Maternal and fetal effects of dexmedetomidine infusion in pregnant ewes anesthetized with sevoflurane

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OBJECTIVE
To characterize the maternal and fetal cardiopulmonary effects of a low-dose infusion of dexmedetomidine without a loading dose in pregnant ewes anesthetized with sevoflurane.

ANIMALS
11 pregnant ewes.

PROCEDURES
Anesthesia was induced with propofol and maintained with sevoflurane. Ewes and fetuses were instrumented with arterial and venous catheters, and thermodilution–pulmonary arterial catheters were placed in the ewes. Baseline measurements were obtained at an end-tidal sevoflurane concentration of 3.4%, then dexmedetomidine (2 µg/kg/h, IV) was infused for 90 minutes without a loading dose. Cardiovascular and blood gas variables were measured at predetermined time points.

RESULTS
Dexmedetomidine infusion resulted in approximately 30% decreases in maternal systemic vascular resistance, blood pressure, and heart rate. Maternal cardiac index, oxygenation variables, and acid-base status remained unchanged, whereas pulmonary arterial pressure, pulmonary vascular resistance, and stroke volume increased, compared with baseline values. Uterine blood flow decreased by approximately 30% to 36%. Fetal heart rate and blood pressure remained unchanged, but significant increases in fetal plasma glucose and lactate concentrations were detected.

CONCLUSIONS AND CLINICAL RELEVANCE
Pregnant ewes receiving a combination of sevoflurane and an infusion of dexmedetomidine without a loading dose had cardiac index in acceptable ranges and maintained normoxia. This balanced anesthesia did not produce significant changes in fetal blood pressure or heart rate. However, the increase in fetal plasma lactate concentration and changes in maternal pulmonary vascular resistance and uterine blood flow require further investigation to better elucidate these effects. (Am J Vet Res 2017;78:1255–1263)

A thorough understanding of maternal and fetal physiology and the effects of anesthetic drugs on each is paramount in assuring safety during anesthesia of pregnant patients.1,2 Physiologic changes during pregnancy are attributed to increases in circulating progesterone concentrations and to the presence of a growing fetus with high metabolic demands. Hemodynamic changes affecting a pregnant patient can affect the fetus; therefore, it is crucial to maintain maternal oxygenation, BP, and perfusion.1,2

High anesthetic concentrations are detrimental to fetal and maternal hemodynamics.3 In addition, volatile anesthetics can exacerbate developmental neuronal cell death.4 Balanced anesthesia is recommended to minimize anesthetic side effects. Of the clinically available α2-AAgs, dexmedetomidine has the highest α2-AR to α1-AR selectivity ratio (1,620:1).5,6 Dexmedetomidine is widely used in anesthesia and intensive care settings for its sedative, anesthetic-sparing, and analgesic properties. Infusions of α2-AAgs are used during maintenance of general anesthesia to provide cardiovascular stability and anesthetic sparing effect.7,8 During postanesthetic recovery and intensive

ABBREVIATIONS
AAg Adrenergic receptor agonist
AR Adrenergic receptor
BP Blood pressure
CaO2 Arterial oxygen content
CI Cardiac index
CmvO2 Mixed venous oxygen content
CO Cardiac output
Do2 Oxygen delivery
Hb Hemoglobin
HR Heart rate
MAP Mean arterial blood pressure
MPAP Mean pulmonary arterial pressure
MRAP Mean right atrial pressure
OER Oxygen extraction ratio
PAOP Pulmonary arterial occlusion pressure or wedge pressure
PaO2 Arterial partial pressure of oxygen
PVR Pulmonary vascular resistance
SVR Systemic vascular resistance
UBF Uterine blood flow
care unit stays, \(\alpha_2\)-AAgs are used to provide comfort and delirium control for human and veterinary patients.\(^8\) Results of laboratory experiments with mice have shown that dexmedetomidine has protective effects against cytotoxic injury to neuronal cells, which make its use during pregnancy more appealing.\(^10\)\(^11\)

The use of dexmedetomidine in anesthesia of pediatric patients has been reported; however, information regarding its use during pregnancy is scarce and limited to use during termination of pregnancy or caesarian sections.\(^12\)\(^13\) To the authors’ knowledge, only 1 report\(^14\) has been published describing its use as an infusion during pregnancy in veterinary species, and the manufacturer states that its use has not been evaluated in breeding, pregnant, or lactating animals.\(^15\) The drug is presently approved for use in dogs and cats; its use in sheep is considered extralabel and its withdrawal time has not been established.

