The Effects of Xylazine on Intrauterine Pressure, Uterine Blood Flow, Maternal and Fetal Cardiovascular and Pulmonary Function in Pregnant Goats

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ABSTRACT. To investigate the effects of xylazine on pregnant goats, xylazine induced changes in heart rate (HR), arterial blood pressure (ABP) and arterial blood pH and gases in the mother and fetus, as well as changes in intrauterine pressure (IUP) and uterine blood flow (UBF), were studied using a chronic preparation model of pregnant goats. Intramuscular administration of xylazine (0.2 mg/kg b.w.) caused a marked decrease in HR and ABP of the mother, which remained significantly reduced up to 120 min. In the fetus, a significant decrease in HR and a significant increase in ABP were recorded after only 5 min. Significant decreases of maternal arterial blood pH and oxygen partial pressure (P_{O_2}) were observed up to 120 and 30 min after the injection, respectively. Fetal arterial blood pH and P_{O_2} also decreased, but these changes were milder and less persistent than those of the mother. Within 2 to 5 min after the administration of xylazine, IUP began to increase and remained high for about 15 min. Thereafter, there was a frequent periodic increase in IUP. After 5 min, UBF decreased significantly and remained low up to 120 min. A fall in UBF was associated with a rise in IUP. These findings suggested that administration of xylazine to pregnant goats results in a decrease in UBF arising from the induction of uterine contractions, a decrease in circulating blood volume, hypoxemia and acidosis in the mother. — KEY WORDS: pregnant goat, xylazine.


Xylazine is an $\alpha_2$-adrenoceptor agonist with analgesic and sedative effects. It is widely used in veterinary medicine, and for the preparation of experimental animal models [3, 13], as is also the case with detomidine and medetomidine. These drugs are used singly or in combination with anesthetic agents (i.e. injectable general anesthetics or inhalation anesthetics), and their inhibitory actions can be suppressed by administering a specific antagonist for each drug. Due to these characteristics, they have been used widely in veterinary medicine, however, they do have some side effects, of which the induction of uterine contraction is of particular concern. Knight [4] reported that xylazine may cause abortion in cattle during the later stages of pregnancy, because of its oxytocin-like uterine contraction inducing action, and advocated that its use must be avoided. Later, xylazine induced uterine contractions were confirmed by electromyography and observations using a catheter inserted into the uterus in cattle [7–9, 12], horses [9], sheep [3] and pigs [5]. Jansen et al. [3] studied the effects of xylazine induced uterine stimulation on pregnant animals and fetuses using a chronically catheterized pregnant goat model, and demonstrated that the administration of xylazine doubled the activity of the uterine muscle, caused respiratory arrest in the fetus, decreased arterial blood oxygen partial pressure (P_{O_2}) in both the mother and fetus, and decreased their heart rates (HR). The mechanism underlying these responses was postulated to be a decrease in the uterine blood flow (UBF) due to contraction of the uterus, however, there have been no detailed studies of the relationships between xylazine induced uterine contraction and UBF, or between the above changes and circulatory changes in both the mother and fetus.

In the present study, we attempted to elucidate if there was any correlation between the circulatory and metabolic changes induced by xylazine in the mother and fetus, and the uterine stimulatory action of xylazine. Using a chronic preparation model of pregnant goats, we analyzed xylazine induced changes in the HR, arterial blood pressure (ABP), arterial blood pH, arterial P_{O_2} and carbon dioxide partial pressure (P_{CO_2}), and base excess in both the mother and fetus, plus changes in the intrauterine pressure (IUP) and UBF in the mother.

MATERIALS AND METHODS

Experimental animals: The studies were carried out on six pregnant Japanese Saanen goats (mean 31 kg ± 5.4 SD in body weight), between 110 and 140 days of gestation. The animals were subjected to the experiments, after checking their clinical soundness by pre-operative examinations, including physical examination, clinical laboratory evaluation, radiograph of the thorax and abdomen, and echographic evaluation of the fetus.

