Anesthesiology
74:292–297, 1991

Maternal and Fetal Effects of Labetalol in Pregnant Ewes

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Labetalol has been advocated to rapidly decrease blood pressure in preeclamptic women and to blunt the hemodynamic response to tracheal intubation. To assess labetalol's actions in a setting of uterine vasoconstriction, saline or labetalol (1 mg/kg) was infused into maternal venous catheters in 12 pregnant ewes receiving continuous maternal intravenous infusions of norepinephrine. Norepinephrine increased maternal mean arterial pressure (MAP) to 120 ± 4% of control and decreased uterine blood flow to 45 ± 6% of control. Labetalol, but not saline, altered these parameters: it decreased MAP to 101 ± 3% and increased uterine blood flow to 70 ± 7% of pre-norepinephrine values. In the second protocol, to assess the degree of labetalol-induced fetal adrenergic blockade, 7 pregnant ewes received, on separate days, saline or labetalol (0.3, 1.0, 3.0 mg/kg) *via* a maternal venous catheter. Maternally administered labetalol produced minor (<12%) decreases in maternal and fetal MAP, without significantly altering heart rate (HR). At each labetalol dose, the degree of α- and β-adrenergic blockade, determined by phenylephrine and isoproterenol challenge, was greater in the ewe than in the fetus. In the near-term pregnant ewe, intravenous (iv) bolus administration of labetalol ameliorated the effects of increased circulating norepinephrine on maternal MAP, uterine blood flow, and fetal *p*H and arterial O_2 tension (Pa_{O_2}), and produced less adrenergic blockade in the fetus than in the mother. (Key words: Anesthesia: obstetric. Fetus: drug effects. Sympathetic nervous system, beta-adrenergic antagonists: labetalol.)

TRACHEAL INTUBATION in women with severe preeclampsia may lead to severe hypertension and tachycardia. Hydralazine, nitroglycerin, sodium nitroprusside, and esmolol have been advocated to treat this maternal hypertension, but each has drawbacks.[1]

Recently, labetalol, a combined α- and β-adrenergic blocking agent, has been advocated to treat maternal hypertension accompanying tracheal intubation.[2] Orally administered labetalol effectively decreases blood pressure without apparent fetal compromise in women with severe preeclampsia.[3–5] Clinical studies demonstrate that orally administered labetalol neither decreases resting fetal heart rate (HR) nor produces signs of significant adrenergic blockade in the newborn.[6] This absence of apparent fetal adrenergic blockade is reassuring, since if present it would disrupt fetal cardiovascular homeostasis, complicate fetal HR monitoring, and interfere with fetal cardiovascular responses to hypoxemic stress.[7] Intravenously administered labetalol does not alter uterine blood flow in preeclamptic women at rest,[8] nor does intravenously administered labetalol alter placental perfusion in pregnant hypertensive rats.[9]

In contrast to the settings described above, anesthesiologists may most frequently use labetalol for acute, untreated hypertension due to sympathetic nervous system activation during tracheal intubation. The first protocol of this study examined the effect of intravenous (iv) labetalol during acute hypertension produced by norepinephrine infusion. Since fetal adrenergic blockade from maternal labetalol therapy may be deleterious and has not been studied directly, the second protocol examined the effect of iv labetalol on maternal α- and β-adrenergic responsiveness.

Materials and Methods

SURGICAL PREPARATION

After approval by the Animal Care and Use Committee had been obtained, a total of 19 pregnant ewes (mean gestation 121 ± 1 days, range 111–130 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 *via* 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 vein, into the fetal aorta and inferior vena cava *via* an anterior tibial artery and superficial saphenous vein, and into the uterine cavity. In animals to be studied in the norepinephrine infusion protocol, a calibrated electromagnetic flow probe was secured on the left uterine artery. All catheters and flow probe cables were tunneled subcutaneously and exited 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). After surgery, each animal was allowed a 3-day recovery period, during which it received penicillin 900,000 U intramuscularly (im). Ewes also received gentamicin 80 mg iv on days of experiments.

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Received from the Department of Anesthesia, Wake Forest University Medical Center, Winston-Salem, North Carolina. Accepted for publication September 28, 1990. Presented in part at the Annual Meetings of the American Society of Anesthesiologists, Las Vegas, Nevada, October 1986 and New Orleans, Louisiana, October 1989.

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Norepinephrine Infusion

For this protocol, a total of 16 experiments were performed in 12 ewes.