Centrally, \(\alpha_2\)-AAgs reduce sympathetic outflow and increase vagal tone.\(^5\) In the periphery, they modulate vasoconstriction by decreasing norepinephrine secretion in sympathetic nerve terminals; however, they can also stimulate postsynaptic \(\alpha_2\)-ARs and produce vasoconstriction. This can result in reduced HR and CO. The effect of \(\alpha_2\)-AAgs on BP is dose- and rate-related and described as biphasic; low plasma concentrations decrease BP, whereas high concentrations increase it.\(^10\) Infusion of low doses of dexmedetomidine may be devoid of hypertensive effects\(^17\)\(^-\)\(^20\) enhancing the potential for its use in anesthesia.\(^17\)

To increase efficient meat and milk production, the livestock industry has turned its attention to producing individual animals with superior genetics. The cost of producing such embryos can be in the hundreds of thousands of dollars, and the health and well-being of the recipient dams and fetuses during gestation is paramount. If general anesthesia is required in the treatment of these recipients, the safety of the agents used for the dam and the fetus is a vital consideration.

In addition, small ruminants are used extensively in biomedical research.\(^21\) Research with pregnant sheep is highly translational for human pregnancy,\(^22\)\(^23\) which makes the findings of these types of studies useful for both veterinary and human medicine. The infusion of dexmedetomidine in nonanesthetized pregnant ewes has been reported; however, to the authors’ knowledge, infusion of this drug as part of balanced anesthesia has not been evaluated, and its effects on the developing sheep fetus have not been examined.\(^14\)

The objective of the study reported here was to evaluate the maternal and fetal cardiopulmonary effects of a low-dose, constant rate infusion of dexmedetomidine without a loading dose in pregnant ewes anesthetized with sevoflurane. Our hypothesis was that this combination would decrease maternal BP and HR, compared with baseline values obtained immediately before dexmedetomidine administration, but that it would not significantly affect those variables in the fetuses.

### Materials and Methods

#### Animals

All aspects of the experimental protocol were approved by the Texas A&M University Institutional Animal Care and Use Committee. Eleven healthy Suffolk ewes (age, 2 to 5 years; mean ± SE body weight, 79.18 ± 4.12 kg) were used. All sheep were between 114 and 118 days of gestation and were determined to be in good health on the basis of physical examination, CBC, and serum biochemical analysis results.\(^24\)

Ten of the 11 ewes were pregnant with singletons; 1 ewe was pregnant with twins, and data from the ewe, but not the twin fetuses, were included in the study. Ewes were allowed free access to drinking water, but food was withheld for 18 hours prior to induction of anesthesia.

#### Anesthetic protocol and monitoring

Surgical instrumentation and catheterization of ewes and fetuses were performed on mean ± SE gestational day 116 ± 2 (full term, approx 147 days). Following aseptic preparation of the skin, a 16-gauge, 3.0-inch IV catheter was placed percutaneously into the left jugular vein and flunixin meglumine\(^4\) (2.2 mg/kg, IV) was administered. Anesthesia was induced by IV administration of propofol\(^b\) (3 mg/kg), and ewes were intubated with a cuffed endotracheal tube and placed in dorsal recumbency. Anesthesia was maintained with sevoflurane at 3.4% delivered in 100% oxygen. The concentration of sevoflurane needed for the procedure had been determined previously in our laboratory. The jugular catheter was used to deliver lactated Ringer solution\(^c\) at 5 mL/kg/h. Ewes were instrumented with a multiparameter patient monitor\(^d\) used for assessment and recording of ECG data, arterial \(O_2\) saturation measured by pulse oximetry, indirect (during instrumentation) and direct BP, and body (esophageal) temperature. The monitor also included a gas analyzer used to measure the inspiratory fraction and end-tidal expiratory concentration of sevoflurane and to perform capnometry. The gas module of the monitoring system was calibrated before and after each experiment.

