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# Effects of Epinephrine on the Renal Vascular Bed of Fetal, Newborn, and Adult Sheep

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**ABSTRACT. The renal hemodynamic response to renal artery infusions of epinephrine were compared in conscious and chronically instrumented fetal (125–139 days gestation; term 145 days), newborn (5–13 days postnatal), and nonpregnant adult sheep. Epinephrine produced similar dose related decreases in renal blood flow velocity in all three groups. The mean estimated concentration of epinephrine in renal blood producing a 50% decrease in renal blood flow velocity, ED50, was 0.008 μg/ml. Epinephrine infusions during renal α-adrenoceptor blockade with phentolamine produced increases in renal blood flow velocity that were of greater magnitude in fetal compared to newborn and adult sheep. The maximal increase in renal blood flow velocity observed were 57 ± 11%, 22 ± 3%, and 18 ± 3% in fetal, newborn, and adult sheep, respectively ($p < 0.001$). This vasodilation produced by epinephrine during α-adrenoceptor blockade was completely inhibited by ICI 118,551, a $\beta_2$-adrenoceptor antagonist. Inhibition of renal vascular β-adrenoceptors with propranolol in fetal sheep did not enhance α-adrenoceptor-mediated renal vasoconstriction with epinephrine infusions. Results of the present study demonstrate similar renal vasoconstrictor responses to renal artery infusion of epinephrine in fetal, newborn, and adult sheep. In contrast, the renal vasodilator responses observed with epinephrine infusions during renal α-adrenoceptor blockade were greater in fetal compared to newborn and adult sheep. However, epinephrine-mediated renal vasoconstriction was not enhanced by blockade of β-adrenoceptors in fetal sheep. (*Pediatr Res* 23: 181–186, 1988)**

### Abbreviations

**RBF, renal blood flow**
**RVR, renal vascular resistance**
**MABP, mean arterial blood pressure**
**D5W, 5% dextrose in water**

The fetus produces high levels of circulating catecholamines during stressful conditions, including uncomplicated vaginal delivery, where plasma concentrations of catecholamines are more than 10-fold higher than in resting adults (1). However, despite these high levels, the phenomenon of birth is associated with an increase in RBF and glomerular filtration (2) suggesting that the developing kidney may respond differently to catecholamine stimulation than the adult.

In this respect, Buckley *et al.* (3) found that the renal vasculature of anesthetized newborn piglets is less sensitive to α-adrenoceptor stimulation than older swine. However, Jose *et al.* (4) have shown that anesthetized puppies were more sensitive to intrarenal epinephrine than adults and had increased renal α-adrenoceptor affinity and density compared to adult dogs (5).

To further investigate the functional role of circulating catecholamines in modulating renal hemodynamics during development, the present study was designed to specifically examine the developmental response of the renal vascular bed to direct intrarenal infusions of epinephrine, using conscious and chronically instrumented fetal, newborn, and nonpregnant adult sheep.

## METHODS

*Animal preparation and surgical procedures.* Fetuses of 14 pregnant sheep of Dorset and Suffolk mixed breeding were studied between 125 and 139 days gestation (term 145 days). Gestational ages were based on the induced ovulation technique as previously described (6).

Ewes were fasted for 48 h before surgery. General anesthesia of the ewe and fetal surgery were performed as previously described (6). Briefly, when the ewe was receiving a mixture of 1% halothane, 33% oxygen, and 66% nitrous oxide, the uterus was opened and bilateral femoral arterial and venous catheters were inserted. A catheter was also secured in the amniotic cavity for intrauterine pressure measurements. The left kidney was exposed through a left flank incision. A Doppler flow probe, constructed in our laboratory, was secured around the renal artery with care being taken to not interfere with renal innervation. Thereafter, a nonobstructive renal artery catheter was implanted using the method described by Herd and Barger (7) and previously used by us (8, 9).

All vascular catheters were impregnated before surgery with dimethylpoly-siloxane (Acumetric, Elizabethtown, CT) to reduce clotting. After surgery, the ewes were kept in a restricted area and fed a standard diet. Experiments were started 3 days after surgery. Fetal weight was estimated according to the following formula: fetal body weight (kg) = [0.096 × gestational age (days)] − 9.233, $r = 0.85$, $p < 0.001$ (10).