On the day of the study, maternal and fetal arterial catheters and the intrauterine catheter were connected to Gould™ transducers for the continuous measurement of arterial pressure and HR with a Grass™ 7D polygraph. The flow probe cables were connected to a Dienco™ monitor for the continuous measurement of uterine blood flow. Following 30 min of baseline measurements, a maternal venous infusion of norepinephrine, 0.5–1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, was begun, and titrated to a 20% increase in maternal mean arterial pressure (MAP). Five min later, saline (n = 5) or labetalol (n = 11) 1 mg/kg was injected into another maternal venous catheter, and the norepinephrine infusion was continued for 30 min. Maternal and fetal arterial blood samples were obtained at 10-min intervals throughout the experiment and analyzed for arterial *p*H and blood gas tensions with a Radiometer™ BMD microanalysis system. Experiments were performed in a random order and were separated by at least 48 h.

Adrenergic Blockade

For this protocol, a total of 19 experiments were performed in 7 ewes.

On the day of the study, monitoring was instituted as in the norepinephrine protocol, and after 20 min of stable baseline measurements, HR responses to iv isoproterenol and MAP responses to iv phenylephrine were determined by injections given in the following order: fetal isoproterenol (0.05 μg/kg fetal weight), maternal isoproterenol (0.1 μg/kg maternal weight), fetal phenylephrine (8 μg/kg fetal weight), and maternal phenylephrine (50 μg/kg maternal weight). Doses were determined in pilot experiments to produce changes of at least 20% in measured parameters. All injections produced transient (<3-min) effects, and parameters returned to baseline prior to the next injection. Fifteen minutes later, saline or labetalol (0.3, 1.0, or 3.0 mg/kg), in random order on separate days, was injected into the maternal venous catheter, and 10 min after labetalol injection, isoproterenol and phenylephrine challenges were repeated. A gestational age-to-weight table was used in estimating fetal weight.[10] At the end of the study, actual fetal weight was determined, and was within 15% of estimated weight in all cases.

Statistical Analysis

Fetal MAP was corrected for changes in intrauterine pressure by subtraction of intrauterine pressure. Effects of norepinephrine alone or with labetalol on hemodynamic variables and arterial *p*H and blood gas tensions were compared by two-way analysis of variance (ANOVA) followed by Dunnett's test. Because saline and labetalol groups differed in baseline arterial *p*H and blood gas tensions, the effect of initial arterial *p*H and blood gas tensions and group treatment on arterial *p*H and blood gas tensions at the end of norepinephrine infusion were examined with covariant ANOVA. Maximal changes in HR and MAP (which occurred 15–45 s after isoproterenol and phenylephrine injections) were used for data analysis. The degree of adrenergic blockade was calculated as the percent reduction, compared to baseline, in HR or MAP response after labetalol. Maternal and fetal dose–response curves for adrenergic blockade were compared by two-way ANOVA. The effective dose required to produce 50% adrenergic blockade (ED_{50}) was calculated for both isoproterenol and phenylephrine challenges for each animal (ewe and fetus) by using first-order linear regression. Comparison of labetalol ED_{50} between ewes and fetuses was performed by using a *t* test. Data are presented as mean ± SEM. $P < 0.05$ was considered significant.

Drugs

The following drugs were used in this study: sodium pentobarbital and ketamine HCl (Barber Veterinary Supply, Richmond, VA); halothane (Ayerst Laboratories, New York, NY); gentamicin (Lyphomed, Rosemont, IL); and isoproterenol, norepinephrine, and phenylephrine (Sigma, St. Louis, MO). Labetalol was a gift from Schering, Kenilworth, NJ.

Results

Norepinephrine Infusion

Maternal norepinephrine infusion (0.79 ± 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$) rapidly increased maternal MAP and decreased uterine blood flow, and these changes were sustained over time in saline control experiments (fig. 1). Labetalol injection returned maternal MAP to control values within 5 min and increased uterine blood flow, although uterine blood flow remained below control values (fig. 1). Maternal norepinephrine infusion increased fetal MAP and decreased fetal HR (fig. 2). Labetalol injection increased fetal HR, but did not significantly alter fetal MAP (fig. 2). Baseline intraamniotic pressure (10 ± 2 mmHg) and maternal arterial *p*H (7.48 ± 0.02), arterial CO_2 tension (Pa_{CO_2}) (30 ± 1 mm Hg), and Pa_{O_2} (92 ± 4 mm Hg) were normal and were unaltered by norepinephrine or labetalol injection. Norepinephrine infusion produced progressive fetal acidemia and sustained hypoxemia in control experiments, and these effects were reversed by labetalol injection (Table 1). Pa_{CO_2} was significantly greater and Pa_{O_2} was significantly less at baseline in saline controls than in the labetalol group. Covariant ANOVA revealed that change in arterial *p*H and blood