A pulmonary arterial catheter\(^e\) was placed percutaneously in the right jugular vein by use of an 8F introducer.\(^f\) Proper placement was confirmed by observation of expected pressure waveforms. The BP transducers\(^g\) were positioned at the level of the heart and zeroed to room air prior to any direct measurements; the point of the shoulder joint was used as a reference point. The pulmonary arterial catheter was used to measure CO, pulmonary arterial blood pressure, right atrial pressure, and PAOP and to sample mixed venous blood for blood gas analysis. Mechanical ventilation\(^h\) was performed to maintain normocapnia (\(PETCO_2\), 35 to 40 mm Hg) and was stopped prior to each CO measurement. For measurement of CO, 10 mL of ice-cold 5% dextrose solution was injected
into the proximal port of the pulmonary arterial catheter during a 3-second period, and a series of ≥ 3 measurements was recorded with values within 10% of each other, and the mean of the readings was used for the reported CO. Esophageal temperature was maintained at approximately 38°C by use of blankets.

**Surgical instrumentation procedure**

After aseptic preparation of the surgical site and infiltration of 20 mL of lidocaine1 along the vertical midline, a ventral midline laparotomy was performed. The uterus was externalized and incised, and a fetal hind limb was exteriorized. An incision was made over the cranialateral aspect of the fetal hind limb. A polyvinyl chloride catheter (inner diameter, 0.030 inches; outer diameter, 0.050 inches) was advanced from the cranial tibial artery into the abdominal aorta to the level of the diaphragm. The procedure was repeated through the saphenous vein, advancing the catheter into the abdominal vena cava. Then the fetal hind limb was returned to the uterus. A catheter was installed inside the amniotic cavity, and the uterus was closed routinely. A 6-mm transit-time ultrasonic perivascular flow probe1 was secured around the primary uterine artery for recording UBF.25 A trocar was passed from the abdominal cavity out through the flank. The fetal catheters and flow probe were passed through the trocar and the trocar was withdrawn. The fetal catheters and flow probe were maintained in a cloth pouch sutured to the skin in the flank region. The midline incision was closed, and polyvinyl chloride catheters (inner and outer diameters, 0.030 and 0.050 inches, respectively) were then advanced from a maternal femoral artery and vein to the level of the diaphragm of the abdominal aorta and vena cava, respectively. The maternal catheters were tunnelled subcutaneously, then exteriorized through the right flank, and also stored in the pouch attached to the skin. This area was infiltrated with 5 mL of lidocaine.1 Both fetal and maternal catheters were filled with saline and sealed immediately after placement.

**Dexmedetomidine protocol and data collection**

Once the ewes and the fetuses were instrumented, baseline (T0) measurements were obtained with end-tidal sevoflurane concentration at 3.4%, and administration of dexmedetomidine6 at a constant rate infusion1 of 2 μg/kg/h20 IV was started and continued for 90 minutes.

Blood samples were collected from the maternal and fetal arterial catheters every 30 minutes after baseline (T30, T60, and T90) until the end of the infusion of dexmedetomidine. Whole blood samples were used to measure blood gases; plasma glucose, lactate, and total protein concentrations; and PCV. At these same time points, mixed venous blood samples were also collected. Blood gas samples were drawn anaerobically and analyzed immediately with a point-of-care portable clinical analyzer.6 Each blood sample consisted of 3 to 5 mL of blood from the fetal arterial catheter and 6 mL of maternal blood. The UBF, amniotic pressure, and maternal and fetal BP were recorded continuously25 with a data acquisition system.8 After 90 minutes of dexmedetomidine infusion, mechanical ventilation, dexmedetomidine administration, and sevoflurane delivery were discontinued. Ewes were placed in sternal position and allowed to recover. If sheep failed to breathe spontaneously within 1 minute after repositioning, breathing was manually assisted at a rate of 2 breaths/min until spontaneous breathing resumed. Once sheep began to swallow and lift their heads, they were extubated and buprenorphine6 (0.01 mg/kg, IV) was administered.

To calculate CI, CaO2, Cmvo2, OER, PVR, SVR, and oxygen consumption, the following formulas were used:

\[
\text{CI (mL/min/kg)} = \frac{\text{CO}}{\text{body weight (kg)}}
\]

\[
\text{CaO}_2 \text{ (mL/dL)} \text{ or } \text{Cmvo}_2 \text{ (mL/dL)} = (1.34 \cdot \text{Hb} \cdot \text{So}_2) + 0.003 \cdot \text{P}_o \]

\[
\text{OER} (%) = \frac{(\text{CaO}_2 - \text{Cmvo}_2)}{\text{CaO}_2} \times 100
\]

\[
\text{PVR (dynes/s/cm}^2\) = \frac{\text{(MAP – PAOP)}}{\text{CO}} \times 80
\]

\[
\text{SVR (dynes/s/cm}^2\) = \frac{\text{(MAP – MRAP)}}{\text{CI}}
\]

\[
\text{Vo}_2 (%) = \frac{(\text{CaO}_2 - \text{Cmvo}_2)}{\text{CI}} \times 100
\]

where So2 represents hemoglobin saturation with oxygen and Vo2 represents oxygen consumption.

