Endothelium-Derived Nitric Oxide Modulates Renal Hemodynamics in the Developing Piglet

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ABSTRACT. The developing mammal exhibits lower renal blood flow (RBF) and higher renal vascular resistance (RVR) than its adult counterpart. The maturational pattern of renal hemodynamics involves the synchronous increase in RBF and decrease in RVR with age. In spite of considerable investigation, the mechanisms involved in the regulation of renal hemodynamics in the developing animal remain largely unexplained. Specifically, the role of the vasodilator endothelium-derived nitric oxide (EDNO) in the regulation of developing renal hemodynamics is not known. These experiments examined the intrarenal effect on the renal hemodynamics of the developing piglet and adult pig of the EDNO competitive inhibitor N-nitro-L-arginine methylester (L-NAME) at three doses (50, 5, and 3 μg/kg/min). During basal conditions, the developing piglet exhibited lower RBF and higher RVR than the adult pig. All doses of intrarenal L-NAME produced significant decreases in RBF and increases in RVR in both groups. The 3-μg/kg/min L-NAME dose did not change mean arterial pressure. The developing piglet exhibited significantly greater changes at all doses. After the 50-μg/kg/min infusion, piglet RBF decreased 45% and adult pig RBF decreased 29%; piglet RVR increased 128% and adult pig RVR increased 51%. After a 5-μg/kg/min infusion, RBF decreased 28% in the piglet and 14% in the adult pig; RVR increased 75% in the piglet compared with 27% in the adult pig. After 3 μ/kg/min L-NAME, piglet RBF decreased 29% and adult RBF decreased 9%; RVR increased 47% in the piglet *versus* 13% in the adult pig. The results of this study suggest that EDNO participates in the regulation of basal renal hemodynamics in the developing piglet and adult pig. Furthermore, it appears that EDNO may play a greater role in maintaining basal renal hemodynamics in the developing piglet than in the adult pig. (*Pediatr Res* 34: 750-754, 1993)

Abbreviations

EDNO, endothelium-derived nitric oxide
MAP, mean arterial pressure
L-NAME, N-nitro-L-arginine methylester
gkw, grams kidney weight

At birth, the renal hemodynamics of the newborn differ from those of the adult. The newborn mammal exhibits lower renal blood flow and higher renal vascular resistance than its adult counterpart (1-6). The maturation of renal hemodynamics with age in the developing mammal involves the synchronous increase in renal blood flow and decrease in renal vascular resistance (1, 2, 4-7). The most rapid increases in renal blood flow occur in the first few weeks of life. The three factors that contribute to the maturational increase in renal blood flow are increases in cardiac output, increases in mean arterial pressure (renal perfusion pressure), and decreases in renal vascular resistance. Gruskin *et al.* (1) demonstrated that in the developing piglet the major factor influencing the maturational increase in renal blood flow was an 86% decrease in renal vascular resistance with age.

The exact mechanisms affecting the maturational change in renal vascular resistance, which initially at birth maintains low renal blood flow, and, with increasing age, facilitates the maturational increase in renal blood flow, remain largely unexplained. Previous investigations to explain the developmental phenomenon of renal hemodynamics have focused on vasoconstrictor mechanisms such as an increased sympathoadrenergic response (8-13), the highly activated renin angiotensin system (14-16), or activation of the prostanoid thromboxane (17). Prostaglandins, the only vasodilators examined, may participate in fetal renal hemodynamics (18) but have not been proven to regulate basal renal hemodynamics in the developing animal (15). Other vasodilators have not been examined.

Specifically, the newly described vasodilator, EDNO has been shown to participate in the regulation of renal hemodynamics (19-29). However, the role of EDNO in the development of renal hemodynamics is not known. EDNO is synthesized in vascular endothelial cells from a single amino acid precursor, L-arginine, mediated by the enzyme nitric oxide synthase (30-32). L-Arginine analogues, such as L-NAME, competitively inhibit the synthesis of EDNO and its vasodilation (33). EDNO inhibition with L-NAME significantly decreases renal blood flow in adult animal models (19, 20, 27, 28). Furthermore, EDNO may serve as an important vasodilator in counterbalancing excessive vasoconstriction of the renal vasculature. This set of experiments sought to answer the following question: What role does EDNO play in the regulation of renal hemodynamics in the developing piglet? The objective of the experiments was to determine the effect of EDNO inhibition using the intrarenal infusion of the competitive inhibitor L-NAME on the renal hemodynamics of the developing piglet and adult pig.