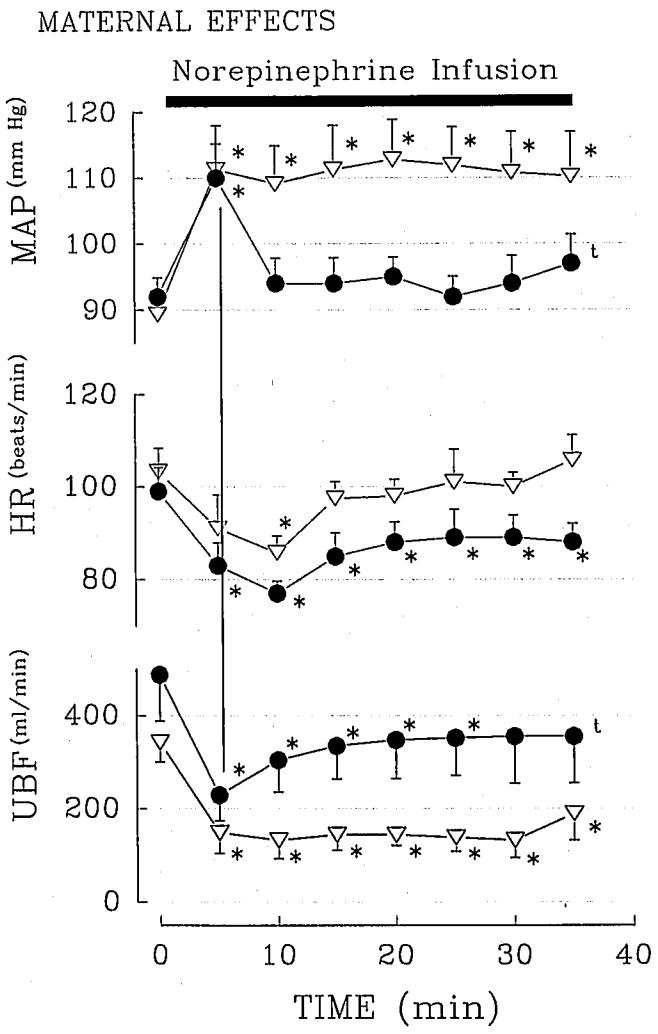

FIG. 1. Maternal MAP, HR, and uterine blood flow (UBF) before and for 30 min during norepinephrine infusion. Saline (triangles) or labetalol 1 mg/kg iv (filled circles) was injected at the time shown by vertical line. Each point represents mean ± SEM of 5–11 animals. *$P < 0.05$ *versus* baseline; †$P < 0.05$ *versus* saline from 10 to 35 min.

gas tensions at the end of norepinephrine infusion was not correlated to baseline values, but varied with treatment group. (Arterial *p*H decreased by 0.07 ± 0.02 units after saline, but only 0.03 ± 0.02 units after labetalol, $P < 0.05$; Pa_{O_2} decreased by 4.0 ± 1.1 mmHg after saline, but only 2.1 ± 0.5 mmHg after labetalol, $P < 0.05$).

Adrenergic Blockade

Baseline parameters (maternal HR = 99 ± 4 beats per min; fetal HR = 173 ± 7 beats per min; maternal MAP = 82 ± 2 mmHg; fetal MAP = 42 ± 2 mmHg) were unaffected by saline injection, whereas labetalol injection decreased maternal and fetal resting MAP without significantly altering HR (fig. 3). Labetalol did not affect maternal behavior, maternal or fetal arterial *p*H, or maternal or fetal blood gas tensions.

Responses to isoproterenol and phenylephrine injection were unaffected by saline injection (table 2). In contrast, maternally administered labetalol produced dose-dependent reductions in these responses in both ewe and fetus (fig. 4). At each dose the degree of α- and β-adrenergic blockade was greater in the ewe than in the fetus. ED_{50} values, expressed in milligrams per kilogram ewe body weight, for maternally administered labetalol for β-adrenergic blockade were 0.037 ± 0.011 mg/kg (ewe) and 2.2 ± 0.8 mg/kg (fetus) and for α-adrenergic blockade were 0.46 ± 0.17 mg/kg (ewe) and 8.9 ± 4.7 mg/kg (fetus). ED_{50} values for both α- and β-blockade differed between ewe and fetus ($P < 0.05$).