Twelve newborn lambs (6.1 ± 0.3 kg) between the ages of 5 and 13 days and nine nonpregnant adult ewes (43 ± 1 kg) were also studied. Surgery in these animals was similar to that described for the fetuses above. An additional catheter was placed in the left ventricle of the newborns and adults for infusion of radioactive microspheres to determine RBF in ml/min. After surgery, the newborn lambs were returned to their mothers.

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Procedures on the use of sheep in this project were approved by the University of Iowa's Animal Care and Use Committee and are in accordance with PHS policies and the Guide for the Care and Use of Laboratory Animals, NIH Publication no. 85-23, revised 1985.

*Physiological studies.* Each pregnant and nonpregnant ewe was transferred into a small cart permitting it to stand during the physiological studies. Each lamb was supported upright with a harness.

A 60-min equilibration period was allowed to permit the animal to adapt to the laboratory environment and to assure stability of the preparation before starting the experiment. Arterial blood was collected from the femoral artery catheter at the beginning of each experiment to determine arterial pH and blood gases ($pO_2$, $pCO_2$). During the studies, D5W was infused continuously into the renal artery at a rate of 0.1 ml/min. Epinephrine was diluted in D5W and given in graded doses starting with 0.00625 μg/kg and thereafter doubling each dose to a maximum of 0.4 μg/kg of body weight. Each dose was infused directly into the renal artery as a 0.3 ml infusion over 30 s using a Harvard pump. In addition, D5W was infused as a vehicle control. Doses of epinephrine and D5W were administered in random sequence and each dose was given twice. There was an interval of at least 5 min between each dose to allow renal flow to return to baseline. Usually RBF was back to baseline 3 min after epinephrine administration. The largest epinephrine dose infused was determined by the dose that produced the maximal renal hemodynamic response without changing blood pressure and heart rate.

In a second series of experiments done the same day and in the same animal, intrarenal infusions of epinephrine and placebo were repeated during intrarenal administration of the nonspecific α-antagonist, phentolamine (4 μg/kg/min). The efficacy of a α-adrenergic blockade was confirmed by the complete inhibition of vasoconstriction to an intrarenal infusion of norepinephrine (0.2 μg/kg).

In a third series of experiments, renal hemodynamic effects of intrarenal epinephrine infusions were compared before and during renal arterial infusion of propranolol at 5 μg/kg/min in six separate fetal sheep studied between 128 and 137 days gestation. This dose of propranolol has been shown to inhibit renal vasodilation after an intrarenal infusion of isoproterenol in fetal sheep (8).

During each experiment, arterial and amniotic pressures were recorded continuously using Statham P23Db pressure transducers (Statham Instruments, Schiller Park, IL). Fetal arterial pressure was corrected relative to concomitant amniotic pressure. Fetal heart rate was monitored with a cardiotachometer triggered from the fetal arterial pressure pulse wave.

Change in RBF velocity to the left kidney was monitored continuously using the ultrasonic pulsed Doppler flowmeter, modified from the original design of Hartley and Cole (11), and constructed by the University of Iowa Bioengineering Resource Facility (12). The pulsed Doppler flow probe consisted of a silastic cuff around a 1 mm diameter 20 MHz piezoelectric crystal with insulated copper wire leads. The techniques for construction, use of probes, and application of the flowmeter have been validated and described in detail (12). In our model, the validity of the pulsed doppler flowmeter for use in determining percent changes (%Δ) in fetal RBF velocity has previously been demonstrated (13).

Baseline RBF in ml/min was measured using the microspheres technique. Approximately $4.0 \times 10^6$ radioactive microspheres (15 ± 3 μm diameter) labelled with either $^{141}Ce$, $^{46}Sc$, $^{85}Sr$, or $^{95}Nb$ (3M Co., Minneapolis, MN) were infused over a 30-s period into the fetal femoral vein catheter and then immediately flushed with 3 ml of 0.9% saline solution (14, 15). In newborns and adults, radioactive microspheres were infused into the left ventricular catheter. Blood for lower body independent reference sample was collected from the femoral artery during a period of 3 min beginning 20 s before the injection of microspheres at a withdrawal rate of 2.91 ml/min using a Harvard infusion-withdrawal pump. Fetal blood collected for lower body independent reference sample was replaced with an equal volume of maternal blood to avoid any hemodynamic effect of sampling. At the end of the experiment, the animals were sacrificed with a lethal dose of pentobarbital sodium (Somlethal, Mid-Tech, Inc., Elwood, KS). Animals were weighed and kidneys were taken for radioactivity determinations.

