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Maternally Administered Esmolol Produces Fetal β-Adrenergic Blockade and Hypoxemia in Sheep

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Although esmolol may be a useful therapeutic agent in obstetrics and obstetric anesthesia, concerns about fetal safety have limited its use. To assess acute fetal hemodynamic effects of maternally administered esmolol, saline or esmolol (4–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in a stepped manner) was infused into maternal venous catheters in nine chronically prepared pregnant ewes, and the degree of β-adrenergic blockade was assessed by isoproterenol challenge. In control experiments saline infusion and repeated isoproterenol challenges did not alter measured parameters, although maternally administered isoproterenol (0.1 μg) transiently decreased uterine blood flow by 20 ± 5% (mean ± SEM; $P < 0.05$). Esmolol produced a dose-dependent decrease in maternal blood pressure and fetal heart rate (maternal blood pressure decreased by 22 ± 8% and fetal heart rate decreased by 27 ± 7% following esmolol, 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $P < 0.05$). Fetal arterial PO_2 decreased from 18.2 ± 1.2 mmHg before to 14.1 ± 1.5 mmHg following esmolol, 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.05$). Maternally administered esmolol produced similar dose-dependent β-adrenergic blockade in both ewe and fetus, with complete blockade following the 80 and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ doses. Thirty minutes following cessation of esmolol infusion, fetal resting heart rate and maternal and fetal isoproterenol-stimulated heart rate remained below control values. These results suggest that maternally administered esmolol may produce adverse fetal effects, limiting its usefulness in the obstetric setting. (Key words: Anesthesia: obstetric. Fetus: drug effects. Sympathetic nervous system, beta adrenergic antagonists: esmolol.)

β-ADRENERGIC BLOCKING DRUGS may be useful therapeutic agents in obstetrics. Examples of indications for β-adrenergic blockade include the treatment of hyperthyroidism, angina, congenital or acquired heart disease, tachycardia (occurring either in reflex response to vasodilator therapy or during other supraventricular tachydysrhythmias), and hypertension (due either to preeclampsia or stress during induction of general anesthesia).[1] A special case of the latter is women with preeclampsia undergoing cesarean section under general anesthesia, in whom severe hypertension may accompany tracheal intubation.[2]

Both acute and chronic administration of β-adrenergic antagonists during pregnancy have been limited by concern over fetal effects. Intrauterine growth retardation[1] and fetal bradycardia[3] have been reported in patients or in studies of chronic β-adrenergic antagonist administration to pregnant women. Initial studies of β-adrenergic antagonist administration in pregnancy reported an attenuation of the tocolytic effects of adrenergic agonists and raised concerns over the incidence of premature labor following therapy with β-adrenergic blocking agents.[4] Administration of β-adrenergic antagonists near the time of delivery may produce neonatal bradycardia,[3] prolonged β-blockade due to longer elimination rates in neonate,[3,5] and neonatal hypoglycemia.[6] Finally, fetal β-adrenergic blockade may decrease umbilical blood flow and interfere with the normal fetal cardiovascular response to hypoxic stress.[7,8]

Esmolol is a cardioselective β-adrenergic antagonist with an extremely short duration of action, and has been successfully used for the treatment of hypertension following tracheal intubation[9] or during surgery.[10] In sheep brief maternal infusions of esmolol (300 and 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$) do not alter fetal blood pressure and produce only minor decreases in fetal heart rate, despite rapid placental transfer of the drug to the fetus.[11] Esmolol elimination is rapid in the sheep fetus; fetal plasma esmolol concentrations decrease to undetectable levels within 10 min following cessation of maternal esmolol infusion.[11] Thus, consideration has been given to the use of esmolol as an anesthetic adjunct in preeclampsia. However, neither the dose–response characteristics of maternally administered esmolol on resting fetal hemodynamics nor the degree of fetal β-adrenergic blockade from this therapy have been evaluated.

