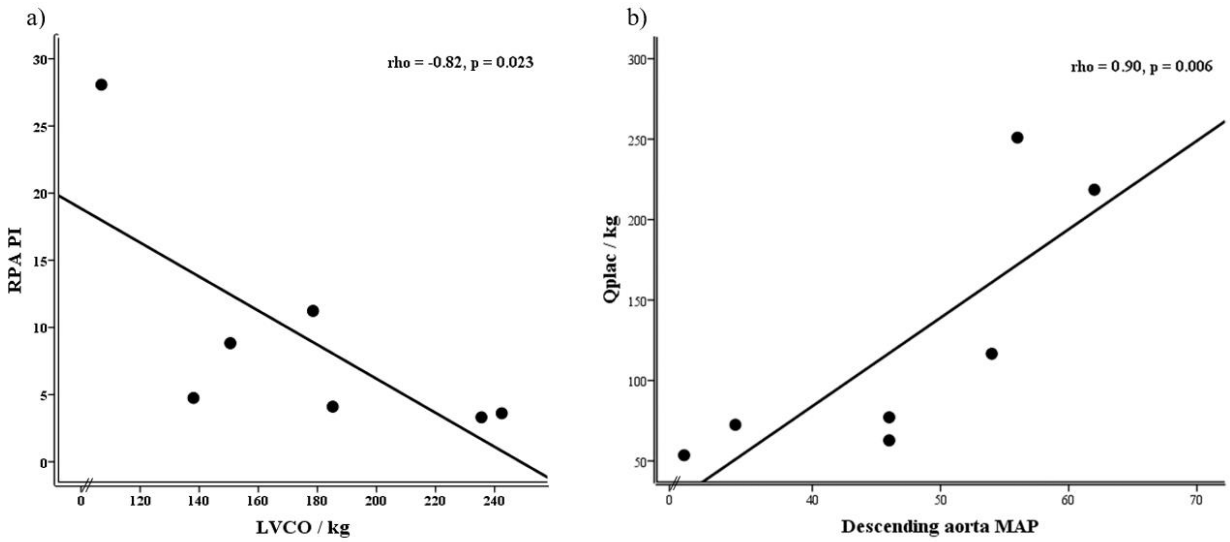

a)
rho = -0.82, p = 0.023
RPA PI
LVCO / kg
b)
rho = 0.90, p = 0.006
Qplac / kg
Descending aorta MAP

Table 1. Maternal arterial blood gas values and lactate concentrations during the experiment (combined data from both groups; n=17).

	Baseline	**Acute hypoxemia**	**Prolonged hypoxemia**	**p-value between different timepoints:**	
				Baseline vs. acute hypoxemia	**Baseline vs. prolonged hypoxemia**
pH	7.38 (0.07)	7.3 (0.07)	7.40 (0.06)	0.51	0.04
pCO_2 (kPa) (mmHg)	5.21 (0.75) 39.08 (5.63)	4.83 (0.44) 36.23 (3.30)	4.65 (0.41) 34.88 (3.08)	**0.013**	**<0.001**
pO_2 (kPa) (mmHg)	20.11 (7.17) 150.84 (53.78)	6.23 (0.93) 46.73 (6.98)	5.66 (1.13) 42.45 (8.48)	**< 0.001**	**<0.001**
Base excess (mmol/l)	-2.4 (2.9)	-3.3 (3.6)	-3.4 (3.2)	0.057	**0.023**
Lactate (mmol/l)	0.48 (0.18)	0.65 (0.29)	0.93 (0.45)	0.27	**0.005**

Abbreviations: pCO_2= partial pressure of carbon dioxide, pO_2= partial pressure of oxygen,

kPa= kilo Pascal, mmHg = millimeters of Mercury, mmol/l= millimole per litre, Values are means with SD in parentheses.

Table 2. Fetal arterial blood gas values and lactate concentrations during the experiment in the carotid artery (n=10) and descending aorta groups (n=7).