MATERIALS AND METHODS

Subjects. Experiments were performed on mixed breed piglets with an average age of 22.5 d or adult pigs with mature renal function with an average age of 73 d. All groups received the same experimental preparation.

Preparation. All animals were fed a standard age-specific pig diet and were fasted overnight before experiments with access to water. All animals received initial anesthesia with intramuscular ketamine (adults 10 mg/kg and piglets 5 mg/kg) followed by i.v.

sodium pentobarbital bolus, 10 mg/kg, then sustaining anesthesia with intermittent i.v. sodium pentobarbital boluses, 0.5 mg/kg each. After tracheostomy, the animals were ventilated with a small-animal respirator (Harvard Apparatus Co., Inc., S. Natick, MA), and constant low flow oxygen was given at 250–500 mL/min. Cannulas were placed in both external jugular veins for infusion of radioisotope and electrolyte solution. The left carotid artery was cannulated for monitoring of MAP and blood sampling. The left kidney was exposed through a retroperitoneal flank incision and the left ureter was cannulated for timed urine collections. An electromagnetic flow probe (Carolina Instruments Electronics, Inc., King, NC) was placed around the renal artery to monitor renal blood flow. A 25-gauge right-angle needle was placed in the proximal renal artery for intrarenal infusions.

Experimental protocol. MAP and renal blood flow were monitored continuously throughout the experiment on a chart recorder (Grass Instrument Co., Quincy, MA). All animals received an i.v. maintenance infusion of 5% dextrose 1/3 normal saline (electrolyte solution) begun at 0.03 mL/kg/min. Glomerular filtration rate was determined by the clearance of ^{125}I-iothalamate (Glofil Isotex, Inc., Friends Wood, TX). A priming dose of 0.4 mBq/kg was followed by constant infusion throughout the experiment of 12 mBq at 0.3 mL/kg/h for adults and 2.4 mBq at 0.3 mL/kg/h for piglets. Intrarenal infusion of 0.9% saline solution at 0.1 mL/min was initiated. After a 60-min recovery period, a 20-min control urine collection was obtained, along with a midpoint blood sampling.

At the end of the control collection period, intrarenal infusion of L-NAME was begun in the saline vehicle at the same rate, 0.1 mL/min. Each age group (developing piglet or adult pigs) received intrarenal infusion of L-NAME at three different doses in separate experiments. The first groups received intrarenal L-NAME at 50 μg/kg/min for 20 min (piglets = 9, adults = 6). Because of the significant systemic effects of intrarenal L-NAME at this dose, another set of experiments was performed using a lower intrarenal L-NAME dose. Intrarenal L-NAME at 5 μg/kg/min was infused for 60 min (piglets = 5, adults = 5). In a third set of experiments, intrarenal L-NAME was infused at 3 μg/kg/min for 90 min (piglets = 6, adults = 5). Both the 5 μg/kg/min and 3 μg/kg/min intrarenal L-NAME doses were selected because they have been previously shown to block EDNO endothelium-dependent vasodilation of bradykinin in adult animal models (27). In all groups, the intrarenal infusion of L-NAME continued through a final 20-min experimental urine collection with a midpoint blood sampling. Blood samples were evaluated for hematocrit, plasma protein, and ^{125}I-iothalamate, and urine samples were evaluated for ^{125}I-iothalamate. Plasma protein was determined by a total solids meter (Reichert Scientific Instruments, Buffalo, NY). The animals were killed with an i.v. supersaturated KCl injection, and kidney weight was obtained.

Statistics. Experimental measurements were compared with control measurements using a paired t test. Differences between groups were determined by an unpaired t test. Statistical significance was considered to be $p < 0.05$. All data are expressed as mean ± SEM.