Discussion

Previous laboratory studies of the uterine vascular and fetal effects of labetalol have been performed at rest and not under conditions of increased catecholamine secretion

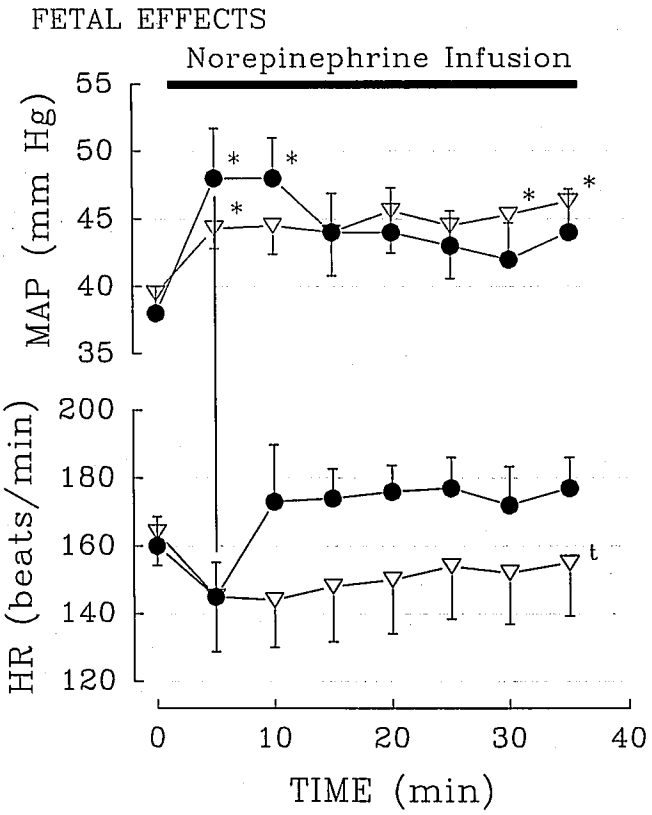

FIG. 2. Fetal MAP and HR before and for 30 min during norepinephrine infusion. Saline (triangles) or labetalol 1 mg/kg iv (filled circles) injected at the time shown by vertical line. Each point represents mean ± SEM of 5–11 animals. *$P < 0.05$ *versus* baseline; †$P < 0.05$ *versus* saline from 10 to 35 min.

TABLE 1. Fetal Arterial *p*H and Blood Gas Tensions during Norepinephrine Infusion

	Baseline	Time after Injection (min) 0	10	20	30
Saline					
*p*H	7.36 ± 0.02	7.34 ± 0.01*	7.34 ± 0.02*	7.29 ± 0.03*	7.29 ± 0.03*
P_{CO_2}	45 ± 1.3	48 ± 1.7	47 ± 2.1	51 ± 2.7*	47 ± 2.9
P_{O_2}	17 ± 0.4	11 ± 1.5*	11 ± 2.0*	12 ± 2.2*	13 ± 1.7*
Labetalol					
*p*H	7.40 ± 0.02	7.37 ± 0.02*	7.36 ± 0.02*	7.36 ± 0.02	7.37 ± 0.02
P_{CO_2}	38 ± 1.3	41 ± 1.7	40 ± 2.0	40 ± 1.7	40 ± 2.3
P_{O_2}	21 ± 1.0	15 ± 1.2*	18 ± 1.5	19 ± 1.1	19 ± 1.1

P_{CO_2} and P_{O_2} in mmHg.

* $P < 0.05$ *versus* baseline.

as seen clinically, and have not assessed fetal adrenergic blockade.[9] Similarly, clinical studies of labetalol use during pregnancy have examined effects at rest[8,11] or at steady state after oral administration[3–5] and have assessed newborn adrenergic blockade at a time remote from maternal administration.[6] In contrast, our aim was to provide data relevant to clinical use of this agent by anesthesiologists—to provide data on iv bolus administration, such as that frequently used during periods of high plasma catecholamine concentration. For this reason, measurements were obtained at times of peak effect after iv bolus, rather than during a pharmacologically purer approach of continuous infusion to steady state.

