Xylazine, an $\alpha_2$-adrenoceptor agonist, has been shown to produce an analgesic effect in ruminants such as cattle, sheep, and goats for surgical procedures. However, xylazine can cause depressed cardiorespiratory functions, decreased gastrointestinal motility, acute pulmonary edema, and delayed convalescence and promote the regurgitation and aspiration of ruminal contents if the airway is left unprotected. Balanced analgesia use, in which various drugs or techniques cooperate with each other to produce the best analgesic effect with the fewest complications, is now common practice. The combined use of xylazine and ketamine has been reported to provide analgesia in ruminants. However, studies have shown that this combination still influences the cardiac and respiratory functions, blood pressure, and body temperature, although the risk of regurgitation and aspiration is greatly reduced as a result of the reduction in the dose of each component.

Acupuncture is a therapeutic technique in Oriental medicine that can be traced back at least 2,500 years and is gaining popularity in the West as a therapeutic intervention for pain. Electroacupuncture is a modern version of traditional hand acupuncture and has been used successfully to ameliorate pain in various operations, such as cesarean section, gastrectomy, enterectomy, and castration, on ruminants in China during the 1970s. Findings of numerous studies indicate that EA has a good analgesic effect and optimal bidirectional regulatory effects (ie, upregulating the suppressed functions and downregulating the excessive excited functions) on circulation, respiration, digestion, and immune function. During EA, an animal’s indexes of physiologic functions, blood pressure, and body temperature were observed at 0, 5, 25, 45, 65, and 85 minutes after xylazine administration.

### Objective
To investigate physiologic effects of electroacupuncture (EA) combined with xylazine administration in goats.

### Animals
48 healthy crossbred goats.

### Procedures
Goats were randomly allotted to 8 groups of 3 (nonpregnant and nonlactating) female goats and 3 male goats each. The 8 treatment groups were as follows: 1 EA group, 3 xylazine (0.1, 0.2, and 0.4 mg/kg, IM) groups, 3 EA plus xylazine (0.1, 0.2, and 0.4 mg/kg, IM) groups, and 1 control group. Electroacupuncture was performed for 90 minutes. Xylazine was administered 20 minutes after EA was performed. Pain threshold, heart rate, mean arterial pressure (MAP), respiration rate, and rectal temperature were observed at 0, 5, 25, 45, 65, and 85 minutes after xylazine administration.

### Results
Xylazine administered at 0.4 mg/kg increased the pain threshold and reduced MAP. Xylazine administered at 0.1, 0.2, or 0.4 mg/kg reduced heart rate, respiration rate, and temperature. Electroacupuncture increased the pain threshold but had no effect on heart rate, MAP, respiratory rate, or rectal temperature. Pain threshold in goats that underwent EA plus xylazine administration was higher than in goats that received EA or xylazine alone. Electroacupuncture combined with xylazine at 0.1 mg/kg did not affect heart rate, MAP, respiratory rate, or rectal temperature. Pain threshold in goats that underwent EA plus xylazine administration at 0.1 mg/kg was higher than in goats given xylazine at 0.4 mg/kg alone.

### Conclusions and Clinical Relevance
Electroacupuncture combined with xylazine, even at 0.1 mg/kg, provided analgesia without significantly affecting cardiorespiratory parameters or rectal temperature in goats. (Am J Vet Res 2009;70:1326–1332)
condition remain stable during a surgical invention, and the postoperative recovery is accelerated.\textsuperscript{8,9} However, EA may cause insufficient suppression of somatic pain in some individuals.\textsuperscript{9} Although this challenging problem can be ameliorated by the selection of better points and an improved acupuncture technique, it may be the main hindrance to the widespread adoption of EA in veterinary clinical surgery.

In recent years, the combination of acupuncture with drug administration, referred to as acupuncture-drug balanced analgesia or acupuncture-assisted analgesia, has been successfully used in human surgical operations.\textsuperscript{15,16} This balanced analgesia has good analgesic effects as well as regulates multiple important organs, which can substantially neutralize some drug-induced adverse effects.\textsuperscript{17}

To our knowledge, the combination of EA plus xylazine administration is not currently used for analgesia in ruminants. However, whether EA and xylazine work synergistically or antagonistically in analgesia and whether their combination affects physiologic functions of ruminants positively or negatively remain to be investigated. The purpose of the study reported here was to determine the effects of the combined EA plus xylazine administration on pain threshold, cardiorespiratory functions, and body temperature.