To assess the approximate epinephrine concentration in renal blood, the epinephrine dose in μg/kg was multiplied by the weight of the animal. This product, divided by blood flow (ml/min), provides an approximation of epinephrine concentration (μg/ml) in the renal vascular bed (8, 16).

*Analytical procedures.* Arterial blood for pH, $pCO_2$, and $pO_2$ was collected anaerobically in heparinized glass syringes and measurements were immediately determined with the appropriate pH, $pCO_2$, and $pO_2$ electrodes at 39° C using a Radiometer PHM 72 MK 2 acid-base analyzer (Radiometer Co., Copenhagen, Denmark).

Gamma emissions generated from the microspheres were measured in the left kidney and reference femoral arterial blood samples using a Beckman 300 γ spectrometer. Energy window ranges were set between 74-102 Kev for $^{141}Ce$, 210–275 Kev for $^{85}Sr$, 320–410 Kev for $^{95}Nb$, and 420–580 Kev for $^{46}Sc$. Handling of the kidney before counting and isotopes separation were as previously described (6, 15).

*Drugs.* The following drugs were used: Epinephrine (Abbott, North Chicago, IL), phentolamine (Regitine, CIBA, NJ), norepinephrine (Levophed, Breon, NY), propranolol (Inderal, Ayerst, NY), and ICI 118,551 (Imperial Chemical Industries, Macclesfield, Cheshire, England).

*Determinations and data analysis.* RBF, using the microspheres technique, was determined according to the following formula: RBF (ml/min) = total kidney counts × reference flow from the femoral artery (ml/min)/total femoral blood counts.

RVR was determined according to the following formula: RVR = RPP/RBF, where RPP is the renal perfusion pressure estimated to be equal to aortic pressure minus inferior vena cava pressure.

Percent changes in RBF velocity (%Δ RBF), using a Doppler flow probe, were calculated using the following formula:

$$\%\Delta \text{ RBF} = [(E_{DS} - B_{DS})/B_{DS}] \times 100$$

where $E_{DS}$ is the maximal doppler shift in KHz during intrarenal epinephrine infusions; $B_{DS}$ is the baseline Doppler shift in KHZ.

Comparisons of dose response curves between fetal, newborn, and adult sheep were performed by simultaneous analysis of physiological dose-response curves as described by DeLean *et al.* (17) and previously used by us (8, 9). These comparisons were done by using the ALLFIT program adapted for an Apple computer by Martin H. Teicher, Department of Psychiatry, Harvard Medical School. ALLFIT was made available by the Biomedical Computing Technology Information Center, Vanderbilt Medical Center, Nashville, TN. Briefly, ALLFIT analysis was based on the logistic function:

$$y = \frac{a-d}{1 + (x/c)^b} + d$$

where x and y were the dose response respectively; and "a," "b," "c," and "d" were the four fitted parameters: response at zero dose (a), slope factor (b), $ED_{50}$ (c), and response at "infinite" dose (d). Goodness of fit of individual dose-response curves was evaluated by: 1) F ratio test, which represented the ratio of residual variance for one curve to the overall residual variance of the other curves, and 2) run test, which evaluated the randomness of distribution of data points around and along the fitted curve. Significant F ratio tests ($p < 0.05$) or run tests ($p < 0.05$) suggested poor fits according to the logistic model. Consequences of forcing parameters to be equal were also evaluated by an F

ratio test. A significant $p$ value $< 0.05$ indicated that data supported the hypothesis that shared parameters were in fact different from each other.

One-way ANOVA with Newman-Keuls multiple comparisons procedure was used to compare baseline parameters. Paired $t$ tests with Bonferroni correction was used to compare responses for specific epinephrine doses before and during $\beta$-adrenoceptor blockade. The term "significant" is used throughout to describe changes with a total $p$ value $< 0.05$ in a two-sided significance limit. Values are expressed as means ± SEM.