	Group	Baseline	Acute hypoxemia	Prolonged hypoxemia	p-value between different timepoints:		
					Baseline vs. acute hypoxemia	Baseline vs. prolonged hypoxemia	Acute vs. prolonged hypoxemia
pH	**Carotid artery**	7.31 (0.05)	7.30 (0.04)	7.24 (0.09)	0.49	**0.005**	**0.021**
	Descending aorta	7.33 (0.07)	7.29 (0.06)	7.14 (0.12)	0.12	**<0.001**	**<0.001**
	Difference between groups	0.02, 95% CI (-0.09, 0.06), p = 0.63	0.01, 95% CI (-0.06, 0.08), p = 0.82	0.10, 95% CI (0.02, 0.17), **p = 0.012**			
pCO_2 (kPa) (mmHg)	**Carotid artery**	6.66 (1.06) 49.95 (7.95)	6.75 (0.44) 50.32 (3.30)	6.84 (0.85) 51.30 (6.38)	0.73	0.51	0.75
	Descending aorta	7.24 (0.67) 54.30 (5.03)	7.62 (1.08) 57.16 (8.10)	7.52 (0.97) 56.41 (7.28)	0.16	0.29	0.69
	Difference between groups (kPa)	0.59, 95% CI (-0.29, 1.46), p = 0.18	0.87, 95% CI (-1.74, 0.00), p = 0.051	0.68, 95% CI (-1.55, 0.20), p = 0.12			
pO_2 (kPa) (mmHg)	**Carotid artery**	2.73 (0.35) 20.48 (2.63)	1.65 (0.29) 12.38 (2.18)	1.61 (0.36) 12.08 (2.70)	**<0.001**	**<0.001**	0.75
	Descending aorta	2.87 (0.46) 21.53 (3.45)	1.49 (0.48) 11.18 (3.6)	1.51 (0.37) 11.33 (2.78)	**<0.001**	**<0.001**	0.90
	Difference between groups (kPa)	0.14, 95% CI (-0.52, 0.24), p = 0.45	0.16, 95% CI (-0.21, 0.54), p = 0.39	0.10, 95% CI (-0.28, 0.47), p = 0.61			
Base excess (mmol/l)	**Carotid artery**	-1.2 (2.5)	-1.7 (2.6)	-5.7 (4.0)	0.69	**0.002**	**0.004**
	Descending aorta	1.6 (2.9)	0.6 (3.4)	-9.6 (5.0)	0.49	**<0.001**	**<0.001**
	Difference between groups	2.8, 95% CI (-0.7, 6.2), p = 0.11	2.8, 95% CI (-5.7, 1.2), p = 0.19	3.9, 95% CI (0.5, 7.3), **p = 0.028**			
Lactate (mmol/l)	**Carotid artery**	1.63 (0.63)	3.68 (1.68)	6.98 (3.39)	**0.022**	**<0.001**	**<0.001**
	Descending aorta	1.44 (0.63)	3.62 (2.57)	11.39 (2.44)	**0.038**	**<0.001**	**<0.001**
	Difference between groups	0.19, 95% CI (-1.97, 2.35), p = 0.86	0.05, 95% CI (-2.10, 2.21), p = 0.96	4.40, 95% CI (2.45, 6.56), **p <0.001**			

Abbreviations: pCO_2= partial pressure of carbon dioxide, pO_2= partial pressure of oxygen, kPa = kilo Pascal, mmHg = millimeters of Mercury, mmol/l=-millimole per litre, CI = confidence interval. Values are means with SD in parentheses.

Table 3. Fetal cardiovascular and placental hemodynamics, and central venous pressure (combined data from both groups; n=17, unless otherwise stated).

	Baseline	**Acute hypoxemia**	**Prolonged hypoxemia**	**p-values between different timepoints:**		
				Baseline vs. acute hypoxemia	**Baseline vs. prolonged hypoxemia**	**Acute vs. prolonged hypoxemia**
FHR (bpm)	172 (28)	181 (30)	183 (40)	0.16	**0.035**	0.45
LVCO (ml/min/kg)	226 (85)	207 (54)	222 (58)	0.23	0.88	0.29
RVCO (ml/min/kg)	300 (62)	290 (95)	300 (86)	0.48	0.86	0.59
CCO (ml/min/kg)	526 (131)	497 (119)	522 (121)	0.21	0.82	0.30
Q_{plac} (ml/min/kg)	99 (25)	84 (44)	83(46)	0.20	0.10	0.71
R_{plac} (mmHg/ml/ min/kg) (n=7)	0.35 (0.07)	0.39 (0.15)	0.48 (0.18)	0.57	0.067	0.18
CVP (mmHg) (n=10)	5 (4)	4 (3)	4 (4)	0.21	0.18	0.72

Abbreviations: FHR= fetal heart rate, LVCO= left ventricular cardiac output, RVCO= right ventricular cardiac output, CCO= combined cardiac output, Q_{plac}= placental volume blood flow, R_{plac}= placental vascular resistance, CVP= central venous pressure, bpm = beats per minute. Values are means with SD in parentheses.

Table 4. Fetal peripheral hemodynamics (combined data from both groups; n=17).

	Baseline	Acute hypoxemia	Prolonged hypoxemia	p-values between different timepoints:		
				Baseline vs. acute hypoxemia	Baseline vs. prolonged hypoxemia	Acute vs. prolonged hypoxemia
RPA PI	8.12 (5.13)	89.80 (133.16)	101.74 (84.32)	**0.013**	**0.004**	0.66
DA PI	1.85 (0.58)	1.74 (0.29)	1.97 (0.59)	0.27	0.47	0.087
UA PI	1.14 (0.22)	1.21 (0.35)	1.35 (0.59)	0.70	0.095	0.19
DAo PI	1.65 (0.23)	1.71 (0.26)	1.76 (0.36)	0.63	0.29	0.58
Pulmvein PIV	3.44 (3.76)	23.57 (17.26)	34.95 (49.10)	0.057	**0.011**	0.45
DV PIV	0.71 (0.23)	0.64 (0.24)	0.66 (0.23)	0.12	0.24	0.68
IVC PIV	1.74 (0.78)	2.44 (1.96)	3.26 (3.36)	0.19	**0.011**	0.18
AoI Net Flow-ratio	7.4 (9.8)	1.4 (0.7)	1.5 (1.7)	**0.007**	**0.008**	0.92

Abbreviations: RPA= right pulmonary artery, DA= ductus arteriosus, UA= umbilical artery, DAo= descending aorta, Pulmvein= pulmonary vein, DV= ductus venosus, IVC= inferior vena cava, PI= pulsatility index, PIV = pulsatility index for vein, AoI= aortic isthmus. Values are means with SD in parentheses.