**Materials and Methods**

**Animal preparation**—Experiments were performed on healthy 1- to 2-year-old crossbred goats that weighed 25 to 30 kg and were purchased from the HuBei Agricultural Academy of Science. Goats were randomly allotted into 8 groups (pens) of 3 (nonpregnant and nonlactating) female goats and 3 male goats each. Goats were maintained on rye grass diet and received a cereal-based concentrate. Water for drinking was made freely available. All goats were dewormed and accustomed to being approached. Feed was withheld for 24 hours before the start of the experiment. The experiment was performed in a quiet environment, and the ambient temperature fluctuated between 23° and 24°C. The experimental protocol was approved by the Animal Care Center, College of Veterinary Medicine, Huazhong Agricultural University (Wuhan, China).

**Experimental design**—The 8 treatment groups were as follows: 1 EA group, 3 xylazine (0.1, 0.2, and 0.4 mg/kg, IM) groups, 3 EA plus xylazine (0.1, 0.2, and 0.4 mg/kg, IM) groups, and 1 control group that involved goats that received sham EA treatments (needle-control group) or saline (0.9% NaCl) solution treatments (saline-control group). Goats in the saline-control group received only an IM injection of saline solution instead of xylazine. Goats in the needle-control group only underwent needle placement without electric stimulation.

This needle-control group was used as a control for EA treatment because the effect of needle placement on physical variables (such as pain threshold) was negligible, compared with EA or manual acupuncture (> 120 insertions/twisting/min).\textsuperscript{15,16} Only data from the needle-control group are reported in this study because no differences in physiologic variables (pain threshold, heart rate, MAP, respiratory rate, and rectal temperature) were found between goats in the 2 control groups.

In EA-treated goats, electric pulses were administered via stainless steel needles inserted through the skin into the deep tissues. In xylazine-treated goats, xylazine was given IM in the neck. In EA plus xylazine–treated goats, EA was performed 20 minutes before xylazine administration. This modality made the analgesic duration of EA and that of xylazine roughly overlap because the induction duration of the former ranges from 20 to 30 minutes and that of the later is approximately 10 minutes.\textsuperscript{8,9}

All of the goats were restrained in a left lateral recumbent position and allowed to be acclimatized for 20 minutes. In goats given xylazine alone, pain threshold, heart rate, MAP, respiratory rate, and rectal temperature were assessed before (0 minutes) and at 3, 25, 45, 65, and 85 minutes after xylazine administration. In contrast, these physiologic variables in goats that received EA alone or EA plus xylazine combined were measured before (0 minutes) and at 25, 45, 65, 85, and 105 minutes after EA was performed.

**Electroacupuncture**—A set of Bai hui (hundred meetings), San tai (3 platforms), Erh gen (car base), and San yan luo (3 Yang communication) points was selected for EA stimulation. The anatomic location of these points have been described in detail for use in veterinary medicine.\textsuperscript{19} The Bai hui point was identified on the dorsal midline between the spinous processes of the last lumbar and the first sacral vertebrae; a stainless steel acupuncture needle (0.3 mm in diameter and 10 cm in length) was perpendicularly inserted into the Bai hui point to a depth of approximately 3 cm. The San tai point was identified on the dorsal midline between the spinous processes of the fourth and fifth thoracic vertebrae; a needle was inserted in a cranioventral direction into the San tai point to a depth of approximately 4 to 5 cm. Erh gen points were identified bilaterally, with each at the pit ventrocaudal to the ear base between the ear base and the cranial border of the transverse process of the atlas on each side. The Erh gen point on the right side of the body was chosen in this study; a needle was inserted into the right Erh gen point and reached the subcutaneous tissue of the right temporal fossa. The San yan luo point was identified approximately 5 cm ventral to the lateral tuberosity of the radius in the groove between the common digital extensor and lateral digital extensor muscles of the right forelimb; a needle was inserted at approximately a 30° angle in a ventromedial direction into the San yan luo point and reached the subcutaneous tissue of the medial side of the forelimb.