RESULTS

The effect on renal blood flow of the intrarenal infusion of L-NAME at the three doses (50, 5, and 3 μg/kg/min) in the developing piglet and adult pig is shown in Figure 1. At all experimental doses, renal blood flow was significantly lower during the control period in the piglet compared with the adult pig. Both age groups significantly decreased renal blood flow in response to all three intrarenal L-NAME doses. Intrarenal L-NAME significantly decreased renal blood flow in the piglet at 50 μg/kg/min from 1.10 ± 0.12 to 0.61 ± 0.07 mL/min/gkw, at 5 μg/kg/min from 1.66 ± 0.16 to 1.16 ± 0.10 mL/min/gkw, and at 3 μg/kg/min from 1.11 ± 0.01 to 0.78 ± 0.10 mL/min/gkw.
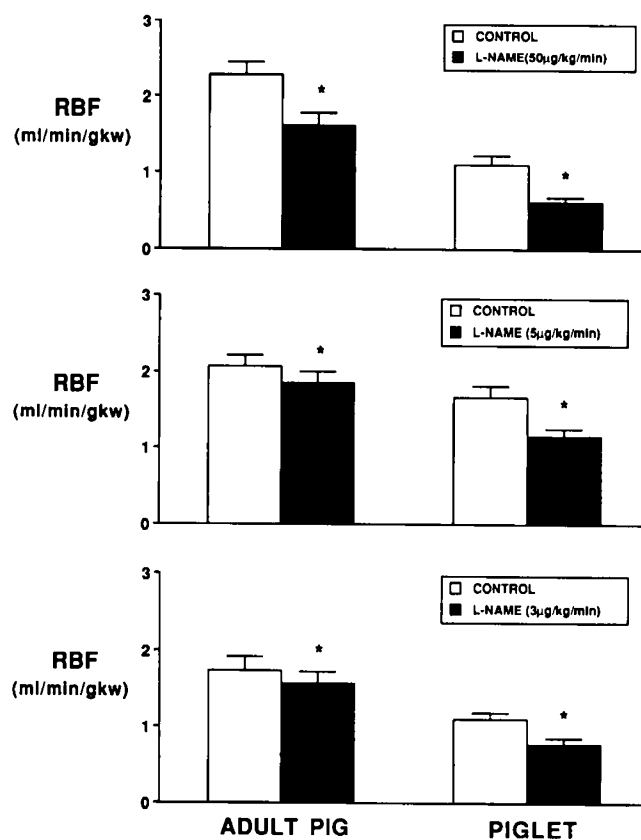

Fig. 1. The effect of intrarenal L-NAME infusion at three doses (50, 5, and 3 μg/kg/min) on renal blood flow (*RBF*) in the adult pig and developing piglet. *, $p < 0.05$ *vs* control.

Renal blood flow in the adult pig significantly decreased in response to intrarenal L-NAME at 50 μg/kg/min from 2.27 ± 0.17 to 1.62 ± 0.16 mL/min/gkw, at 5 μg/kg/min from 2.05 ± 0.18 to 1.76 ± 0.15 mL/min/gkw, and at 3 μg/kg/min from 1.73 ± 0.20 to 1.56 ± 0.10 mL/min/gkw. A similar pattern was seen in the effect on renal vascular resistance in the two age groups in response to the intrarenal infusion of L-NAME at doses of 50, 5, and 3 μg/kg/min (Fig. 2). Again during the control period at all three experimental doses, renal vascular resistance was significantly higher in the piglet than in the adult pig. Intrarenal L-NAME at all three doses significantly increased renal vascular resistance in both age groups. Intrarenal L-NAME significantly increased renal vascular resistance in the piglet at 50 μg/kg/min from 4.03 ± 0.39 to 9.31 ± 1.5 mm Hg/mL/min, at 5 μg/kg/min from 3.01 ± 0.26 to 5.14 ± 0.67 mm Hg/mL/min, and at 3 μg/kg/min from 3.40 ± 0.20 to 5.02 ± 0.70 mm Hg/mL/min. In the adult pig, intrarenal L-NAME significantly increased renal vascular resistance at 50 μg/kg/min from 1.08 ± 0.10 to 1.66 ± 0.14 mm Hg/mL/min, at 5 μg/kg/min from 1.00 ± 0.11 to 1.24 ± 0.13 mm Hg/mL/min, and at 3 μg/kg/min from 1.13 ± 0.20 to 1.29 ± 0.20 mm Hg/mL/min. The effect of L-NAME intrarenal infusion at the highest dose, 50 μg/kg/min, and the lowest dose, 3 μg/kg/min, on glomerular filtration rate in both age groups is shown in Figure 3. Glomerular filtration rate significantly decreased in both age groups in response to the highest (50 μg/kg/min) intrarenal L-NAME infusion. Glomerular filtration rate decreased in the adult pig from 0.45 to 0.24 mL/min/gkw and decreased in the piglet from 0.26 to 0.11 mL/min/gkw. In response to the lowest intrarenal infusion, 3 μg/kg/min, glomerular filtration rate did not significantly change in the adult pig. However, at 3 μg/kg/min, glomerular filtration rate decreased in the piglet from 0.35 to 0.17 mL/min/gkw.