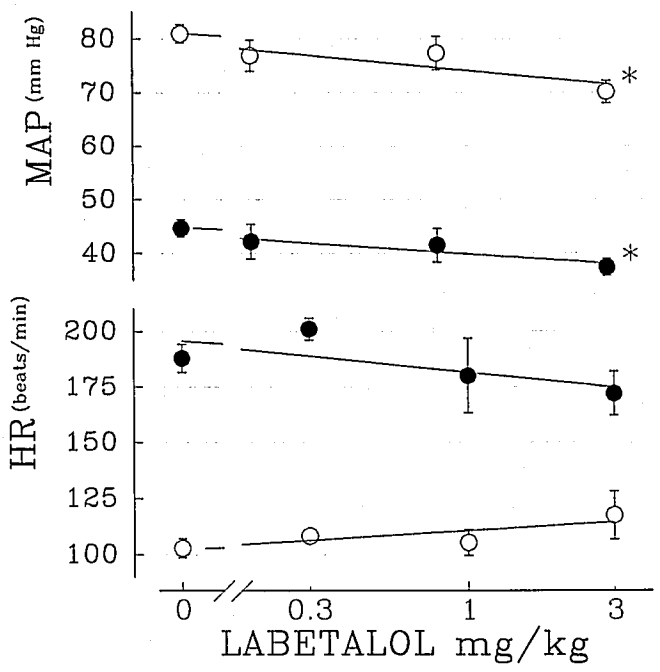

FIG. 3. Fetal (filled circles) and maternal (open circles) MAP and HR 10 min after iv maternal labetalol administration. Each point represents mean ± SEM of four to five animals. Lines represent first-order linear regression. *$P < 0.05$ *versus* baseline.

NOREPINEPHRINE INFUSION

Knowledge of labetalol's effect on a background norepinephrine infusion are relevant to anesthesia practice for three reasons. First, whereas norepinephrine infusion is not a model of preeclampsia, its effect may mimic cardiovascular effects of acute stress and increased sympathetic nervous system activity, such as those occurring during tracheal intubation. Since vascular sensitivity to constriction from catecholamines is increased in women with preeclampsia compared to normal pregnant women,[12] labetalol's effects after norepinephrine infusion may be particularly relevant to this group. Second, effects on uterine blood flow of an agent at rest may differ considerably from that during periods of high sympathetic nervous system activity. Third, previous studies in this laboratory of other antihypertensive agents using this model[13,14] allow for comparison with other clinically used drugs.

In the current study, labetalol decreased maternal MAP toward normal during norepinephrine infusion, while it increased uterine blood flow toward normal. One could argue that an increase in total uterine blood flow may not reflect an increase in placental perfusion,[15] but progressive fetal acidemia and hypoxemia accompanying norepinephrine infusion in control studies and resolution after labetalol injection argue for an increase in placental as well as total uterine blood flow. One could argue that greater deterioration in the saline controls than in the labetalol group simply reflect less reserve, because arterial *p*H and Pa_{O_2} were lower and Pa_{CO_2} was higher at baseline in the saline controls. However, covariant analysis did not support this argument, since deterioration in these parameters did not correlate with initial values but did correlate with treatment group. Nitroglycerin, sodium nitroprusside, verapamil, and nifedipine have been examined in this norepinephrine infusion model,[13,14] and all have decreased maternal MAP and increase uterine blood flow. Labetalol differs from these in producing these effects with the least effect on maternal HR.

TABLE 2. Responses to α- and β-Adrenergic Stimulation before and after Saline Injection

	Isoproterenol		Phenylephrine	
	Pre	Post	Pre	Post
Before saline				
Maternal HR (beats per min)	99 ± 4	185 ± 17		
Maternal MAP (mmHg)			82 ± 2	117 ± 4
Fetal HR	173 ± 7	211 ± 10		
Fetal MAP			42 ± 2	65 ± 2
After saline				
Maternal HR	103 ± 4	186 ± 14		
Maternal MAP			81 ± 2	115 ± 6
Fetal HR	188 ± 6	214 ± 8		
Fetal MAP			45 ± 2	63 ± 4

Isoproterenol and phenylephrine injected separately in ewe and fetus as described in Materials and Methods.

No significant differences before and after saline injection in either baseline or drug-stimulated values.

ADRENERGIC BLOCKADE

The effect of adrenergic blockade on resting HR and blood pressure depends on preexisting sympathetic tone and circulating catecholamine concentrations.[16] This likely explains the relatively small changes after labetalol injection on resting MAP observed in this protocol, as opposed to the marked effect during norepinephrine infusion.

In the current study, maternally administered labetalol was well tolerated by the fetus and produced only minor degrees of fetal adrenergic blockade, while effectively blocking the response of the mother. These results are in contrast to those obtained in our laboratory with the short-acting β-adrenergic antagonist, esmolol.[17] In that study, esmolol produced equivalent degrees of β-blockade in fetus and ewe, accompanied by fetal hypoxemia. The etiology of this difference is unclear, since both agents extensively cross the placenta.