The principle of disinfection was strictly observed for needle insertion. Inserted needles at Bai hui and San tai points were connected to a single output of a multifunctional electric pulse generator,\textsuperscript{20} and needles at Erh gen and San yan luo points were connected to the other output of the generator. The EA frequency was held at 36 Hz. The intensity was slowly increased until it reached a level at which a mild twitch of the muscles adjacent to the points was observed, and then the intensity was decreased until the muscle twitch was not observed. This intensity (approx 3 V) was held constant.
Physiologic variables—The pain threshold was measured on the center of the right flank by use of potassium iontophoresis. Pain was induced by potassium iontophoresis through gradual increases in potassium ions passing through the skin, which were positively proportional to the increase in voltage and current. The pain threshold was estimated from the voltage and current application that resulted in mild contraction of the local skin and muscle. The stimulation of potassium iontophoresis was different from that of EA. During potassium iontophoresis, potassium ions (an effective pain stimulus) were delivered into the skin by direct electric current, which stimulated sensory nerve endings and gave rise to muscle and skin contraction through a nerve reflex. During EA, an electric pulse (approx 3 V) acted directly on the muscle and caused the muscle to twitch at the set rate of the stimulator.

The site to measure pain threshold was shaved, cleaned with soap and water, and sterilized with 75% ethyl alcohol. Two electrodes soaked with saturated potassium chloride were placed 1 to 2 cm apart on the skin in position. A modified peripheral nerve stimulator was used to deliver pulsed direct current to the electrodes. The voltage was increased stepwise. Obvious contraction of the local skin and muscle was taken as the endpoint; the current was then terminated, and the volt level was recorded. Voltages before and during the experiment were expressed as Vo and Vn, respectively. Percentage change in the pain threshold during the experiment was calculated as follows:

\[
\Delta \% = \left( \frac{V_n - V_o}{V_o} \right) \times 100\%
\]

Blood pressure was measured by use of a digital sphygmomanometer with a narrow cuff (6 cm width) that was placed on the femoral artery at the medial aspect of the thigh of the left hind limb proximal to the abdominal inguinal groove. Diastolic and systolic pressures (mm Hg) displayed on the sphygmomanometer were recorded. The MAP was calculated as follows:

\[
\text{MAP (mm Hg)} = \text{diastolic pressure} + \frac{1}{3} \times \text{systolic pressure} - \text{diastolic pressure}
\]

Heart rate (beats/min), respiratory rate (breaths/min), and rectal temperature (°C) were monitored by use of a multiparameter monitor.

Statistical analysis—Factors affecting variation in the data included EA and xylazine. Pain threshold data were analyzed with a general linear model to evaluate the interactions and main effects. Physiologic variables, including the pain threshold, heart rate, MAP, respiratory rate, and rectal temperature, were used for a 2-way ANOVA followed by the Bonferroni post hoc test. Values of P ≤ 0.05 were considered significant. Analysis was performed with a commercially available software program.

Results

Analgesic effects of EA and xylazine administration in goats—The analgesic effects of EA and xylazine were expressed on the basis of the pain threshold. A 2 × 4 repeated-measures ANOVA revealed significant main effects of EA (P < 0.001), xylazine (P < 0.001), and time (P < 0.001) on pain threshold; it also revealed significant interactions between EA and time (P < 0.001) and xylazine and time (P < 0.001) and among EA, xylazine, and time (P < 0.001). The post hoc mean comparisons revealed that EA, xylazine administered at 0.4 mg/kg, and EA plus xylazine administration (0.1, 0.2, or 0.4 mg/kg) significantly (P = 0.036) increased the pain threshold, while xylazine administered at 0.1 mg/kg or 0.2 mg/kg alone did not (P = 0.107). The pain threshold in goats that underwent EA plus xylazine administration at 0.1 mg/kg was significantly (P = 0.036) higher than in goats that received EA or xylazine alone throughout the experiment but significantly (P < 0.001) lower than in goats that underwent EA plus

Table 1—Effects of EA and xylazine administration on the mean ± SE percentage change in the pain threshold in goats (n = 6 for each group).*  