Table 1 displays the effect of intrarenal L-NAME at all three doses on MAP. At the 50-μg/kg/min dose, intrarenal L-NAME

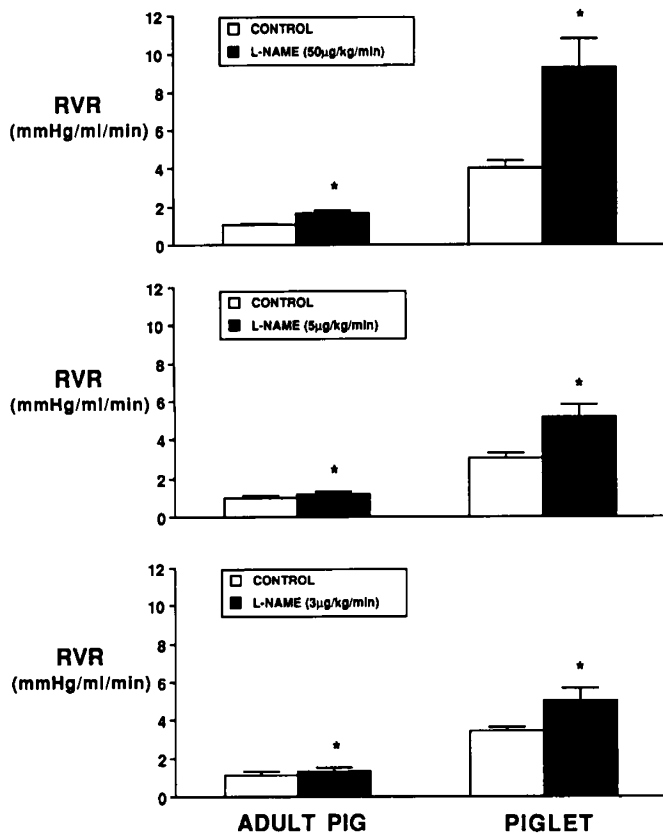Fig. 2. The effect of intrarenal L-NAME infusion at three doses (50, 5, and 3 μg/kg/min) on renal vascular resistance (*RVR*) in the adult pig and developing piglet. *, *p* < 0.05 *vs* control.
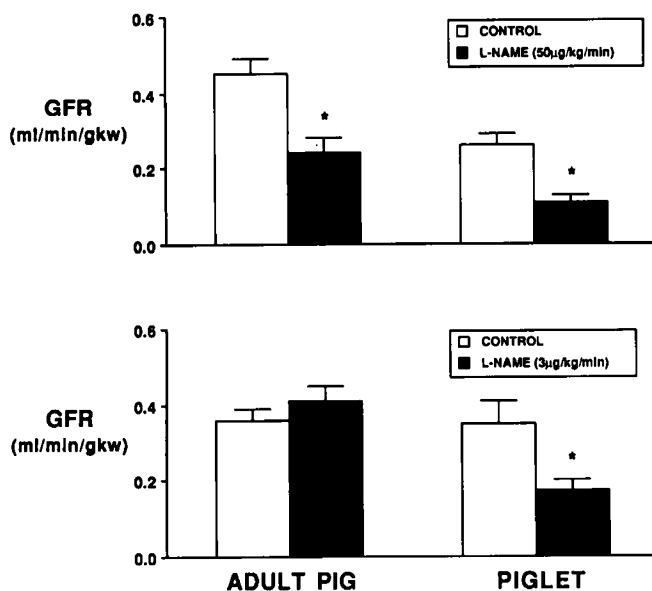