**Statistical analysis**

One-way repeated measures ANOVA was performed on the maternal and fetal data by use of statistical software.9 Statistical analysis was performed only if the data set for each variable passed the default normality test that was assigned by the software. All pairwise comparisons were performed with the Holm-Sidak method. Values of P < 0.05 were considered significant.

**Results**

All ewes recovered from anesthesia uneventfully. At the end of the study, the pregnant ewes were transferred to another study in which the animals were humanely euthanized and the fetal body weight was determined (mean ± SD, 2.76 ± 0.08 kg).

**Maternal hemodynamics**

Cardiovascular effects of combining sevoflurane general anesthesia with the infusion of dexmedetomidine at a rate of 2 μg/kg/h were summarized (Table I). During infusion of dexmedetomidine, maternal HR, systemic BP (systolic, mean, and diastolic), and SVR were reduced (by approx 30%) from the baseline values at T30, T60, and T90; the T30, T60, and T90 values did not differ significantly from each other for any of these measures. Stroke volume was increased significantly, compared with the baseline value, at T30, T60, and T90, but the respective values at these 3 time points did not differ from each other. The CI was stable throughout the experiment.
Table I—Mean ± SE maternal and fetal cardiovascular variables before and during IV infusion of dexmedetomidine (2 µg/kg/h) in 11 pregnant ewes during anesthesia induced with propofol and maintained with sevoflurane.

<table>
<thead>
<tr>
<th>Variable</th>
<th>T0</th>
<th>T30</th>
<th>T60</th>
<th>T90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl (mL/kg/min)</td>
<td>71.56 ± 8.97</td>
<td>60.36 ± 7.12</td>
<td>61.66 ± 7.47</td>
<td>65.80 ± 8.26</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>105.20 ± 4.52</td>
<td>76.44 ± 4.42*</td>
<td>75.93 ± 4.09*</td>
<td>77.00 ± 4.888*</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>115.85 ± 4.81</td>
<td>82.34 ± 1.85*</td>
<td>80.63 ± 2.32*</td>
<td>77.86 ± 2.19*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>101.78 ± 4.52</td>
<td>70.00 ± 1.98*</td>
<td>67.84 ± 1.89*</td>
<td>65.84 ± 1.89*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>94.74 ± 4.70</td>
<td>63.83 ± 2.37*</td>
<td>61.44 ± 1.92*</td>
<td>60.36 ± 1.44*</td>
</tr>
<tr>
<td>SVR (dynes/s/cm⁵)</td>
<td>1,551.174 ± 193.10</td>
<td>1,193.60 ± 173.49*</td>
<td>1,151.70 ± 183.05*</td>
<td>1,066.43 ± 212.18*</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>54.52 ± 5.73</td>
<td>63.68 ± 8.50*</td>
<td>66.34 ± 9.60*</td>
<td>69.12 ± 10.27*</td>
</tr>
<tr>
<td>PVR (dynes/s/cm⁵)</td>
<td>119.75 ± 21.38</td>
<td>116.75 ± 22.64</td>
<td>187.32 ± 37.33*</td>
<td>197.66 ± 45.02*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>114.44 ± 1.09</td>
<td>183.12 ± 1.08*</td>
<td>189.94 ± 1.03*</td>
<td>186.66 ± 0.85*</td>
</tr>
<tr>
<td>MRAP (mm Hg)</td>
<td>7.87 ± 1.32</td>
<td>10.89 ± 1.72*</td>
<td>11.97 ± 2.01*</td>
<td>11.83 ± 1.71*</td>
</tr>
<tr>
<td>PAOP (mm Hg)</td>
<td>9.27 ± 1.26</td>
<td>10.60 ± 1.46</td>
<td>10.95 ± 1.37</td>
<td>10.3 ± 1.44</td>
</tr>
<tr>
<td>UBF (L/min)</td>
<td>0.36 ± 0.08</td>
<td>0.22 ± 0.04*</td>
<td>0.22 ± 0.04*</td>
<td>0.24 ± 0.04*</td>
</tr>
</tbody>
</table>