Materials and Methods

Surgical Preparation

Following approval by the Animal Care Committee, nine pregnant ewes (mean gestation 116 days; range 107–135 days; term 140 days) of mixed Western breeds were studied. Animals were fasted for 2 days and deprived of water for 1 day prior to surgery. Anesthesia was induced with sodium pentobarbital (4 mg/kg iv) and ketamine (4 mg/kg iv), the trachea intubated, and anesthesia maintained with halothane, 1–2%, in oxygen by mechanical ventilation. Under strict aseptic conditions, polyvinyl catheters were inserted into the maternal aorta and inferior vena cava *via* a femoral or mammary artery and

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vein, into the fetal aorta and inferior vena cava *via* an anterior tibial artery and superficial saphenous vein, and into the uterine cavity. In four animals a calibrated electromagnetic flow probe was secured on the left uterine artery. All catheters and flow probe cables were tunneled subcutaneously, exiting the skin through a small incision in the left flank, where they were maintained in a canvas pouch. Intravascular catheters were flushed daily with sterile heparinized saline and were filled with sterile heparin (1,000 U/ml). Each animal was allowed a 3-day recovery period following surgery during which they received penicillin, 900,000 units intramuscularly (im). Ewes also received gentamicin, 80 mg iv, on days of experiments.

Experimental Protocol

On the day of the study, maternal and fetal arterial catheters and the intrauterine catheter were connected to Gould™ transducer for the continuous measurement of arterial pressure and heart rate using a Grass™ 7D polygraph. The flow probe cables were connected to a Dienco™ monitor for the continuous measurement of uterine blood flow. Following 15 min of stable baseline measurements, each ewe received 15 min stepped infusions of esmolol (20, 40, 80, and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv) *via* a Harvard pump. Four ewes also received lower infusion rates (4 and 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$). To assess the degree of maternal and fetal β-adrenergic blockade, isoproterenol was injected iv first in the fetus (0.05 μg/kg), and then 2 min later in the ewe (0.1 μg/kg). Isoproterenol challenges were administered prior to esmolol infusion and at the end of each 15-min infusion period, prior to increasing the infusion rate. A gestational age to weight table was used in estimating fetal weight. Actual fetal weight was determined at the end of the study and actual fetal isoproterenol dose ranged from 0.042 to 0.054 μg/kg. Maternal and fetal arterial blood samples were obtained prior to esmolol infusion and at the end of each 15 min period (prior to isoproterenol challenge) and analyzed for arterial blood gas tensions using a Radiometer™ BMD microanalysis system. Thirty minutes following cessation of the highest esmolol infusion, arterial blood gas tensions, hemodynamic measurements, and isoproterenol challenges were repeated. In control experiments four of the nine ewes received saline instead of esmolol infusion, with an experimental protocol identical to that of esmolol infusion.

Statistical Analysis

Fetal arterial blood pressure was corrected for changes in intrauterine pressure by subtraction of intrauterine pressure. Effects of esmolol on heart rate, arterial blood pressure, intraamniotic pressure, uterine blood flow, and arterial blood gas tensions were evaluated by a one-way analysis of variance (ANOVA) with a repeated measures design (CRISP™ Statistical Package, San Francisco, California). A post hoc Dunnetts test was employed in determining significant changes from baseline measures prior to esmolol infusion. Maximal changes in heart rate and blood pressure (which occurred 15–45 s following isoproterenol injection) were used for data analysis. The degree of β-adrenergic blockade was calculated as the percent reduction in heart rate response to isoproterenol injection during esmolol infusion compared with this heart rate response during baseline conditions. Maternal and fetal dose–response curves for β-adrenergic blockade were compared using a two-way ANOVA. In addition, effective dose to produce 50% β-adrenergic blockade (ED_{50}) was calculated for each animal (ewe and fetus) using first order linear regression. Comparison of esmolol ED_{50} between ewes and fetuses was performed using a *t* test. Linear regression analysis was used to assess correlation between fetal gestational age and fetal heart rate response to isoproterenol or fetal esmolol ED_{50}. Data are presented as mean ± SEM. Significance was established at the $P < 0.05$ level.

Drugs

The following drugs were used in this study: sodium pentobarbital and ketamine HCL (Barber Veterinary Supply Co., Richmond, Virginia); halothane (Ayerst Laboratories Inc., New York, New York); penicillin G (Pfizer, New York, New York); gentamicin (LyphoMed, Rosemont, Illinois); and isoproterenol (Sigma Chemical Co., St. Louis, Missouri). Esmolol was provided as a gift from Americal Hospital Supply Co., McGraw Park, Illinois.