Fig. 3. The effect of intrarenal L-NAME infusion at two doses (50 and 3 μg/kg/min) on glomerular filtration rate (*GFR*) in the adult pig and developing piglet. *, *p* < 0.05 *vs* control.

produced significant increases in MAP in both the piglet (from 79 ± 5 to 95 ± 6 mm Hg) and the adult pig (from 104 ± 3 to 115 ± 4 mm Hg). At an intrarenal L-NAME dose of 5 μg/kg/min, only the piglet MAP significantly increased from 88 ± 2 to 104 ± 6 mm Hg. The 3-μg/kg/min intrarenal L-NAME infusion did not significantly alter MAP in either the piglet or adult pig.

The intrarenal L-NAME infusion produced significantly

greater renal hemodynamic responses in the piglet than in the adult pig at all three doses (Fig. 4). Intrarenal L-NAME at 50 μg/kg/min decreased renal blood flow in the piglet 44.6 ± 4% *versus* 29 ± 3% in the adult pig, and increased renal vascular resistance in the piglet 128.2 ± 21% compared with an increase of 57.2 ± 8% in the adult pig. The 5-μg/kg/min intrarenal L-NAME infusion decreased renal blood flow 27.7 ± 9% in the piglet compared with 10.3 ± 4% in the adult pig, and increased renal vascular resistance 75.4 ± 25% in the piglet compared with 20.3 ± 9% in the adult pig. At 3 μg/kg/min, intrarenal infusion of L-NAME decreased piglet renal blood flow by 28.9 ± 5% and adult pig renal blood flow by 9.4 ± 3%; renal vascular resistance was increased in the piglet 46.6 ± 13% compared with 13.1 ± 4% in the adult pig.

DISCUSSION

The role of EDNO in the renal hemodynamics of the developing animal is not known. The newly described vasodilator EDNO is synthesized from a single amino acid precursor, L-arginine, mediated by the enzyme nitric oxide synthase. Nitric oxide synthesized in the vascular endothelial cell diffuses into the adjacent smooth muscle cell, where its second messenger, cGMP, mediates the vascular vasodilation (30–32). EDNO activity is stimulated by several agonists including L-arginine, acetylcholine, and bradykinin shear stress and inhibited by several L-arginine analogues including L-NAME by competitive inhibition (31–34). EDNO is an important regulator of renal hemodynamics in the adult (19–29). EDNO inhibition with L-NAME significantly decreases renal blood flow in adult animal models (19, 20, 27, 28). The importance of EDNO in the regulation of renal hemodynamics in the developing animal is not known. These experiments compared intrarenal EDNO inhibition on the renal hemodynamics of the developing piglet and adult pig.

Inhibition of basal EDNO activity with the intrarenal infusion of the competitive EDNO inhibitor L-NAME produced significant alterations in renal hemodynamics in both the developing piglet and the adult pig at all three infusion doses (50, 5, and 3 μg/kg/min). Renal blood flow significantly decreased in both the developing piglet and the adult pig with all three intrarenal L-NAME infusion doses. Similarly, all intrarenal L-NAME infusion doses created significant increases in renal vascular resistance in both age groups. This suggests that EDNO participates in the regulation of renal vascular resistance during development and in the mature adult. The contribution of EDNO to basal renal vascular tone in other adult animal models has been previously demonstrated (27–29). However, this is the first description of a role for EDNO in the renal hemodynamics of the developing animal.

Both age groups significantly altered renal hemodynamics in response to EDNO inhibition. Additionally, intrarenal inhibition of EDNO with all three infusion doses produced greater changes in renal hemodynamics of the developing piglet than of the adult pig. Therefore, not only does EDNO participate in the maintenance of renal vascular tone in the developing piglet and adult pig, but inhibition of EDNO creates greater renal hemodynamic changes in the piglet than in the adult pig, suggesting a more important role for EDNO in the developing piglet.