The scheme for the chronic preparation model in the goats is shown in Fig. 1. The operation was divided into two steps to reduce the surgical stress. The first operation was performed on the mothers. 4.7F polyethylene catheters (PE160, Intramedic, Clay Adams, Parsippany, New Jersey, U.S.A.) were inserted into the femoral artery and vein, under local anesthesia. The goats were then kept without food or water for 24 to 48 hr before the second operation.

The second surgical procedure was performed under rachianesthesia with mepivacaine hydrochloride (3 mg/kg b.w.). An incision was made in the peritoneum, and a blood flow meter probe (type - FH020T, FC-040T, Nihon Kouden...
Co., Japan) with an inner diameter of 2–4 mm was mounted on the middle uterine artery. After this, the gravid uterus was exposed, and the fetal head was exteriorized through a small hysterotomy incision. 3.8F polyethylene catheters (PE90, Intramedic, Clay Adams, Parsippany, New Jersey, U.S.A.) were inserted into the fetal carotid artery and vein. Electrocardiogram (ECG) electrodes were attached to the three subcutaneous points of bilateral precordium and the dorsal cervix. A 4.7F polyethylene catheter (PE160, Intramedic, Clay Adams, Parsippany, New Jersey, U.S.A.) was placed in the amniotic cavity for measurements of IUP. The fetus was returned to the amniotic cavity and the uterine and peritoneal incisions were closed.

The animals were allowed to recover for at least 48 hr after surgery.

Measurements: The maternal HR, ABP, IUP and fetal ABP were measured continuously via the catheters, which were connected to previously calibrated, sterile pressure transducers (4–327–C, Bell & Howell, Loss Angeles, California, U.S.A.). The ECG electrodes were connected to a variability polygraph (VPR-01, Atom Co., Tokyo, Japan) to monitor the fetal HR. The flow probe was connected to an electromagnetic blood flow meter (MFV-1200, Nihon Kouden Co., Tokyo, Japan), which was then balanced. All the above data were recorded on a pensillograph (8K24–1–L, San-ei Co., Tokyo, Japan). The maternal and fetal arterial blood pH, Po2, and Pco2 were measured by a blood gas analyzer (AVL995, AVL Scientific Co., U.S.A.), and corrected for body temperature. The base excess was derived using standard formulae.

Experimental protocol: On the day of the experiment, the animal was allowed to sit quietly in her cage. Following the control period, xylazine was administered intramuscularly at a dose of 0.2 mg/kg b.w. Maternal and fetal cardiovascular measurements and arterial blood sampling were obtained immediately before the xylazine injection and at 5, 15, 30, 60, and 120 min after the xylazine injection. Based on the changes in IUP, a uterine contraction was defined as a rise in IUP sustained for more than 30 sec. The contraction duration of the uterus (CDU) per 10 min was calculated every 10 min up to 120 min after the injection of xylazine.

Statistics: The measurements immediately before the xylazine injection were used as control values. All values are expressed as the mean ± SD. The UBF is expressed as the percentage change from the control value. Statistical differences in the various parameters were analyzed by repeated measures ANOVA, and Schefé's method was used for simultaneous multiple comparisons. P<0.05 was considered significant.

RESULTS

Effects on maternal and fetal hemodynamics: The

![Diagram](image-url)
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maternal HR and ABP decreased after the injection of xylazine. The values after 120 min were still significantly lower than the control values (Fig. 2).

The fetal HR showed a significant decrease and ABP showed a significant increase only at 5 min after the injection. No significant differences were obtained from 15 to 120 min after the administration of xylazine (Fig. 2), although, throughout the experimental period, changes in these values tended to follow changes in IUP. A rise in IUP tended to be accompanied by a fall in fetal heart rate and a rise in fetal arterial blood pressure (Figs. 4-1 and 4-2).

