Maternal and Fetal Catecholamine Responses to Acute Hypoxemia in Japanese Saanen Goats

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ABSTRACT. Our purposes were to investigate the effects of acute hypoxemia on maternal and fetal physiological and biochemical responses in Japanese Saanen goats and to compare these responses to those obtained in other species in the previous studies. Five pregnant Japanese Saanen goats at about 120 days of gestation were operated to make fetal chronic preparation models. After a minimum of 4 days of postoperation, hypoxemia was induced by having the ewe breathe a hypoxic gas mixture (10% O2, 3% CO2 in N2) for 30 min. Maternal PO2 decreased from 84 to 40 mmHg, and fetal PO2 decreased from 22 to 16 mmHg. Only the fetal pH was significantly decreased by hypoxemia. Maternal heart rate increased with increases in arterial pressures. On the other hand, fetal heart rate showed Bradycardia with a transient increase in blood pressure. During hypoxemia, maternal catecholamines minimally increased, while fetal plasma concentrations of epinephrine and norepinephrine were significantly increased. These changes in Japanese Saanen goats were first revealed by the current study and were compatible with the previous reports with sheep and monkeys. These observations suggest that the Japanese Saanen goats may be an adequate animal model for investigation of fetal physiology. — Key words: cardiovascular response, catecholamine, goat (Japanese Saanen), hypoxemia.


Fetal hypoxemia has been one of the most challenging fields in modern obstetrics during the past three decades. Several means to detect fetal hypoxemia have been advocated. Fetal heart rate monitoring is one of the most widely used means [3, 6]. Clinically, the persistent late decelerations in fetal heart rate are known to be well correlated with fetal hypoxemia. However, the pathophysiology and the mechanisms for the fetal heart rate decelerations induced by hypoxemia is not fully understood. Several investigators showed that fetal reflexes account for the decelerations observed in the acute phase of hypoxemia [8]. Some investigators reported that fetal catecholamines play important roles in these phenomena [5]. However, these studies were performed mainly on sheep or monkeys.

In Japan, the Japanese Saanen goats are the most popular species and currently have been widely used as a fetal experimentation model. Unfortunately, little is known about maternal and fetal responses to acute hypoxemia in this species. Thus, in the present study, we used the Japanese Saanen goats to observe the effects of acute hypoxemia on maternal-fetal responses. The degree of hypoxemia is arbitrarily chosen to cause the fetal heart rate decelerations, during which we also measured maternal and fetal plasma concentrations of catecholamines.

MATERIALS AND METHODS

Animal preparation: All animals used in the current study were cared for in accordance with the principles outlined in the “Guide for the Care and Use of Experimental Animals” of the Animal Ethical Committee, Faculty of Agriculture, Kagoshima University.

Five Japanese Saanen goats at 120 days of gestation (term 147 days) were used. Under spinal anesthesia (2% solution of mepivacaine hydrochloride, 0.15 ml/kg) with an intravenous administration of ketamine hydrochloride (1 mg/kg), a fetal chronic preparation model was established. A polyethylene catheter (outer diameter=0.6 mm, PE60, Intramedic, Clay Adams, U.S.A) was placed into the fetal carotid artery, jugular vein, femoral artery and vein, trachea, and the amniotic cavity. An electrode (TL10M2-D70-EE, Data Sciences International, U.S.A) was placed on the fetal chest to record electrocardiograms (ECG) for fetal heart rate (FHR). A polyethylene catheter (outer diameter=0.9 mm, PE90) was inserted into both the maternal femoral artery and vein. These catheters were exteriorized through the maternal flank. A 3.5 Fr. endotracheal tube (Malincred, Ireland) was inserted to the maternal trachea through a tracheotomy, which was subcutaneously secured to the neck.

Fetal and maternal blood pressure (BP), fetal tracheal pressure (TP), and intrauterine pressures were measured by pressure transducers (Gould Statham P23Db, Oxnard, U.S.A) and recorded on a polygraph (Sanel, Japan). Fetal BP and TP were referenced to the intrauterine pressure. FHR was determined by measuring R-R intervals obtained from ECG and recorded simultaneously on the polygraph.