Peripheral chemoreflex activation and cardiac function during hypoxemia in near term fetal sheep without placental compromise

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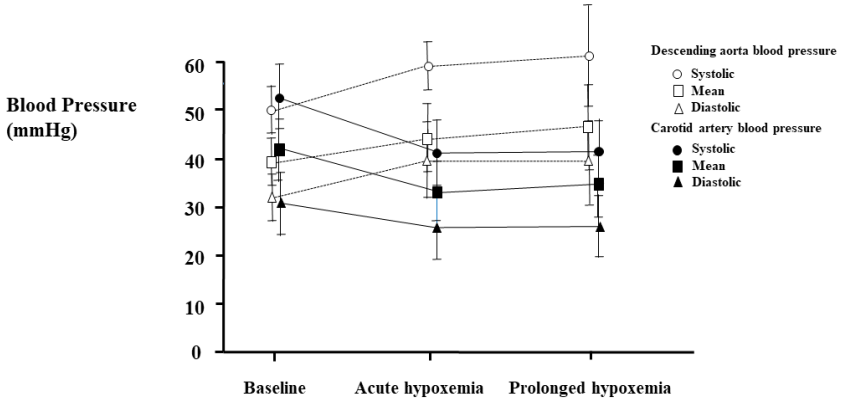
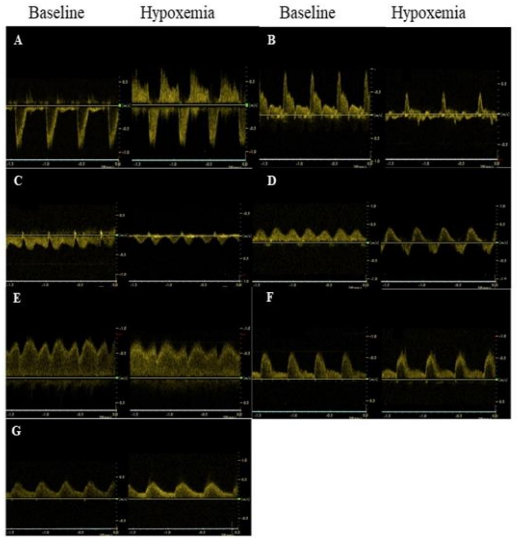
A drop in arterial oxygen content activates fetal chemoreflex including an increase in sympathetic activity leading to peripheral vasoconstriction and redistribution of blood flow to protect the brain, myocardium, and adrenal glands.

By using a chronically instrumented fetal sheep model with intact placental circulation at near-term gestation, we investigated the relationship between peripheral chemoreflex activation induced by hypoxemia and central hemodynamics. A total of 17 Åland landrace sheep fetuses at 115-128/145 gestational days were instrumented. Carotid artery was catheterised in 10 fetuses and descending aorta in 7 fetuses. After a 4-day recovery, baseline measurements of fetal arterial blood pressures, blood gas values, and fetal cardiovascular hemodynamics by pulsed Doppler ultrasonography were obtained under isoflurane-anesthesia. Comparable data to baseline was collected 10 (acute hypoxemia) and 60 minutes (prolonged hypoxemia) after maternal hypo-oxygenation to saturation level of 70-80% was achieved.



Fetal systolic, mean, and diastolic blood pressures in the carotid artery (n=10) and the descending aorta (n=7) during the experiment. Symbols represent mean values and vertical bars represent one standard deviation.

During prolonged hypoxemia, pH and base excess (BE) were lower, and lactate levels higher in the descending aorta than in the carotid artery. During hypoxemia mean arterial blood pressure (MAP) in the descending aorta increased, while in the carotid artery MAP decreased. In addition, right pulmonary artery pulsatility index values increased, and the diastolic component in the aortic isthmus blood flow velocity waveform became more retrograde thus decreasing the aortic isthmus antegrade/retrograde blood flow (AoI Net Flow) ratio. Both fetal ventricular cardiac outputs were maintained even during prolonged hypoxemia when significant fetal metabolic acidemia developed.



Blood flow velocity waveforms of A) aortic isthmus, B) right pulmonary artery, C) pulmonary vein, D) inferior vena cava, E) ductus venosus, F) descending aorta and G) umbilical artery at baseline and during hypoxemia.

Fetal chemoreflex activation induced by hypoxemia decreased the perfusion pressure in the cerebral circulation. Fetal weight-indexed LVCO or AoI Net Flow-ratio did not correlate with a drop in carotid artery blood pressure.