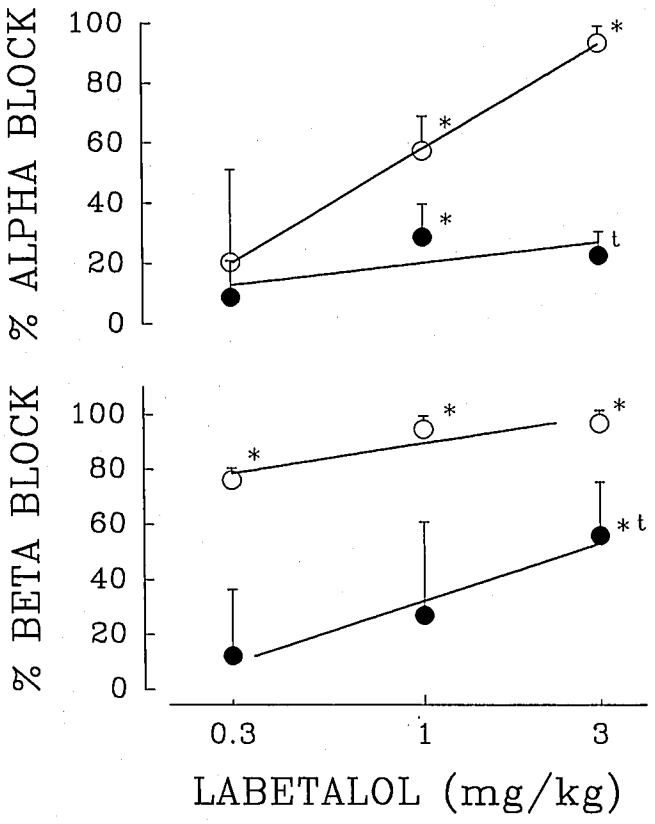

FIG. 4. Percent blockade of α-adrenergic response (*top*, MAP to phenylephrine) and β-adrenergic response (*bottom*, HR to isoproterenol) in ewe (open circles) or fetus (filled circles) 10 min after maternal iv labetalol administration. Each point represents mean ± SEM of four to five animals. Lines represent first-order linear regression. $^{*}P < 0.05$ *versus* baseline; $^{t}P < 0.05$: curves of ewe and fetus differ.

CLINICAL IMPLICATIONS

Clinical use of labetalol in obstetrics should not be based solely on animal work. A brief norepinephrine infusion in a normal animal will not completely reproduce the actions of increased sympathetic nervous system activity accompanying tracheal intubation in women with preeclampsia. Nonetheless, the current results of labetalol's effect on norepinephrine-induced hypertension agree with preliminary clinical studies that demonstrated blunting of maternal systemic hemodynamic responses to tracheal intubation by labetalol without adverse fetal effects.[2] Similarly, the current data agree with findings in preeclamptic women at rest[8] and in a rodent model of preeclampsia[9] that labetalol does not decrease uterine blood flow.

Placental transfer of drug may differ considerably between sheep and human, due to differences in placental structure and pathologic alterations in placental permeability in preeclampsia. However, limited fetal adrenergic blockade observed in the second part of the current study agrees with clinical experience. Side effects associated with other β-adrenergic antagonists,[18] such as neonatal bradycardia, hypoglycemia, respiratory depression, and growth retardation are rarely seen with labetalol.[3-5] Labetalol 1

mg/kg iv does not change fetal HR or aortic blood flow in preeclamptic women.[8] Likewise, newborns of mothers who have received labetalol show insignificant to no evidence of sympathetic blockade, as measured by serum glucose and sudomotor, vasomotor, and oxygen consumption responses to thermal stress.[6] Taken together, these studies suggest that maternally administered labetalol may be less likely than other adrenergic blockers to interfere with fetal stress responses.

The ultimate use of labetalol in obstetric anesthesia will depend on clinical demonstration of safety and efficacy as well as on consideration of disadvantages such as large variability in effective dose and duration of action[11,19] and possible depression of cardiac output in some individuals. Careful postnatal observation should be exercised after maternal iv bolus administration of any adrenergic antagonist, particularly when used in a patient carrying a compromised fetus.

The authors wish to thank James Rose, Ph.D. for assistance in study design and Barbara Tucker and Bill Brooks for technical support.

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