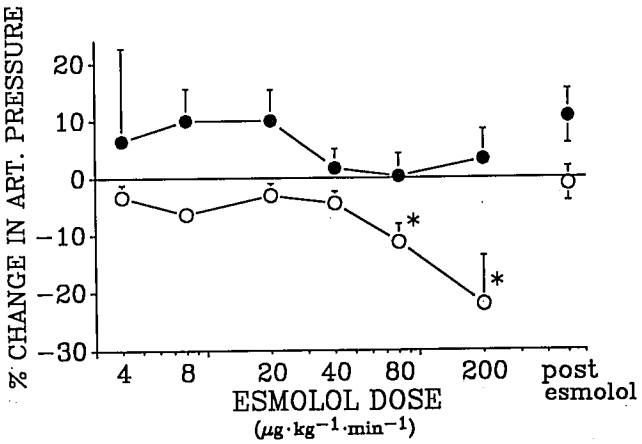

FIG. 1. Resting mean arterial pressure in ewes (○) and fetuses (●) at the end of 4, 8, 20, 40, 80, and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ esmolol infusions to the ewe, and at 30 min following cessation of maternal esmolol infusion. All values are expressed as mean (±SEM) percent change from baseline. *$P < 0.05$ *versus* baseline.

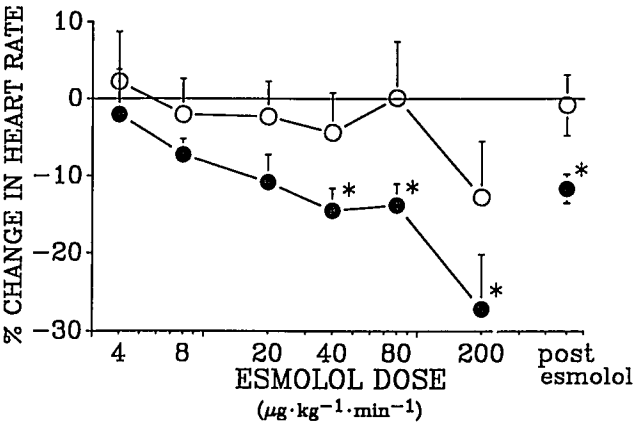

FIG. 2. Resting heart rates in ewes (○) and in fetuses (●) at the end of 4, 8, 20, 40, 80, and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maternal esmolol infusions to the ewe, and at 30 min following cessation of maternal esmolol infusion. All values are expressed as mean (±SEM) percent change from baseline. *$P < 0.05$ *versus* baseline.

Results

RESTING MEASURES

Saline control infusions did not alter resting blood pressure or heart rate. Baseline mean arterial pressure prior to esmolol infusion was 88 ± 3 mmHg in the ewe and 38 ± 5 mmHg in the fetus. Esmolol (200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) decreased resting maternal, but not fetal blood pressure, and maternal blood pressure returned to baseline levels 30 min following cessation of esmolol (fig. 1). Baseline heart rate was 96 ± 5 beats/min in the ewe and 194 ± 8 beats/min in the fetus. In contrast to its effect on blood pressure, esmolol decreased resting heart rate in the fetus but not in the ewe, and fetal heart rate remained below control levels 30 min following cessation of esmolol (fig. 2). Baseline maternal arterial blood gas tensions were *p*H 7.49 ± .01, P_{CO_2} 30 ± 0.9 mmHg, and P_{O_2} 97 ± 5.6 mmHg. Esmolol infusion did not alter maternal arterial blood gas tensions but produced fetal hypoxemia and acidemia, which resolved 30 min following cessation of esmolol (table 1). Saline infusion did not alter maternal or fetal arterial blood gas tensions. Baseline intrauterine pressure was 13 ± 2.1 mmHg and baseline uterine artery blood flow was 530 ± 140 ml/min. Neither saline nor esmolol altered resting intrauterine pressure or uterine blood flow.

β-ADRENERGIC BLOCKADE

Repeated isoproterenol challenges in saline controls produced consistent heart rate responses in ewe (89 ± 6% increase) and fetus (22 ± 3% increase). Maternal isoproterenol injection produced a decrease (20 ± 5%; $P < 0.05$) in uterine artery blood flow returning to baseline within 60–90 s. Fetal isoproterenol challenges did not influence uterine artery blood flow.

Prior to esmolol infusion, isoproterenol injection increased heart rate by 76 ± 8 beats/min in the ewe and 37 ± 2 beats/min in the fetus. Fetal response to isoproterenol injection and fetal sensitivity to esmolol (ED_{50}) were not related to gestational age. Although esmolol ED_{50}, calculated from each individual dose–response curve, was slightly less in the ewe than in the fetus (26 ± 9 *vs.* 66 ± 18 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $P < 0.05$), the overall dose–response curves did not differ significantly between ewe and fetus (fig. 3). Thirty minutes following cessation of esmolol infusion, significant β-adrenergic blockade was still present in both ewe and fetus (fig. 3).