Experimental protocol: All the experiments were performed at least 4 days after surgery, when maternal and fetal physiologic conditions were assumed normalized from the surgical stress. Fetal and maternal parameters were observed for 30 min as controls. Acute hypoxemia was induced by having the ewe spontaneously breathe a mixture...
of 10% O₂, 3% CO₂ in N₂ at 40 l/min for 30 min. For this purpose, a transparent polyethylene bag was placed over the maternal head, and loosely fixed around the neck. A wait of at least 48 hr were allowed for recovery prior to the next experiment.

Fetal blood was sampled from the carotid artery. Maternal blood was sampled from the femoral artery. Fetal and maternal blood for blood gas determination was obtained 10 min prior to the experiment, at 5 and 25 min during hypoxemia, and at 60 min after the experiments. These blood specimens were immediately measured by a blood gas analyzer (AVL, Copenhagen).

**Catecholamine measurements:** Fetal and maternal blood was sampled with EDTA before, at 5 and 25 min during, and after the experiments. These samples were immediately centrifuged at 3,000 rpm for 15 min at 4°C, and the plasma was stored at -20°C until assayed. Epinephrine (E), norepinephrine (NE), and dopamine (DOA) were measured by HPLC (Hitachi-HPLC 635A). Inter and Intra-assay correlation coefficients were between 5 and 10%.

**Statistics:** All data are expressed as the mean ± SE. One way analysis of variance with paired t-test was applied for statistical analyses and p values of less than 5% were considered to be significant.

**RESULTS**

Eleven experiments in 5 animals were performed. All animals recovered from the hypoxemic experiments.  

**Blood gas changes during hypoxemia:** Maternal and fetal blood gases and pH values are shown in Fig. 1. Fetal pH values were significantly decreased by hypoxemia, while maternal pH values did not show statistical significance during hypoxemia. Fetal and maternal PO₂ were significantly decreased from 22.1 ± 0.7 mmHg to 16.2 ± 0.46 mmHg and from 83.5 ± 4.6 mmHg to 39.9 ± 1.2 mmHg, respectively. PCO₂ values of maternal and fetal blood did not change significantly during hypoxemia.

**Maternal cardiovascular changes:** Maternal cardiovascular changes during hypoxemia are depicted in Fig. 2. Maternal heart rate increased significantly during hypoxemia from 115 bpm to 140 bpm. Maternal blood pressure (both systolic and diastolic pressures) also increased during hypoxemia. These changes returned to the pre-hypoxic levels by 90 min after cessation of the experiments.

**Fetal cardiovascular changes:** Fetal cardiovascular changes during hypoxemia are also depicted in Fig. 2. Fetal heart rate significantly decreased from 190 bpm to 174 bpm.

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**Fig. 1.** Maternal and fetal blood gas changes in hypoxemic experiments. Each point represents the mean ± SE (N=10). * Significantly different from control (p<0.05).
at 5 min of hypoxemia. This deceleration was transient and lasted for 10 min. Thereafter fetal heart rate gradually increased during the period of hypoxemia. Fetal systolic blood pressure was significantly increased at 5 min of hypoxemia. This hypertension lasted throughout the hypoxicemic 30 min, but showed significance only at 5 min. Fetal diastolic blood pressure did not change during hypoxemia.

**Catecholamine response:** Maternal catecholamine changes during hypoxemia are shown in Fig. 3. The hypoxicemic stress used in the present study did not cause significant changes in maternal plasma catecholamine levels. Fetal catecholamine changes are also shown in Fig. 3. Epinephrine concentrations were significantly increased from 0.012 ± 0.003 ng/ml to 0.035 ± 0.011 ng/ml at 5 min of hypoxemia, and to 0.032 ± 0.010 ng/ml at 25 min of hypoxemia. Similarly, norepinephrine concentrations were significantly increased from 0.332 ± 0.087 ng/ml to 0.769 ± 0.146 ng/ml at 5 min of hypoxemia, and to 0.815 ± 0.127 ng/ml at 25 min of hypoxemia. However, dopamine concentrations did not significantly increase during hypoxemia.

**DISCUSSION**

The present study has shown that, in Japanese Saanen goats, fetal physiological and biochemical responses to acute hypoxemia are different from maternal responses in several respects. First, fetal heart rate decreases transiently while maternal heart rate increases throughout the hypoxicemic experiments. This response is accompanied by a transient increase in fetal systolic blood pressure, while maternal blood pressure stays elevated throughout the hypoxicemic period. Second, hypoxemia significantly increases fetal plasma concentrations of epinephrine and norepinephrine. In contrast, maternal catecholamines showed only minimal changes during hypoxemia.