<table>
<thead>
<tr>
<th>Group</th>
<th>5</th>
<th>25</th>
<th>45</th>
<th>65</th>
<th>85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.02 ± 0.05*</td>
<td>0.03 ± 0.10*</td>
<td>0.02 ± 0.08*</td>
<td>0.05 ± 0.05*</td>
<td>0.04 ± 0.06*</td>
</tr>
<tr>
<td>Xylazine at 0.1 mg/kg</td>
<td>0.42 ± 0.08</td>
<td>0.46 ± 0.02</td>
<td>0.39 ± 0.10</td>
<td>0.46 ± 0.06</td>
<td>0.29 ± 0.04</td>
</tr>
<tr>
<td>Xylazine at 0.2 mg/kg</td>
<td>0.43 ± 0.07</td>
<td>0.78 ± 0.06</td>
<td>0.81 ± 0.14</td>
<td>0.57 ± 0.09</td>
<td>0.43 ± 0.03</td>
</tr>
<tr>
<td>Xylazine at 0.4 mg/kg</td>
<td>1.70 ± 0.53</td>
<td>2.87 ± 0.67</td>
<td>2.46 ± 0.019</td>
<td>1.73 ± 0.57</td>
<td>0.97 ± 0.16</td>
</tr>
<tr>
<td>EA</td>
<td>1.63 ± 0.17</td>
<td>1.84 ± 0.55</td>
<td>1.75 ± 0.44</td>
<td>1.72 ± 0.06</td>
<td>1.34 ± 0.37</td>
</tr>
<tr>
<td>EA plus xylazine at 0.1 mg/kg</td>
<td>2.68 ± 0.32</td>
<td>3.57 ± 0.56</td>
<td>3.40 ± 0.64</td>
<td>2.89 ± 0.91</td>
<td>1.48 ± 0.18</td>
</tr>
<tr>
<td>EA plus xylazine at 0.2 mg/kg</td>
<td>3.18 ± 0.36</td>
<td>4.97 ± 0.56</td>
<td>5.18 ± 0.72</td>
<td>4.68 ± 0.47</td>
<td>1.73 ± 0.24</td>
</tr>
<tr>
<td>EA plus xylazine at 0.4 mg/kg</td>
<td>6.35 ± 0.98</td>
<td>8.34 ± 0.43</td>
<td>7.84 ± 0.63</td>
<td>7.59 ± 0.95</td>
<td>2.77 ± 0.50</td>
</tr>
</tbody>
</table>

*Pain threshold values were measured before (0 minutes) and at 5, 25, 45, 65, and 85 minutes after xylazine administration or at 0, 25, 45, 65, 65, and 105 minutes after EA.

Significantly (P < 0.05) different from value of goats that underwent EA plus xylazine administration at 0.1 mg/kg in the same column. Significantly (P < 0.05) different from value of control goats in the same column.
xylazine administration at 0.2 mg/kg at 25, 45, and 65 minutes after drug administration or in goats that underwent EA plus xylazine administration at 0.4 mg/kg throughout the experiment (Table 1).

**Effects of EA and xylazine administration on cardiorespiratory functions and rectal temperature—** Based on the observation that the combination of EA plus xylazine administration at 0.1 mg/kg (low dose) had a good analgesic effect in goats, changes in heart rate, MAP, respiratory rate, and rectal temperature in goats that underwent EA plus xylazine administration at 0.4 mg/kg throughout the experiment (Table 1).

Xylazine administration caused heart rate to decrease. Heart rate in goats given xylazine at 0.1 mg/kg at 25, 45, 65, and 85 minutes after drug administration and goats given xylazine at 0.4 mg/kg at 5, 25, 45, 65, and 85 minutes after drug administration was significantly (P = 0.038) lower than in control goats. Heart rate in goats that underwent EA increased but was not significantly (P = 0.582) different from that of control goats. Heart rate in goats that underwent EA plus xylazine administration at 0.1 mg/kg was significantly (P = 0.028) greater than in goats given xylazine at 0.4 mg/kg alone (Figures 1–4).