Fetus

<table>
<thead>
<tr>
<th>Variable</th>
<th>T0</th>
<th>T30</th>
<th>T60</th>
<th>T90</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>134.44 ± 3.26</td>
<td>133.00 ± 3.17</td>
<td>129.78 ± 3.62</td>
<td>128.08 ± 3.61</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>50.04 ± 1.30</td>
<td>53.60 ± 2.25</td>
<td>52.90 ± 2.40</td>
<td>53.47 ± 2.51</td>
</tr>
</tbody>
</table>

One of 11 ewes was pregnant with twins and data from the ewe, but not the twin fetuses, were included in the study. Baseline (T0) measurements were collected after instrumentation and before administration of dexmedetomidine. The IV infusion of dexmedetomidine was delivered over 90 minutes, and data were recorded 30, 60, and 90 minutes after the start of the infusion (T30, T60, and T90, respectively).

Values of P < 0.05 were considered significant.

*Value is significantly different from baseline.

SV = Stroke volume.

Data represent percentage of the baseline value.

V̇O₂ = Calculated oxygen consumption.

See Table 1 for remainder of key.

There were significant increases in MPAP (approx 20%) and MRAP (up to approx 50%), compared with baseline values, at T30, T60, and T90; the T30, T60 and T90 values did not differ significantly from each other for either of these measures (Table 1). The PVR was increased significantly (up to approx 65%) from baseline and T30 measurements at T60 and T90; there was no significant difference between the T60 and T90 measurements or between the baseline and T30 measurements.

Significant decreases in UBF (approx 30% to 36%, compared with the baseline value) were detected at T30, T60, and T90. The values at these 3 time points did not differ significantly from each other (Table 1).

Maternal blood gases

The maternal CaO₂ (range, 10.60 ± 0.42 mL/dL to 10.13 ± 0.34 mL/dL), OER (range, 24.88 ± 0.02% to 28.20 ± 0.02%), and oxygen saturation of mixed venous blood (range, 81.72 ± 2.2% to 78.00 ± 2.32%) did not change significantly at T30 through T90, compared with baseline values, nor was there any significant difference among time points. The percentage change from baseline for each of these variables was tabulated (Table 2). The D₂O was not compromised, and mean D₂O was maintained at > 80% of the baseline value throughout the experiment. The PCV; circulating Hb, plasma lactate, and arterial blood CO₂ concentrations; PaO₂; base excess; and acid-base status were maintained within the expected ranges and did not change significantly during the infusion of dexmedetomidine.

Plasma glucose concentrations steadily increased throughout the infusion, with significant differences from baseline at all time points and significant differences among multiple time points during the experiment.

Fetal effects

There were no significant changes from baseline at any time point and no significant differences among any time points during dexmedetomidine infusion for fetal HR, MAP, or PaO₂ (Tables 1 and 3). Fetal plasma glucose and lactate concentrations were significantly increased at T60 and T90, compared with those at baseline and T30; there was no significant difference between the T60 and T90 concentrations or between baseline and T30 concentrations for these variables.

Discussion

Results of the present study confirmed our hypothesis that infusion of a low dose of dexmedetomidine, without a loading dose, would decrease BP...
and HR in pregnant ewes but would not significantly affect those variables in the fetuses. To avoid a potential initial positive vasopressor effect of dexmedetomidine,²⁶ no loading dose was used,²⁷ and a clinical infusion rate similar to those reported for various species, including sheep, was chosen.²⁰,²⁶,²⁸ Our protocol reflected a typical combination used under clinical and research conditions. Inhalant anesthetics are used for cesarean deliveries and fetal surgery.²⁵ Propofol has a very short half-life, produces smooth and stress-free induction, allows quick airway protection,³⁰ and does not adversely affect maternal or fetal BP or HR, or UBF in pregnant ewes.³¹ We attributed the observed hemodynamic changes to the effect of dexmedetomidine; however, the contribution of other factors such as sevoflurane and body position could not be excluded.