Discussion

This study examines the effects of a stepped esmolol infusion in fetal lambs of varying maturity. The gestational ages studied, corresponding to 30–38 weeks gestation in humans, are clinically relevant because cesarean delivery in women with severe preeclampsia frequently occurs during this period. Although β-adrenergic responses in fetal lamb kidney vary considerably over this gestational age range,[12] our data suggest that cardiac responses to a β-adrenergic agonist and β-adrenergic antagonist do not.

The stepped dose–response paradigm performed in this study assumes that a steady state concentration of esmolol is achieved at the end of a 15-min infusion. Preliminary data in pregnant sheep[11] suggest that esmolol's half-life is brief enough (2–3 min) to achieve steady state concentrations in 10–15 min. However, residual β-adrenergic blockade 30 min following cessation of esmolol in this

TABLE 1. Maternal and Fetal Arterial Blood Gas Tensions Following Maternal Esmolol Infusions

	Esmolol Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)							30 min Postesmolol
	0	4	8	20	40	80	200	
Fetal								
*p*H	7.37 ± .01	7.35 ± 0.02	7.36 ± 0.02	7.40 ± 0.03	7.35 ± 0.02	7.35 ± 0.01	7.31 ± 0.02*	7.33 ± 0.02
P_{CO_2}	43.7 ± 1.5	45.2 ± 3.3	41.8 ± 2.4	40.7 ± 1.7	44.2 ± 2.6	42.0 ± 1.9	43.9 ± 2.7	43.3 ± 1.8
P_{O_2}	18.2 ± 1.2	16.3 ± 1.3	15.3 ± 1.5	18.2 ± 1.4	16.4 ± 1.6	15.1 ± 1.3	14.1 ± 1.5*	18.9 ± 1.5

Values represent the mean ± SEM of 4–9 animals. * $P < 0.05$ *versus* baseline.

study suggests a longer half-life. It is possible, therefore, that steady state conditions were not met in this study, leading to an underestimation of esmolol's potency in the pregnant ewe and fetal lamb. Despite this possibility, esmolol's potency in this study in sheep is greater than its potency in dogs and humans (fig. 4).[13-15] These data suggest that the appropriate dose to produce complete β-adrenergic blockade in the pregnant sheep (80–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) may produce significant but not complete blockade in humans.

Esmolol (2-methoxy-metoprolol) shares with metoprolol a relatively β-selective action, thereby producing a negative inotropic and chronotropic effect. The effect of such agents on resting heart rate and blood pressure depends on preexisting sympathetic tone and circulating catecholamine concentrations.[16] As such, esmolol may either not alter or decrease resting blood pressure and heart rate. These data agree with others in humans[15] that esmolol decreases blood pressure, and in sheep[11] that esmolol decreases maternal blood pressure and fetal heart rate. Although these effects are minor, they do suggest that maternally administered esmolol may produce maternal hypotension and fetal bradycardia.

Esmolol does not alter intrauterine pressure or produce uterine contractions in sheep. This is consistent with the observation that, although β-adrenergic agonists are effective tocolytics, β-adrenergic antagonists are associated with no or slight increases only in the risk of premature onset of labor.[2,17] Similarly, esmolol does not alter uterine blood flow in sheep, consistent with the absence of effect of β-adrenergic activity on resting uterine vascular tone. In contrast, maternally administered isoproterenol transiently decreases uterine blood flow. Because this effect occurs without a change in arterial blood pressure, one may speculate that isoproterenol reduces resistance in other vascular beds, thereby producing a "steal" from the uterine circulation.[18] Although this effect is minor and well tolerated in the healthy fetal lamb, its effect in the stressed human fetus is less certain, suggesting caution in the use of isoproterenol (2.5–5 μg), as an "intravenous test dose" in epidural anesthesia during labor.[19]