## RESULTS

Baseline arterial blood pH, blood gas values, and hematocrit are presented in Table 1. Baseline renal hemodynamics, MABP, and heart rate values in fetal, newborn, and adult sheep are presented in Table 2. RBF values measured by the microsphere technique increased with maturation and were lower in fetuses than in newborn or adult sheep when expressed in ml/min ($F = 49.9$, $p < 0.05$), or when corrected for kidney weight (ml/min/g kidney weight) ($F = 17.4$, $p < 0.05$). Moreover, RVR was significantly higher in fetal than in newborn and adult sheep ($F = 62.4$, $p < 0.05$), and declined progressively with age. However, when RVR was corrected for kidney weight, RVR tended to be higher in fetuses than in newborn or adult sheep, but the differences were not found to be significant ($F = 1.7$, $p = 0.22$).

*Effect of intrarenal epinephrine infusions on MABP and heart rate.* Intrarenal infusions of epinephrine had no effect on the systemic circulations of fetal, newborn, or adult sheep. As shown in Figure 1, MABP and heart rate did not vary during renal artery infusions of different epinephrine concentrations.

*Effect of intrarenal epinephrine infusions on percent changes (%Δ) in mean RBF velocity.* Epinephrine produced dose-related decreases in mean RBF velocity in fetal, newborn, and adult sheep (Fig. 2). All three dose-response curves were appropriately fitted, as evidenced by goodness of fit ($F = 0.38$, $p = 0.160$) and run test ($p > 0.05$) for the fetus, newborn (goodness of fit $F = 2.68$, $p = 0.150$; run test $p > 0.05$), and adult (goodness of fit $F = 0.86$, $p = 0.782$; run test $p > 0.05$). Maximal and zero dose responses were similar for all three groups, and all curves showed

Table 1. *Baseline arterial blood values (means ± SE)*

| | Fetal sheep ($n = 9$) | Newborn sheep ($n = 12$) | Adult sheep ($n = 9$) |
|---|---|---|---|
| pH | 7.39 ± 0.01 | 7.41 ± 0.01 | 7.49 ± 0.01 |
| $pCO_2$ (mm Hg) | 40 ± 3 | 37 ± 1 | 33 ± 1 |
| $pO_2$ (mm Hg) | 23 ± 1 | 98 ± 4 | 104 ± 4 |
| Hematocrit (%) | 31 ± 1 | 25 ± 1 | 20 ± 2 |

Table 2. *Baseline renal and systemic hemodynamic values (means ± SE)*

| | Fetal sheep ($n = 7$) | Newborn sheep ($n = 11$) | Adult sheep ($n = 9$) |
|---|---|---|---|
| RBF to left kidney | | | |
| ml/min | 23 ± 3* | 77 ± 7† | 469 ± 58‡ |
| ml/min/g kidney wt | 1.49 ± .16* | 3.00 ± 0.21† | 4.92 ± 0.61‡ |
| RVR in left kidney | | | |
| mm Hg/ml/min | 2.68 ± .23* | 1.21 ± 0.13† | 0.26 ± 0.07‡ |
| mm Hg/ml/min/g kidney wt | 45 ± 5 | 29 ± 4† | 28 ± 10 |
| MABP mm Hg | 51 ± 2* | 83 ± 2 | 93 ± 4‡ |
| Heart rate beats/min | 168 ± 8* | 212 ± 10† | 83 ± 4‡ |

* Values statistically different from newborn ($p < 0.05$).
† Values statistically different from adults ($p < 0.05$).
‡ Values statistically different from fetus ($p < 0.05$).