Xylazine administration decreased MAP in a dose-dependent manner (Figure 1). The MAP in goats given xylazine at 0.4 mg/kg was significantly (P = 0.037) lower than in control goats at 25, 45, and 65 minutes after drug administration. No significant (P = 0.837) difference was observed in MAP between goats given xylazine at 0.1 mg/kg and goats given xylazine at 0.4 mg/kg throughout the experiment. Administration of EA alone or the combination of EA plus xylazine at 0.1 mg/kg did not have a significant influence on MAP.

Xylazine administered at 0.1 and 0.4 mg/kg significantly (P = 0.035) reduced the respiratory rate of goats throughout the experiment. The respiratory rate of goats that underwent EA increased but was not significantly (P = 0.504) different from that of control goats.
The respiratory rate of goats that underwent EA plus xylazine administration at 0.1 mg/kg was significantly (P = 0.012) greater than that of goats given xylazine at 0.4 mg/kg alone but was not significantly (P = 0.126) different from that of control goats (Figure 3). Xylazine caused the rectal temperature to slightly increase, but not significantly, at 5 and 25 minutes after drug administration followed by a significant (P = 0.014) decrease (xylazine at 0.1 mg/kg at 65 minutes; xylazine at 0.4 mg/kg at 65 and 85 minutes). No significant difference was observed in the rectal temperature between control goats and goats that underwent EA alone. The rectal temperature of goats that underwent EA plus xylazine administration at 0.1 mg/kg was not significantly (P = 0.610) different from that of control goats (Figure 4).

Discussion

Veterinary acupuncture has a long history that parallels that of human acupuncture for relieving pain. Traditional acupuncture was manipulated manually, and the induction time was as long as 60 minutes. In the 1960s, it was discovered that the manipulation of acupuncture needles could be replaced by electric stimulation (EA) and the induction time shortened to approximately 20 minutes while retaining the analgesic effects. Since that time, EA in veterinary medicine has been successfully used in various operations such as cesarean section, gastrectomy, enterectomy, and castration in China. Relevant factors involved in the use of acupuncture for analgesia in ruminants have been determined, and the correct selection of acupuncture points is an essential element in successful EA. The stimulation of the set of Bai hui, San tai, Erh gen, and San yan lu points prove to be effective for analgesia in surgery at the neck, chest, and abdomen of ruminants. Frequencies between 30 and 100 Hz and an intensity range of 1 to 3.25 V are believed to be appropriate to provide analgesia in ruminants. We found that 36 Hz and an intensity just below the point of inducing a mild muscular twitch adjacent to the point (approx 3 V depending on the individual goat) produced a good analgesic effect without causing irritation and pain or tetany to the goats and maintained physiologic variables (heart rate, respiratory rate, and body temperature) within reference ranges. The level of analgesia is commonly determined by scores based on an animal’s response to a pinprick at a particular region. Obviously, this method is influenced by subjective factors. Lubudbrok et al and Grant and Upton measured the pain threshold in goats by use of an algesimetry method based on a leg-lifting response to a subcutaneous electric stimulus. This method is not an involuntary reflex but is instead a learned cognitive behavior. Additionally, it cannot be used for restrained animals. Potassium iontophoresis is a convenient and reliable experimental pain stimulus that can be presented rapidly and repeatedly with minimal loss in consistency of a subject’s reported pain level. In our study, potassium iontophoresis provided a tool for investigating changes in the pain thresholds of EA-treated goats. Electroacupuncture significantly increased the pain threshold, indicating good analgesia. The pain threshold induced by EA increased and reached a maximal level at approximately 45 minutes, decreased at 85 minutes, and then remained at a high level at 105 minutes after EA, which demonstrated that sustained EA can induce a tolerance effect (a gradual decrease of the EA effect) and aftereffect (ie, an analgesic effect lasting for a while after EA is discontinued). These findings are in accordance with some reports in rats and humans. The aftereffect usually lasts for approximately 30 minutes. The tolerance commonly appears 1 hour after EA and can be overcome by altering the intensity. In fact, the efficacy of EA cannot be strengthened by an unlimited increase of the stimulation intensity because this would in itself lead to the production of severe pain. Analgesics can increase the degree of analgesia until the pain is completely eliminated as their doses increase, but analgesics at high doses would produce severe adverse effects in animals, especially in ruminants. The combined use of EA and analgesics has been shown to produce good analgesia with few adverse effects in humans for some surgeries. Therefore, balanced analgesia through the combined use of EA and an analgesic appears to be promising for veterinary surgery.