The maternal and fetal baseline cardiovascular data in this study were consistent with values reported by other authors.³³,³⁴,⁴⁰,⁴² A biphasic BP response with a concomitant decrease in HR of approximately 50% has been described in nonpregnant sheep receiving a bolus of dexmedetomidine while under anesthesia.⁶,³² Similar responses have been reported in several species.¹⁹,³³,‒³⁵ This is in contrast with our results, where HR, BP, and SVR decreased without initial increases. The cardiovascular effects of α₂-AAgs are attributed to both peripheral and central actions. Presynaptic stimulation of α₂-AAgs decreases norepinephrine release, and direct postsynaptic stimulation of α₂AAgs can produce vasoconstriction that results in decreased HR.³⁶,³⁷ In the present study, the presynaptic effect appeared to predominate, reflecting the fact that the cardiovascular effects of α₂-AAgs are influenced by the dose, rate, and route of administration. This was in agreement with results of a study that demonstrated the effects of various plasma concentrations of medetomidine, with low doses producing a decrease in BP and high doses increasing both BP and SVR. Our findings were consistent with reports of studies in nonanesthetized pregnant and nonpregnant sheep receiving similar doses of dexmedetomidine where boluses of dexmedetomidine were avoided.

Severity of bradycardia is associated with the dose and the rate of α₂-AAg administration.⁵⁴,⁵⁶ Accordingly, we detected mild maternal bradycardia with HR approximately 30% below the baseline rate, which was milder than the bradycardia reported in ewes receiving higher rates of dexmedetomidine in other studies.³²,³³ Dexmedetomidine can depress both sinus and atrioventricular nodal function, and atrioventricular blocks are common,³⁹,⁴⁰ however, no arrhythmias were observed in the present study.

Whereas rapid administration or high doses of α₂-AAGs decrease CO owing to low HR and an increase in afterload,³²,³³,⁴¹ we found that CO was maintained with decreases in BP and SVR, reflecting a decrease in afterload. This supported the idea that the cardiovascular effects of α₂-AAGs are influenced by the dose and rate used, with more substantial effects occurring at high doses and high rates.³⁴,³⁸,⁴² Because dexmedetomidine does not have any inotropic effects, the increase in stroke volume that we observed reflected an increase in preload, a decrease in afterload, or both.⁴⁵,⁴⁶ The static indices of volume status, MRAP and PAOP, varied somewhat as MRAP was significantly increased during dexmedetomidine infusion and the PAOP was numerically, but not significantly, increased relative to baseline data. We assume the CI was maintained because the decreased HR allowed a longer filling time, and the MRAP increased afterload contributed to a higher stroke volume occurring at high doses and high rates.³⁴,³⁸,⁴²

Because the present study might have increased because of direct pulmonary vasoconstriction, and this may have contributed to the increase in MRAP and the increase in PVR as well. Different findings have been reported in regard

**Table 3**—Mean ± SE maternal and fetal blood gas variables before and during IV infusion of dexmedetomidine for the same 11 ewes as in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>T0</th>
<th>T30</th>
<th>T60</th>
<th>T90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PₐO₂ (mm Hg)</td>
<td>332.64 ± 34.46</td>
<td>298.09 ± 44.60</td>
<td>332.64 ± 34.46</td>
<td>285.60 ± 45.22</td>
</tr>
<tr>
<td>PₐCO₂ (mm Hg)</td>
<td>44.82 ± 1.49</td>
<td>46.22 ± 1.53</td>
<td>47.47 ± 1.20</td>
<td>49.80 ± 2.42</td>
</tr>
<tr>
<td>PₐHCO₃ (mm Hg)</td>
<td>47.54 ± 1.23</td>
<td>45.64 ± 2.17</td>
<td>50.4 ± 2.67</td>
<td>49.70 ± 2.52</td>
</tr>
<tr>
<td>Lactate (mg/dL)</td>
<td>0.81 ± 0.07</td>
<td>0.92 ± 0.05</td>
<td>0.95 ± 0.09</td>
<td>0.95 ± 0.09</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>106.63 ± 4.83</td>
<td>152 ± 7.66</td>
<td>229.45 ± 17.75</td>
<td>240.50 ± 22.51</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol/L)</td>
<td>28.74 ± 0.82</td>
<td>28.74 ± 0.82</td>
<td>28.65 ± 0.58</td>
<td>29.53 ± 0.53</td>
</tr>
<tr>
<td>Fetus</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PₐO₂ (mm Hg)</td>
<td>18.25 ± 0.67</td>
<td>15.50 ± 0.78</td>
<td>16.57 ± 1.26</td>
<td>18.14 ± 1.52</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>27 ± 2.51</td>
<td>31.87 ± 2.50</td>
<td>63 ± 5.12</td>
<td>85 ± 8.2</td>
</tr>
<tr>
<td>Lactate (mg/dL)</td>
<td>2.7 ± 0.42</td>
<td>3.56 ± 0.26</td>
<td>4.26 ± 0.37</td>
<td>5.22 ± 0.21</td>
</tr>
</tbody>
</table>

Values of P < 0.05 were considered significant.