Effects on maternal and fetal arterial blood pH and gases (Fig. 3): From 15 to 120 min after the intramuscular xylazine injection, the maternal arterial blood pH decreased significantly. The maternal Po2 decreased remarkably after the administration of xylazine, and the change was still significant after 30 min. The maternal Pco2 was significantly higher than the control value from 15 to 120 min after injection, but the maternal base excess showed no significant changes.

Intramuscular xylazine caused a significant decrease in fetal arterial blood pH and Po2, but the changes were milder than those of the mothers. The fetal base excess tended to decrease after the injection of xylazine, but the changes were not statistically significant.

Effects on intrauterine pressure: A rise in IUP, which started between 2 and 5 min and peaked at 12 to 13 min after the injection of xylazine, continued for 15 min (Fig. 4-1). The mean values of CDU (control values: 3.7 ± 0.71 min/10 min) showed significant changes 10 min after the injection (values after 10 min: 8.6 ± 0.58 min/10 min) (Fig. 5). These changes indicated the appearance of a persistent contraction in the uterus.

Following this persistent contraction, periodic contractions appeared frequently (Fig. 4-2), and the values of CDU after the injection tended to be higher than the

Fig. 2. Changes in maternal and fetal heart rate and arterial blood pressure after administration of xylazine (0.2 mg/kg b.w. i.m.) (mean ± SD, n=6). *: p<0.05, **: p<0.01, ***: p<0.001 compared with the control values.

Fig. 3. Changes in maternal and fetal arterial blood pH and gases after administration of xylazine (0.2 mg/kg b.w. i.m.) (mean ± SD, n=6). *: p<0.05, **: p<0.01, ***: p<0.001 compared with the control values.
control values (Fig. 5).

Effects on uterine arterial blood flow: UBF decreased most remarkably 5 min after the injection of xylazine (53 ± 6.3%). It tended to recover gradually, but was still significantly depressed after 60 min (79 ± 9.2%) (Fig. 5). Throughout the experimental period, a fall in UBF was associated with a rise in IUP (Figs. 4-1 and 4-2).

DISCUSSION

This study aimed to elucidate the correlations between the responses to xylazine in the circulatory and metabolic systems of both the mother and fetus, and xylazine induced uterine contractions in the mother.

Circulatory changes in the mother after the administration of xylazine, including marked decreases in HR and ABP,
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suggested a decrease in circulating blood volume. In the fetus, a decrease in HR and an increase in ABP were observed. These results agreed closely with those reported by Jansen et al. [3], although the decrease in maternal blood pressure was greater in our study.

After the administration of xylazine, maternal arterial blood pH and Po2 increased, and Pco2 decreased, but base excess showed no significant changes. These changes in maternal arterial blood pH and gases indicated respiratory acidosis and hypoxemia.

The fetal arterial blood pH and Po2 also decreased significantly. The fetal Pco2 and base excess showed no significant changes, but base excess tended to decrease. The decrease of fetal pH might predominantly represent metabolic acidosis, indicated by the change of the base excess.

Xylazine induced changes in the fetus were relatively mild and transient compared with those in the mother. This was also observed by Jansen et al. [3]. On the basis of this difference in the response of the mother and fetus, they suggested the existence of a compensatory mechanism at the placental level, which protects the fetus from the undesirable effects of xylazine [3].

IUP gradually increased within 2 to 5 min after the injection of xylazine and reached a peak at 12 to 13 min after its administration, when the value was doubled. This uterine contraction lasted about 15 min, and frequent

Fig. 4-2. Responses of fetal heart rate (FHR), fetal arterial blood pressure (FABP), maternal heart rate (MHR), maternal arterial blood pressure (MABP), intrauterine pressure (IUP) and uterine arterial blood flow (UBF) 60 min after administration of xylazine (0.2 mg/kg b.w. i.m.).