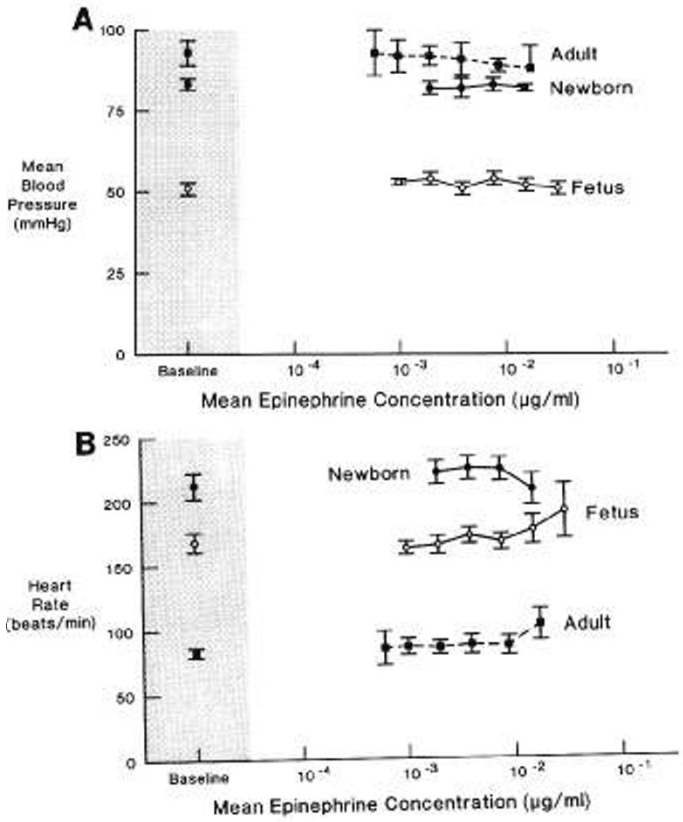


Fig. 1. Mean arterial blood pressure ($A$) and heart rate ($B$) during intrarenal epinephrine infusions. Values are means ± SE. Mean epinephrine concentration refers to estimated concentration in renal blood. Baseline refers to placebo infusion of vehicle. No differences were noted in mean blood pressure or heart rate when different doses, including placebo, were compared ($p > 0.05$, ANOVA).

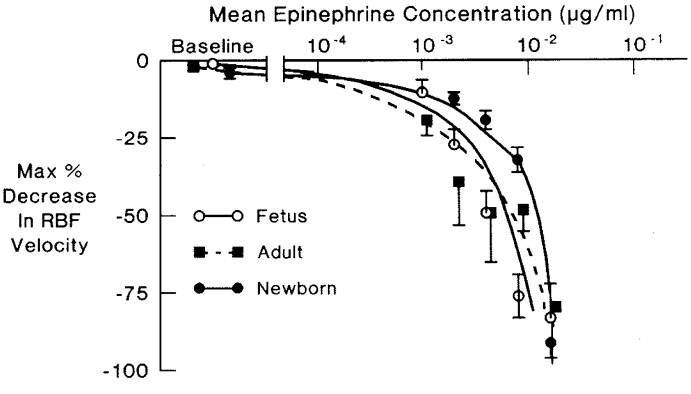


Fig. 2. Effect of intrarenal epinephrine infusion on percentage changes in RBF velocity. Values are means ± SE. Mean epinephrine concentration refers to estimated concentration in renal blood. Baseline refers to placebo infusion of vehicle. The effective estimated concentration of epinephrine in renal blood producing a 50% decrease in renal flow velocity ($ED_{50}$) was 0.008 µg/ml and was similar in all three groups.

no deviation from parallelism ($F = 2.83$, $p = 0.07$). The effective estimated concentration of epinephrine in renal blood producing a 50% decrease in renal flow velocity, ED50, was 0.008 µg/ml, and was similar in all three groups.

*Effect of intrarenal epinephrine infusions on percent change in mean RBF velocity during renal α-adrenoceptor blockade.* To demonstrate that the vasoconstriction produced by infusion of epinephrine was secondary to α-adrenoceptor stimulation and to

study the development of epinephrine induced renal vasodilation by β-adrenergic receptor stimulation, the same protocol was repeated during continuous intrarenal infusion of phentolamine. During intrarenal infusion of phentolamine, no changes in MABP and heart rate were observed. Renal vasoconstriction produced by epinephrine was completely inhibited during renal α-adrenoceptor blockade. Moreover, intrarenal epinephrine infusions produced renal vasodilation in fetal, newborn, and adult sheep (Fig. 3). A dose-response relation was noted in fetal (goodness of fit $F = 4.82$, $p = 0.07$; run test $p > 0.05$), newborn (goodness of fit $F = 0.26$, $p = 0.114$; run test $p > 0.05$), and adult sheep (goodness of fit $F = 0.38$, $p = 0.250$; run test $p > 0.05$). No differences in minimum response, slope, ED50, and maximum response were noted between newborn and adult sheep ($F = 1.01$, $p = 0.466$). However, the slope of the fetal dose response curve and the maximum response were different when compared to newborn and adult sheep ($F = 66.9$, $p < 0.001$). The maximal increases in RBF velocity were 57 ± 11% in fetal, 22 ± 3% in newborn, and 18 ± 3% in adult sheep, respectively.