†Value is significantly different from that at T30. ‡Value is significantly different from that at T60. §Value is significantly different from that at T90.

PₐO₂ = Mixed venous blood partial pressure of oxygen. — = Not applicable (missing data).

See Table 1 for remainder of key.
to the effect of α₂-AAgs on pulmonary hemodynamics, and even the sampling time may influence the results when comparing results among reports, considering that some of the effects may be transient. In our study, maternal MPAP, PAOP, and PVR had (mean) maximum increases of 23%, 18%, and 65%, respectively, relative to baseline values. Similar results have been reported in nonpregnant sheep exposed to the same conditions; however, the increments were less than those in anesthetized sheep receiving a bolus of dexmedetomidine. Our results were similar to results reported for human patients in which PAP, PVR, and PAOP increased as the plasma concentration of dexmedetomidine increased. Varying responses could be attributed not only to differences in doses or delivery rates but also to individual variation in the pulmonary response to dexmedetomidine owing to differences in α₂-AR density or polymorphisms.

In sheep, α₂-AAgs can induce dose-dependent arterial hypoxemia as a consequence of pulmonary vasoconstriction, acute vascular congestion, and pulmonary interstitial edema, and this can potentially result in reduced pulmonary compliance. Low doses and slow infusion rates preserve normoxemia, which is consistent with our findings of no demonstrable oxygen debt in pregnant ewes of this study. The high inspiratory concentration of oxygen contributed to the maintenance of normoxemia in the present study, where maternal $\text{Pa}_2$ data were similar to values reported by other authors for anesthetized ewes. Intercapillary variability has been reported with the use of α₂-AAgs with respect to hypoxemia, and whether these individual differences depend on the distribution of α₂-ARs in the lungs still needs to be determined.

The unchanged CI and $\text{CaO}_2$ allowed preservation of $\text{Do}_2$ in pregnant ewes throughout the dexmedetomidine infusion and were confirmed by the maintenance of other variables such as calculated oxygen consumption and OER and plasma concentrations of HCO$_3^-$ and lactate. This is notable, because anesthetized ewes receiving dexmedetomidine as a bolus had increased venous admixture and OERs in another study.

The mean baseline UBF for the sheep of this study was 0.36 L/min, decreasing significantly by approximately 30% (up to 36%) of this value during the infusion. In a study of awake pregnant ewes receiving dexmedetomidine, the mean baseline UBF reported was 183 ± 63 mL/min and varied between 85% and 115% of the baseline value during the treatment, but direct comparison cannot be made because the sheep in that study were awake and those in the present study were anesthetized. A decrease in UBF is a concern because it could predispose the fetus to hypoxia, hypercapnia, and acidosis. Possible mechanisms for the decrease in UBF include uterine adrenergic vasoconstriction or adrenergic myometrial contraction that may indirectly reduce the UBF by occluding output and input vessels, thereby increasing resistance to flow. Furthermore, UBF varies directly with the MAP and SVR, and systemic circulation can deplete some flow from the uterine circulation once the SVR and MAP decrease, as has been reported with the use of vasodilators in pregnant ewes. In our study, the magnitude of the reduction in MAP paralleled that detected for the UBF. The UBF can also be affected by anesthetic drugs and by aortic compression in a dorsally recumbent position leading to a decrease in venous return, CO, and uterine gradient perfusion pressure. The ewes in this study were kept in dorsal recumbency to simulate conditions where the infusion of dexmedetomidine would likely be used.

Fetal body weight was 2.76 ± 0.08 kg; the total volume of fetal blood collected by 90 minutes of infusion was 18 mL, representing < 5% of the blood volume. We identified a single report in the literature describing the effects of dexmedetomidine in fetal sheep, but the study was performed in nonanesthetized ewes; those investigators reported minimal effects of dexmedetomidine on fetal cardiovascular values, and our findings in fetal sheep during anesthesia of the dam were in agreement with those results. Placental transfer of dexmedetomidine has been demonstrated during delivery of human babies by cesarean section. In addition, in the case of pregnant ewes, sufficient placental transfer of medetomidine has been reported to produce conditions suitable for fetal surgery. However, the low dose of dexmedetomidine used in our study, the lower permeability of the sheep epitheliochorial placenta compared with the human hemochorial placenta, and placental tissue retention of the drug may have resulted in a low passage of dexmedetomidine to fetuses, and these factors could potentially explain the minimal effects observed.