Systemic effects of intrarenal L-NAME were seen in both the piglet and adult pig at the higher 50-μg/kg/min dose. MAP was significantly increased in both age groups. The 5-μg/kg/min infusion dose, which significantly increased MAP in the piglet, did not alter MAP in the adult pig. These changes in systemic arterial pressure may have contributed to the increases in renal vascular resistance by autoregulatory adjustments. However, the intrarenal L-NAME infusion of 3 μg/kg/min did not significantly change MAP in either the piglet or the adult pig, yet it produced significant renal hemodynamic responses in both age groups.

In addition to altering MAP in both age groups, the highest intrarenal L-NAME infusion dose, 50 μg/kg/min, significantly

Table 1. *Effect of intrarenal L-NAME infusion at three doses (50, 5, and 3 µg/kg/min) on MAP in adult pig and developing piglet*

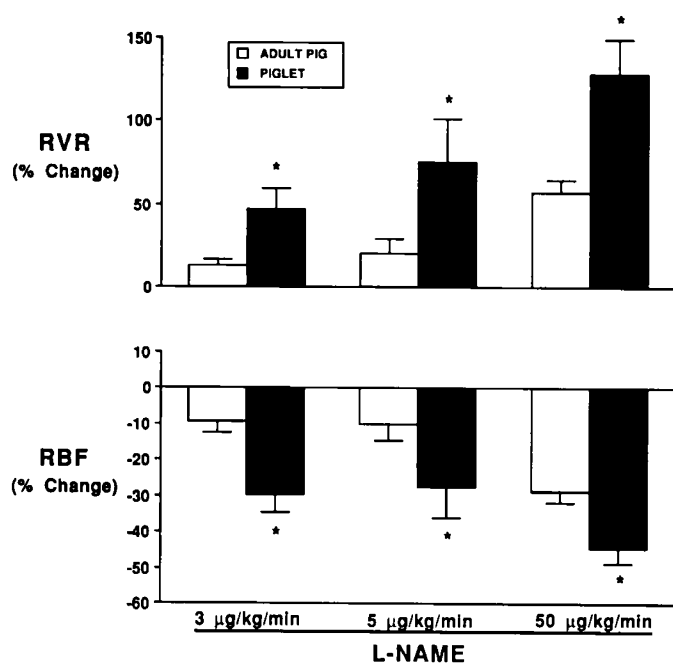| | MAP (mm Hg) | | | | | |
| | Piglet | | | Adult | | |
	3	5	50	3	5	50
Control	74 ± 1	88 ± 2	79 ± 5	91 ± 4	97 ± 4	104 ± 3
L-NAME	75 ± 3	104 ± 6*	95 ± 6*	94 ± 4	104 ± 3	115 ± 4*

* $p < 0.05$ vs control.

Fig. 4. The percent changes in renal vascular resistance (RVR) and renal blood flow (RBF) in response to intrarenal L-NAME infusion at three doses (50, 5, and 3 µg/kg/min) in the adult pig and developing piglet. *, $p < 0.05$ developing piglet vs adult pig.

decreased glomerular filtration rate in both the adult pig and the developing piglet. Glomerular filtration rate did not significantly change in the adult pig in response to the lowest intrarenal L-NAME dose, 3 µg/kg/min. The 3-µg/kg/min infusion dose significantly decreased glomerular filtration rate in the piglet without altering systemic MAP. This responsiveness of intrarenal L-NAME EDNO inhibition on glomerular filtration rate in the piglet could be consistent with previously described effects of EDNO on preglomerular arterioles (35).

Renal hemodynamics in the developing mammal differ from those of its adult counterpart. At birth, the newborn has a lower renal blood flow and higher renal vascular resistance than the adult (1–4, 6). The maturational pattern of renal hemodynamics involves the synchronous increase in renal blood flow and decrease in renal vascular resistance with age (1, 2, 4–7). In these experiments, the developing piglet exhibited a lower basal renal blood flow and higher basal renal vascular resistance, consistent with the hemodynamic patterns described in piglets (1, 4).