*Effect of intrarenal β-adrenoceptor antagonists on epinephrine induced renal vasodilation during renal α-adrenoceptor blockade.* To demonstrate that the vasodilation noted was mediated by β-adrenoceptors, intrarenal propranolol was infused at 5 μg/kg/min. Propranolol completely inhibited renal vasodilation produced by epinephrine during renal α-adrenoceptor blockade in fetal (Fig. 4) ($n = 8$), newborn ($n = 5$), and adult ($n = 4$) sheep. Moreover, no changes in MABP, heart rate, or baseline mean RBF velocity were noted during intrarenal propranolol infusions.

To demonstrate that the β-adrenoceptor antagonist subtype mediating renal vasodilation was a $\beta_2$-adrenoceptor, in some animals, ICI 118,551, a highly specific and potent $\beta_2$-adrenoceptor antagonist, was infused intrarenally at 10 μg/kg/min. As shown in Figure 5, renal vasodilation was completely inhibited by ICI 118,551 in all three groups (fetus, $n = 3$; newborn, $n = 3$; adult, $n = 3$) without changes in systemic hemodynamics or baseline mean RBF velocity.

*Effect of intrarenal β-adrenoceptor blockade on epinephrine-induced renal vasoconstriction.* To test the hypothesis that the measured renal vascular response to epinephrine could be a summation of α- and β-adrenoceptor stimulation, doses of epinephrine were infused before and during renal artery infusion of propranolol (5 μg/kg/min). Renal β-adrenoceptor blockade did not effect the vasoconstriction to renal artery infusions of epinephrine (Fig. 6).

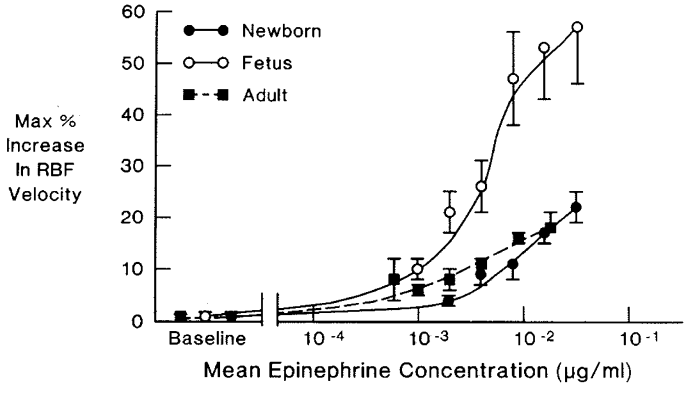


Fig. 3. Effect of intrarenal epinephrine infusion on percentage changes in RBF velocity during α-adrenoceptor blockade. Values are means ± SE. Mean epinephrine concentration refers to estimated concentration in renal blood. Baseline refers to placebo infusion of vehicle. α-Adrenoceptor antagonist, phentolamine, was infused intrarenally at 4 μg/kg/min. The slope and maximum response of the fetal dose response curve were different when compared to both newborn and adult sheep ($p < 0.001$).