Hyperglycemia produced by administration of α₂-AAgs is due to the inhibition of insulin release. Hyperglycemia was the only fetal effect detected during dexmedetomidine infusion in awake pregnant ewes in a previous study and was likewise observed in the fetuses of our study. Glucose provides approximately 80% of fetal energy, and lactate, ketoacids, amino acids, and other sources contribute the rest. Fetal and maternal insulin have similar sensitivity and increase similarly during hyperglycemia to reduce circulating glucose to normal concentrations. The maternal-fetal glucose gradient determines the transfer of glucose across the placenta. Therefore, the maternal hyperglycemia may have been responsible for the increase in fetal glucose concentration detected; however, the inhibition of fetal insulin secretion by dexmedetomidine cannot be ruled out, as it has been reported to occur with other α₂-AAgs.

Fetal $\text{PaO}_2$ was apparently lower than the baseline value during dexmedetomidine infusion, but the changes were not significant and the mean measurement remained > 15 mm Hg at all times. Potential causes of decreased fetal $\text{PaO}_2$ include maternal hypox-
emia, restriction of UBF, or impaired placental function.53 Neither the ewes nor the fetuses were hypoxic during the study.

Depression of fetal oxygen consumption occurs when umbilical venous PO2 falls below 15 to 16 mm Hg. Because the mean fetal PaO2 in our study remained > 15 mm Hg, we assumed that umbilical venous PO2 remained above this threshold and the fetuses did not develop a supply-dependent oxygen consumption, as has been reported to occur when the PaO2 is < 10 mm Hg.64 Once this point is reached, a decrease in pH and base excess can occur, precipitating fetal bradycardia followed by hypertension,64 neither of which was observed in our study. However, the significant increases in fetal plasma lactate concentration at T60 and T90 in this study could have indicated that some tissues incurred oxygen debt, even though the global DO2 remained above the critical point. When UBF is reduced, placental needs are initially maintained at the expense of the fetus; glycogen stores are mobilized to provide glucose and lactate to the placenta.65 Fetal hyperlactatemia and hyperglycemia can develop in the absence of hypoperfusion or hypoxia when glycolysis and lactate production are increased, so this is another potential explanation for the observed increases in fetal plasma lactate concentrations.5,66 Because the ewes were part of another study, the lambs were not followed to birth and a single standardized treatment had to be used; a control group for comparison was not available. Inability to collect data over a longer term was a limitation of the present study because it is possible that the temporary increases in lactate may not have been clinically important in terms of viability of the fetus.

The increases in fetal plasma lactate concentrations and maternal PVR in this study of anesthetized sheep require further investigation to better elucidate these effects, especially considering that pregnant sheep require further investigation to better elucidate the pulmonary and uterine vasculature.

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Footnotes

a. Banamine, 50 mg/mL, Merck Animal Health, Unterschleißheim, Germany.
b. Propofol, 10 mg/mL, Zoetis, Kalamazoo, Mich.
c. Lactated Ringer solution, Hospira Inc, Lake Forest, Ill.
d. DPM6, Mindray Medical International Ltd, Shenzhen, China.
e. Swan Ganz 7.5 F, 110-cm flow-directed thermodilution pulmonary catheter, Edwards Lifesciences, Irvine, Calif.
g. PowerLab, ADInstruments, Colorado Springs, Colo.
i. Lidocaine HCl 1%, Hospira Inc, Lake Forest, Ill.
k. Dexdomitor, Orion Corp, Espoo, Finland.
l. Per fusor, B. Braun Medical Inc, Bethlehem, Penn.
m. VetScan i-STAT 1, Abaxis, Union City, Calif.
n. PowerLab 8/30, model ML870, LabChart software, ADInstruments Inc, Colorado Springs, Colo.
o. Buprenex, 0.3 mg/mL, Reckitt Benckiser Pharmaceuticals Inc, Richmond, Va.
p. Sigma Plot, version 11, Systat Software Inc, San Jose, Calif.

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