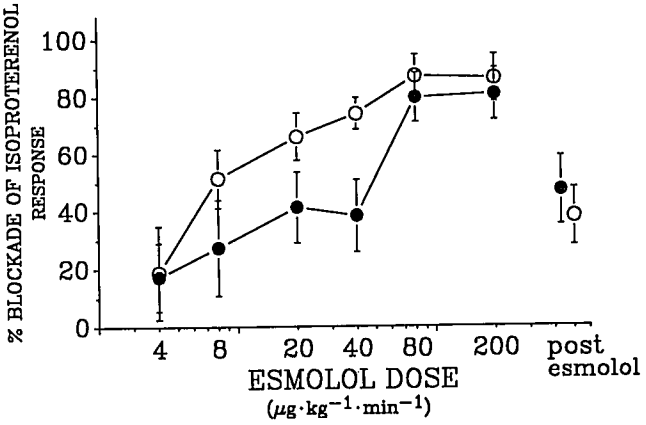

FIG. 3. Percent β-blockade following 4, 8, 20, 40, 80, and 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maternal esmolol infusion and at 30 min following cessation of esmolol infusion in ewe (○) and fetuses (●). All values are expressed as mean (±SEM) percent change from baseline. All maternal values, except 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and all fetal values, except 4 and 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, differ from baseline.

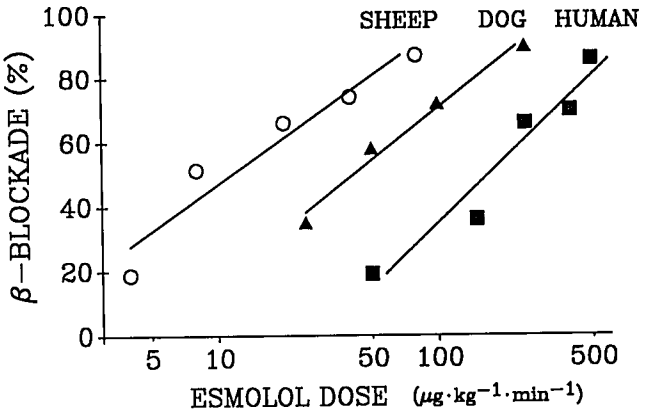

FIG. 4. Percent β-blockade (determined by change in heart rate response to isoproterenol challenge) *versus* esmolol infusion rate in sheep (○), dogs (▲),[12] and humans (■).[15] Dose–response curves were determined by first order linear regression. ED_{50} values (in $\mu g \cdot kg^{-1} \cdot min^{-1}$) are 26 (sheep), 45 (dog), and 195 (human).

Maternally infused esmolol decreases resting fetal heart rate and arterial P_{O_2} and produces fetal β-adrenergic blockade, all of which may be detrimental. Decreased fetal heart rate decreases fetal cardiac output, and may complicate interpretation of fetal heart rate monitoring. Fetal hypoxemia following esmolol may be due to decreased umbilical blood flow and gas exchange.[20,21] Fetal hypoxemia and acidosis was not observed in a previous study of esmolol in pregnant sheep,[11] perhaps because of the short duration of esmolol infusion (10 min) in comparison with this study (60–90 min). Maintenance of umbilical blood flow during fetal stress and fetal secretion of vasoconstricting substances depends in part on a vasodilatory action of β-adrenoceptor stimulation.[22] Fetal β-adrenergic blockade reduces umbilical blood flow and further reduces blood flow during fetal stress.[7,21] Finally, fetal β-adrenergic blockade may inhibit the fetus' ability to increase cardiac output during hypoxemic or hypovolemic stress,[7,8,21,22] and may lead to neonatal hypoglycemia and hemodynamic instability.[4,6]

Esmolol's duration of action in the fetus has been suggested to be brief and plasma esmolol concentrations decrease to undetectable levels 10 min following cessation of a brief esmolol infusion.[11] The effect of prolonged esmolol infusions on the fetus have not, however, been examined, and decreased fetal heart rate and residual blockade of isoproterenol's effect 30 min following ces-

sation of the 60–90 min esmolol infusion in this protocol suggests that prolonged effects may occur.

Based on these data, should the anesthesiologist refrain from administering esmolol to pregnant patients? It is hazardous to extrapolate results from healthy animals to pathologic states in humans because benefit might outweigh risk. For example, esmolol may improve maternal and fetal well-being by decreasing blood pressure in preeclamptic women with abnormally increased cardiac output, or by decreasing reflex tachycardia and hence blood pressure in preeclamptic women receiving vasodilator agents. Although these data do not determine whether it is esmolol dose or infusion time that produces adverse fetal effects, this study does suggest that one should limit esmolol infusion and carefully assess fetal and neonatal well-being when this drug is used.

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