The fetal responses to acute and non-acidemic hypoxemia depend on fetal age. Walker et al. [10] reported that in sheep fetuses at between 109 and 120 days of gestation, fetal heart rate response to acute hypoxemia was insignificant, while fetuses more than 120 days of gestation bradycardia occurred. They also suggested that this age-dependent difference was due to the maturational changes in autonomic heart rate control balanced between sympathetic and parasympathetic activities. Therefore, the

![Maternal heart rate](image1)

![Fetal heart rate](image2)

![Maternal blood pressure](image3)

![Fetal blood pressure](image4)

Fig. 2. Changes in maternal and fetal heart rate and systolic and diastolic arterial blood pressures (SAP and DAP) in hypoxicemic experiments. Each point represents the mean ± SE (N=10). * Significantly different from control (p<0.05).
fetal responses to acute hypoxemia in different species should be calibrated for similar developmental stages. When comparing sheep and goats, experiments were performed at a similar gestational age as their term is identical (about 147 days). As comparing with other species, experiments with fetuses of 0.85 gestational maturity were selected.

The fetal heart rate deceleration induced by acute hypoxemia is mainly through reflex mechanisms. Martin et al. [8] have demonstrated that an acute decrease in fetal \( P_{O_2} \) stimulates the peripheral chemoreceptors, which causes parasympathetic activation as well as sympathetic excitation. The parasympathetic activation stimulates vagal tone to slow fetal heart rate. The sympathetic activation induces both alpha and beta adrenergic pathways. Alpha adrenergic pathway causes transient fetal hypertension, which is shown in Fig. 3, and stimulates fetal baroreceptors. This baroreflex also results in slowing of the heart rate. Beta adrenergic pathway directly increases fetal heart rate. Thus the fetal heart rate is controlled by the balances between parasympathetic and sympathetic tones. During the fetal life more than 0.8 gestation, parasympathetic tone is much higher than sympathetic tone [5]. Therefore, the fetus slows heart rates in response to hypoxemia.

Maternal and fetal responses in heart rate and blood pressure during acute hypoxemia in the present study are very similar to those reported previously in other species. For example, in sheep models, Boddy et al. [1] and Walker et al. [10] showed that fetuses responded to acute hypoxemia by slowing heart rates, while mothers responded by accelerating heart rates. Martin et al. [8], Murata et al. [9], and Ikenoue et al. [4] also showed that heart rate of the monkey fetuses decreased when exposed to an acute decline in \( P_{O_2} \). In the clinical cases of human fetuses also showed fetal heart rate decelerations in response to acute hypoxemia [3]. Thus, the goat fetuses appear to be an adequate animal model for studying maternal and fetal biological changes during hypoxemia.

Maternal and fetal endocrine responses to acute hypoxemia have been reported mainly with sheep and monkey models. Lewis and Sischo [7] showed that sheep fetal plasma concentrations of epinephrine and norepinephine at rest are 0.02 ng/ml and 0.25 ng/ml, respectively. These values are roughly compatible with the present data on Japanese Saanen goats. In human fetuses, it has been described that epinephrine and norepinephrine concentrations average 0.05 ng/ml and 0.20 ng/ml, respectively. These results, again, are consistent with our present results in Japanese Saanen goats.
Jones and Robinson [5] showed that fetal endocrine responses to acute hypoxemia are much greater than those of maternal responses in sheep. In their experiments, fetal epinephrine and norepinephrine always rose, while in the mother, there were no consistent changes in catecholamines. Cohn et al. [2] investigated hypoxic influences on fetal catecholamines in rhesus monkeys, which revealed that both epinephrine and norepinephrine concentrations markedly increased during hypoxemia. Our results with Japanese Saanen goats are compatible with their results.

The present study is the first report that reveals that maternal and fetal responses in cardiovascular and endocrine systems to acute hypoxemia of the Japanese Saanen goats are compatible with those seen in the sheep and monkeys used extensively in previous studies. The current study will enable us to further utilize this model to investigate in the field of fetal physiology.

REFERENCES