Fig. 5. Changes in contraction duration of uterus (CDU) and uterine blood flow (UBF) after administration of xylazine (0.2 mg/kg b.w. i.m.) (mean ± SD, n=6). *: p<0.05, ***,: p<0.001 compared with the control values.
contractions occurred periodically thereafter. This persistent stimulatory effect has been demonstrated to be due to the direct action of xylazine via \( \alpha_2 \)-receptors \([5, 6, 12]\). Rodriguez-Martinez et al. \([12]\) reported that IUP began to increase within one min after intravenous administration of xylazine at a dose of 0.02 mg/kg b.w. to cattle. The value was nearly doubled at the peak, and persisted for 15 to 20 min. Kündig et al. \([7]\) administered 10 mg/body of xylazine intravenously to cattle and observed an increased IUP for as long as 17 to 19 min. Compared with these results, the time to initiation of the increase in IUP, in our present study, tended to be delayed, and the duration of the increase tended to be somewhat shorter, although the peak value was almost the same. The differences in the time to onset and duration of the increase in IUP are surmised to be due to the difference in the administration route. In \textit{in vitro} experiments, xylazine induced contraction of the uterine muscle has been proven to be dose-dependent \([5, 6]\). It is readily apparent that various maternal and fetal factors are involved in the changes in intrauterine pressure. If we assume that the contraction of the uterine muscle is directly reflected by the intrauterine pressure, the concentration of xylazine acting on the uterine muscle is thought to be nearly the same as in the previous studies, because the peak IUP value observed in the present study was the same as that reported by other investigators \([7, 12]\), in spite of the fact that the dose and administration routes were different. Accordingly, it can be predicted that the increase in IUP resulting from an intravenous injection of 0.055 to 0.11 mg/ kg b.w., which is considered the clinically optimum intravenous dosage in cattle and goats \([11]\), would be more severe than that recorded in our present study. Subsequent to the persistent uterine contraction, the frequency of periodic uterine contractions increased. The mechanism behind this phenomenon has not been discussed in any of the earlier reports, however, in the report of Jansen et al., it is stated that more than 3 hr was required before uterine activity returned to predelivery levels \([3]\). It is surmised that xylazine itself or the xylazine induced persistent uterine contraction triggers activation of the process causing further periodic uterine contractions.

Administration of xylazine decreased UBF, and this change was negatively correlated with the change in IUP. In other words, UBF decreased when IUP increased. In pregnant guinea pigs, Weiner et al. \([14]\) confirmed, using a Doppler flow probe, that uterine arterial blood flow decreases under anesthesia with xylazine and ketamine. They surmised that at least one of these two drugs reduces UBF. However, Ford et al. \([1]\) and Isla and Dyer \([2]\) conducted \textit{in vitro} studies using pigs and sheep, respectively, and reported that both \( \alpha_1 \) and \( \alpha_2 \)-receptors were present in the uterine artery of the animals during the late stage of pregnancy, and that the action mediated by \( \alpha_1 \)-receptors was predominant, while the response mediated by \( \alpha_2 \)-receptor was not marked. In view of these findings and the fact that the decrease in UBF observed in the present study coincided with the increase in IUP, the decrease in UBF is thought to result more predominantly from the uterine contraction than the direct responses of xylazine via the \( \alpha \)-receptors.

There was a relationship between the response of the fetal circulatory system and the changes in IUP and UBF. That is, in synchronization with the increase in IUP, UBF and fetal HR decreased, while fetal ABP increased. This indicates a deceleration pattern of the fetal HR \([10]\), in which application of pressure to the fetal head due to uterine contraction causes an increase in fetal intracranial pressure, hypertension as a result of the response of the fetal vascular system, and a decrease in the fetal heart rate via vagal control. This fetal heart rate pattern indicates the occurrence of mild, transient hypoxia and an uterine contraction of a force close to that observed before delivery, although not harmful to the fetus.

In summary, our study indicated that the administration of xylazine to pregnant animals causes a decrease in the circulating blood volume, hypoxemia, respiratory acidosis, induction of uterine contraction and a resultant decrease in the uterine arterial blood flow. Because the effects on the fetus were slight, the existence of a mechanism by which the fetus is protected from external stresses is inferred. However, if this mechanism is damaged, the injection of xylazine may be dangerous to the fetus and lead to abortion.

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