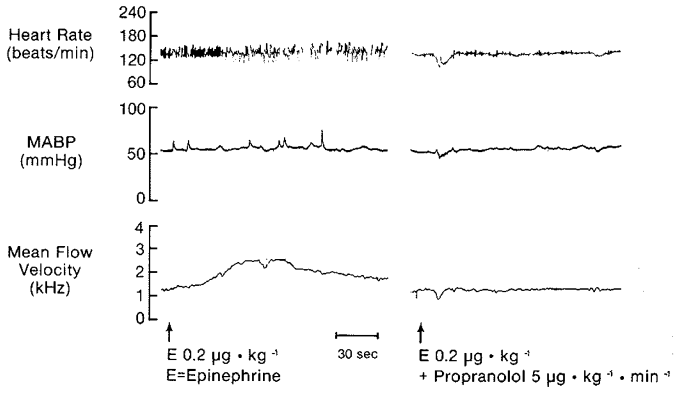


Fig. 4. Effect of propranolol on epinephrine mediated renal vasodilation during intrarenal phentolamine infusion in a fetal sheep (132 days gestation). *Arrows* indicate start of infusion. Phentolamine infusion = 4 μg/kg/min.

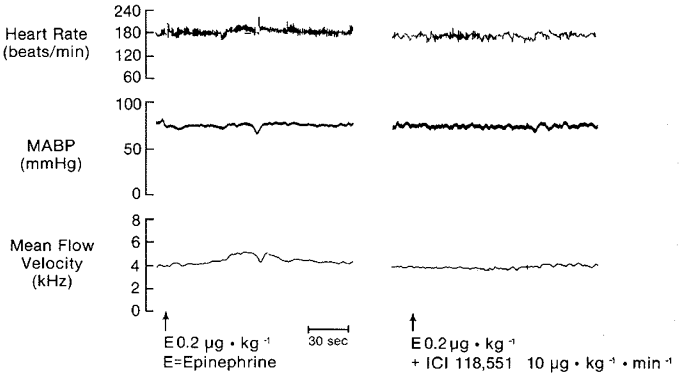


Fig. 5. Effect of ICI 118,551 on epinephrine mediated renal vasodilation during intrarenal phentolamine infusion in a newborn lamb (6 days). *Arrows* indicate start of infusion. Phentolamine infusion = 4 μg/kg/min.

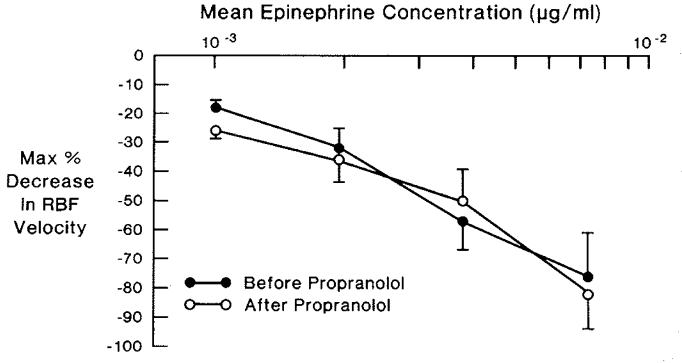


Fig. 6. Effect on intrarenal β-adrenoceptor blockade on epinephrine-induced renal vasoconstriction in fetal sheep. Values are mean ± SE. Mean epinephrine concentration refers to estimated concentration in renal blood ($n = 6$). Propranolol infusion = 5 μg/kg/min. No differences were noted before and after propranolol infusion ($p > 0.05$, paired $t$ test).

## DISCUSSION

Herein we demonstrate that intrarenal infusion of epinephrine produces a similar α-adrenoceptor mediated renal vasoconstriction in fetal, newborn, and adult sheep. These results are consistent with known α-adrenergic vasoconstrictive mechanisms that predominate over β-adrenergic-mediated vasodilation dur-

ing catecholamine stimulation (18). However, the present results are somewhat different from previous studies in anesthetized animals during development (3, 4). Jose *et al.* (4) demonstrated that the renal vascular response to intrarenal infusion of epinephrine is of greater magnitude in anesthetized newborn dogs than in adult dogs. However, Buckley *et al.* (3) showed that the renal vasculature of anesthetized swine at birth is less responsive to systemic administration of norepinephrine than older piglets. Reasons to explain these differences are not very clear. However, one may speculate that the use of conscious animals in our study versus anesthetized animals in previous studies (3, 4) and species variation may partially explain these differences. It is known that anesthesia may alter RBF (19, 20), depress smooth muscle tone (21), and modify the vascular response to endogenous catecholamines in some vascular beds (22).