Xylazine is a α2-adrenoceptor agonist that is commonly used in ruminants. Depending on the dose, it can act as a sedative and analgesic. Xylazine at 0.2 mg/kg is used for sedation of goats. Ndeereh et al found that xylazine administered at 0.4 mg/kg had a good analgesic effect and can be used in various operations in goats. In the present study, a significant interaction in terms of the pain threshold was found between EA and xylazine, indicating that EA and xylazine have a synergistic effect for analgesia in goats. In our study, the combination of EA plus xylazine administration at 0.1 mg/kg provided satisfactory analgesia. Whether EA combined with xylazine at 0.1 mg/kg can be used for some surgical procedures in goats needs to be further investigated. In combination treatments, EA was performed 20 minutes before xylazine administration. This timing allowed the analgesic durations of EA and xylazine to roughly overlap, thereby strengthening the analgesic effectiveness, as the induction duration of the former ranges from 20 to 30 minutes and that of the later is approximately 10 minutes. In balanced analgesia, the efficacy of EA-induced analgesia can be estimated by the reduction of the amount of analgesics consumed. Ren and Han reported that the analgesic effect produced by EA in rats was roughly equivalent to that of morphine at a dose of 4 mg/kg. As the full dose of morphine in a rat is 8 to 10 mg/kg to produce a strong analgesic effect, the efficacy of EA-induced analgesia is estimated to be half that produced by a full dose of morphine. In this study, the EA plus xylazine combination in goats reduced the dose of xylazine by 75%, compared with xylazine use alone.

Analgesia produced by xylazine is probably caused by an inhibition of the release of neurotransmitters and decrease in neuronal activity through the stimulation of α2-adrenoceptors in the spinal cord and CNS. Electroacupuncture activates the endogenous pain inhibition system and thereby decreases nociceptive responses in animals. Studies in rats have shown that...
different frequencies of EA trigger the release of different opioid peptides in the CNS. Electroacupuncture at 2 Hz induces the release of enkephalin, endorphin, and endomorphin, while EA at 100 Hz leads to the release of dynorphin.18,23,33 However, EA at 15 Hz produces partial activation of all 4 of these endogenous opioid peptides.39 The frequency range (30 to 100 Hz) induces adequate analgesia in goats is higher than in rats and humans (2 to 15 Hz).69 Therefore, the endogenous opioid peptides induced at 36 Hz in our study remain to be investigated. The mechanism by which the combination of EA plus xylazine administration causes analgesia in goats has not been elucidated.

Xylazine induced a profound and sustained hypotension and decreased heart rate in goats, which are consistent with the results of previous studies.7,30 Although EA alone did not affect MAP and heart rate significantly, the decrease in MAP and heart rate was of a greater magnitude in goats given xylazine alone than in goats given the combination of EA plus xylazine, which showed that the EA improved MAP and heart rate. Electroacupuncture regulation of hypotension and bradycardia may be related to excitation of sympathetic nerves and increases in serum concentrations of calcium, renin, angiotensin, and catecholamines.36,37

Xylazine caused a significant reduction in the respiratory rate, which is similar to findings reported by Afshar et al1 and Trim.4 The decrease in the respiratory rate in xylazine-treated goats may be the result of direct depression of the respiratory centers.5,28 Kumar and Thurman29 observed no rectal temperature alteration in goats after IM administration of xylazine, whereas Pond and Clarke28 reported that xylazine prolonged the depression of rectal temperature. This difference may be caused by observations from different durations of xylazine administration because xylazine only alters body temperature in the late stage of analgesia.3 In the present study, the rectal temperature decreased significantly 65 minutes after xylazine administration. The decrease in rectal temperature in response to xylazine administration may be the result of a decrease in the metabolic rate, muscle relaxation, and depression of the CNS.23,38 Findings in our study indicated that EA can correct depressed respiratory function and body temperature. However, the mechanism of this action is not clear.

References