Gruskin et al. (1) examined the three factors that influence the maturation of renal blood flow with age in piglets: increasing cardiac output, increasing renal perfusion pressure, and decreasing renal vascular resistance. The major factor creating the maturational increase in renal blood flow in developing piglets was an 86% decrease in renal vascular resistance with age. The alterations of renal hemodynamics in the developing animal from birth to mature function are pivotal to the development of several physiologic functions, including the maturational increase in glomerular filtration rate (7, 36–39), and participation in the immature animal's blunted natriuresis of an acute saline

load (40). Considering the critical contribution that maturation of renal hemodynamics plays in the development of mature renal function, the mechanisms that produce these functional alterations in the immature renal vasculature remain largely unexplained.

Ultimately, the maintenance of vascular tone is a balance between vasoconstrictor and vasodilator mechanisms. Most of the experimental investigation of developing renal hemodynamics has been directed at vasoconstrictor mechanisms. A role for renal sympathetic nerve activity in influencing renal hemodynamics has been shown for the newborn (12) and in early development (8). But the functional contribution of renal nerves throughout the developmental spectrum is not known. Enhanced sensitivity of the developing puppy renal vasculature to catecholamines (9–11, 13) and renal α-adrenoreceptor blockade (41) have been reported, perhaps due to increased α-adrenoreceptors compared with the adult dog (42). The renin angiotensin system is highly activated at birth and during the maturation of renal hemodynamics (43–45). However, the contribution of angiotensin II as a vasoconstrictor in maintaining immature renal hemodynamics has not been demonstrated (14–16). The participation of vasodilators in the maturation of renal hemodynamics has received limited examination. Prostaglandins may participate in fetal renal hemodynamics (18), but Osborn et al. (15) were unable to demonstrate prostaglandin participation in the renal hemodynamics of the developing piglet. The experiments reported here establish for the first time that EDNO participates in basal renal hemodynamics in the developing piglet, suggesting a role as an important vasodilating factor. The greater response to EDNO inhibition in the developing piglet further suggests that EDNO may be a more critical vasodilator in the renal hemodynamics of the developing animal than of the adult. However, a role for EDNO as an important modulator in the maturation of renal hemodynamics needs to be integrated with operant vasoconstrictor mechanisms.

The finding in these experiments that intrarenal L-NAME exhibits a greater hemodynamic response in the developing piglet suggests that EDNO activity is increased in the immature animal compared with its adult counterpart. In adult rats, anesthesia may enhance renal hemodynamic responses to nitric oxide inhibition by modifying regulatory reflex mechanisms, in particular amplifying the renal influence of the vasoconstrictor activity of angiotensin II (46). In the conscious developing animal, various vasoconstrictor systems including the renin angiotensin system are known to already exist in a highly activated state (8–13, 41–45). Studies have indicated that EDNO synthesis is increased by alteration in nitric oxide synthase activity in several physiologic and pathophysiologic conditions (22, 27, 34). Recent studies in adult animal models indicate that EDNO may protect the renal vasculature by counterbalancing excessive vasoconstriction induced by constrictors such as angiotensin II (27, 47). It is possible that increased EDNO action through elevated nitric oxide synthase activity in the developing piglet serves as a counterregulatory mechanism against the well-known highly activated vasoconstrictors. Additional studies are necessary to determine whether nitric oxide synthase activity differs between the developing piglet and adult pig and whether EDNO is functioning as a protective renal vasodilator against vasoconstrictors.

In summary, EDNO inhibition with intrarenal infusion of the

competitive inhibitor L-NAME at 50, 5, and 3 μg/kg/min significantly decreases renal blood flow and increases renal vascular resistance in both the developing piglet and adult pig. MAP and glomerular filtration rate significantly decreased in response to the 50-μg/kg/min L-NAME infusion in both the piglet and adult pig. Only the piglet decreased MAP with the 5-μg/kg/min intrarenal L-NAME infusion. The 3-μg/kg/min L-NAME infusion decreased glomerular filtration rate in the piglet, but did not significantly change MAP in either the piglet or adult pig. Intrarenal L-NAME at all three doses produces significantly greater decreases in renal blood flow and increases in renal vascular resistance in the developing piglet compared with the adult pig. We conclude from these experiments that EDNO participates in the basal regulation of renal hemodynamics in the developing piglet and adult pig. Furthermore, it appears that EDNO may play a greater role in maintaining basal renal hemodynamics in the developing piglet than in the adult pig.

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