Inhibition of $\alpha$-adrenoceptors during intrarenal infusion of phentolamine did not change baseline RBF in fetal, newborn, and adult sheep suggesting that the $\alpha$-adrenoceptor tone during resting conditions does not account for the low RBF during development. However, intrarenal infusions of epinephrine during $\alpha$-adrenoceptor blockade produced renal vasodilation which was of greater magnitude in fetuses than in newborn and adult sheep. This response could be inhibited by ICI 118,551, a specific $\beta_2$-adrenoceptor antagonist (23), supporting the concept that vascular $\beta_2$-adrenoceptors are functional early during renal maturation. These results are consistent with our previous study demonstrating enhanced renal $\beta$-adrenergic response to renal nerve stimulation (24) and infused norepinephrine (9) in fetal sheep and provide evidence of an age-dependent $\beta$-adrenergic renal vasodilator mechanism during development in sheep. Furthermore, one may speculate that the ontogeny of renal vascular $\beta$-adrenoceptor-mediated responses are similar whether adrenoceptor stimulation occurs with neurotransmitter release or by activation of extrajunctional adrenoceptors via circulating catecholamines (25). The possibility that $\beta_1$-adrenoceptors may also mediate the renal vasodilation observed (26) was not investigated herein. However, since 100% of the renal vasodilation was inhibited using ICI 118,551, it seems unlikely that activation of $\beta_1$-adrenoceptors has a major role in controlling the renal vascular response to epinephrine infusion in immature animals.

The greater renal vasodilation observed between fetal compared to newborn and adult sheep is somewhat different from previous studies during the postnatal period in anesthetized piglets (3, 27). These studies (3, 27) have shown that the $\beta$-adrenergic mechanism in the renal vascular bed of swine is absent at birth and appears postnatally at 2 wk. Species differences, the use of anesthetized animals, and systemic rather than intrarenal infusions of agonists in previous studies (3, 27) may account for differences between these studies and the present results. Factors that could explain the greater renal vasodilation observed in fetal sheep when compared to older animals were not investigated in detail herein. However, it is unlikely to be secondary to initial differences in adrenergic vasoconstrictor smooth muscle tone between various ages since as mentioned previously, intrarenal phentolamine did not change RBF velocity in any age group. Moreover, it is unlikely that fetal renal vessels are more responsive to vasodilatory stimulation due to intrinsic differences in vascular smooth muscle. Previous studies by our group found no differences in maximal renal vasodilation induced by dopamine when fetal, newborn, and adult sheep were compared (8).

In an effort to demonstrate that increased renal vasodilation in fetuses could modulate the vasoconstrictor response to epinephrine, renal artery infusions of epinephrine were administered during intrarenal propranolol infusion. Renal $\beta$-adrenoceptor blockade in fetal sheep during resting conditions did not enhance $\alpha$-adrenoceptor-mediated renal vasoconstriction. These results are consistent with our previous observation that the fetal renal vasoconstrictor response to renal nerve stimulation is not enhanced after administration of propranolol (24). However, results of the present study do not preclude the importance of $\beta$-adrenoceptor mechanisms in modulating renal vasoconstrictor tone during stressful conditions. Gustafsson *et al.* (28) have shown that in cats subjected to hemorrhage, renal vascular resistance increased by 39% following administration of ICI 118,551. Thus, one may speculate that increased $\beta$-adrenergic responsiveness may be important in modulating the massive neurosympathetic response that occurs in the perinatal period. In support is a recent study (29) demonstrating that $\beta_2$-adrenergic stimulation is important for survival during hypoxia in newborn rats from birth to 1 wk of age.

In summary, the present study demonstrates that: 1) epinephrine infusions into the renal artery produce similar renal vasoconstriction in fetal, newborn, and adult sheep; 2) this vasoconstriction is mediated by an $\alpha$-adrenoceptor; 3) intrarenal epinephrine infusions during renal $\alpha$-adrenoceptor blockade produce greater renal vasodilation in fetal compared to newborn and adult sheep; this vasodilation is mediated by a $\beta_2$-adrenoceptor; and 4) epinephrine-mediated renal vasoconstriction is not enhanced by blockade of $\beta$-adrenergic receptors in fetal sheep. Mechanisms to explain these maturational changes and the possible advantage of increased renal vascular $\beta$-adrenergic responses in near-term fetal sheep require further investigation.

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