

# Sympathetic responses to cardiopulmonary vagal afferent stimulation during development

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<sup>1</sup>Departments of Obstetrics and Gynecology and Pediatrics, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52442; and <sup>2</sup>Department of Pediatrics, University of Michigan, Ann Arbor, Michigan 48109-0718

**Merrill, David C., Jeffrey L. Segar, Oliva J. McWeeny, and Jean E. Robillard.** Sympathetic responses to cardiopulmonary vagal afferent stimulation during development. *Am. J. Physiol.* 277 (Heart Circ. Physiol. 46): H1311–H1316, 1999.—Previous work in our laboratory has demonstrated impairment of cardiopulmonary reflex control of renal sympathetic nerve activity (RSNA) during the newborn period. The present study was designed to test the hypothesis that this delayed maturation is secondary to incomplete central integration of vagal afferent input. Term fetal (135–140 days;  $n = 6$ ), newborn (3–7 days of age;  $n = 8$ ), and young adult (6–8 wk old;  $n = 8$ ) sheep anesthetized with  $\alpha$ -chloralose underwent vagal afferent nerve stimulation. All animals had undergone prior sinoaortic denervation to eliminate influences from the arterial baroreceptors. After determination of optimal stimulation parameters, RSNA responses to gradual increases in stimulation frequency (1.0–16 Hz) were recorded and compared by one-way ANOVA. RSNA decreased progressively with increased frequency of stimulation in all three groups of animals. When comparing the three groups at any given frequency of stimulation, reflex withdrawal of RSNA tended to be more pronounced in newborn lambs ( $P < 0.05$  for 1 and 4 Hz). Heart rate (HR) was also noted to decrease significantly with vagal afferent stimulation in each of the groups, but no significant differences in the reflex decreases in HR were noted among the three groups of animals. These results demonstrate that central integration of vagal afferent input is intact in fetal and newborn sheep. These results suggest that the delayed maturation of cardiopulmonary reflex-mediated changes in RSNA seen early in development appears to depend on intrinsic alterations in baroreceptor function rather than incomplete central integration.

renal nerves; sheep; fetus; ontogeny

THE CARDIOPULMONARY reflexes play an important role in controlling efferent sympathetic nerve activity to the kidneys and modulating sodium and water excretion (8, 15). In adults, activation of cardiopulmonary receptors either by exposure to chemical irritants (chemosensitive receptors) or increases in pressure or stress (mechanosensitive receptors) results in reflex bradycardia, vasodilation, and sympathoinhibition. In a recent series of studies (10), we observed that volume expansion significantly reduced renal sympathetic nerve activity (RSNA) in newborn and 8-wk-old lambs. The decrease in RSNA in response to volume expansion was abolished by sinoaortic denervation (SAD) in newborn

lambs but was not affected by SAD in 8-wk-old sheep, suggesting that the arterial baroreceptors mediate the sympathoinhibition in the newborn and that the sensitivity of the cardiopulmonary reflex is attenuated early after birth compared with that seen in older animals. In addition, we have also observed that renal denervation decreases the natriuretic response to volume expansion in newborn lambs (23) but has no effect in near-term fetal sheep (22), suggesting that the sensitivity of the cardiopulmonary reflex in response to volume expansion is impaired in the fetus. In support of this hypothesis, it has been shown that the heart rate (HR) and arterial blood pressure responses to stimulation of chemosensitive cardiopulmonary receptors are smaller early during development than later in life (2).

Alterations in the cardiopulmonary reflex early during development may involve maturational changes in the cardiopulmonary receptor organ itself, the mechanical properties of the cardiac tissue in which the baroreceptors are located, the cardiac vagal afferent fibers, the central neural processing of afferent input, and/or the efferent sympathetic nerve fibers. Previous work in cats (12) and rats (11, 13) has demonstrated that nonmyelinated vagal afferents (C-fibers) of cardiopulmonary origin can be selectively activated by utilizing stimulation parameters of relatively long duration (1–2 ms) and low frequency (~1–16 Hz). In contrast, myelinated A-fibers could be activated by stimulation with high frequency (80 Hz) and short duration (0.02 ms). In the present study, we used similar stimulation parameters to test the hypothesis that impairment of cardiopulmonary reflex-mediated changes in sympathetic activity early in life is secondary to incomplete central integration of vagal afferent input.

## METHODS

Studies were conducted in acutely instrumented fetal ( $n = 6$ ), newborn ( $n = 8$ ), and 6- to 8-wk-old lambs ( $n = 8$ ). Fetuses of pregnant sheep of Dorset and Suffolk mixed breeding were studied between 135 and 141 days of gestation (full term, 145 days). Gestational ages were based on the induced ovulation technique as previously described (7). Fetal body weight was calculated according to the following formula: fetal weight (kg) =  $0.0961 \times$  gestational age (days) – 9.228 (16). Newborn lambs were studied between 3 and 7 days of age. For all surgical and experimental procedures, “Guiding Principles for the Care and Use of Laboratory Animals” approved by the Council of the American Physiological Society and governed by the Animal Care and Use Committee of the University of Iowa were strictly adhered to.

**Surgical preparation.** Anesthesia and surgery of the ewe and fetus were performed as previously described (17, 20). In brief, the ewe was fasted for 24 h before surgery and was

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anesthetized using a mixture of halothane (1%), oxygen (33%), and nitrous oxide (66%). A maternal flank incision was used for exposure of the uterus. The uterus was opened over the fetal hindlimbs, and polyethylene catheters were placed in the fetal femoral arteries and veins. A catheter for recording amniotic pressure was secured to the fetal skin. The left kidney, renal artery, and renal nerves were exposed through a flank incision. After isolation of a branch of the left renal nerve bundle, platinum electrodes were secured on the nerve for recording of RSNA as previously described (20). Function of the renal nerve was tested by audible monitoring of pulse-synchronous bursts of neural activity and by examining changes in oscilloscope tracings during rapid intravenous infusion of phenylephrine (5 µg/kg). When function was demonstrated, electrodes were secured using Sil-Gel (Sil-Gel 604A and 604B; Wacker-Chemie, Munich, Germany), as previously described (20). A plastic-coated copper wire, used as a ground wire, was secured to the paravertebral muscle, and the flank incision was closed in separate layers. A second uterine incision was made near the fetal head. SAD was then performed as previously described (6). Briefly, SAD was accomplished 1) by bilateral vascular stripping of the nervous and connective tissue rostral and caudal to the origin of the occipital and lingual arteries, 2) by applying 10% phenol to the bifurcation of the common carotid to external and internal carotid arteries, and 3) by sectioning bilaterally the aortic depressor nerve and the superior laryngeal nerve at their junction with the nodose ganglion. Completeness of SAD was confirmed at the time of surgery and before each experiment by observing the absence of changes in RSNA and HR when arterial pressure was increased by a bolus infusion of phenylephrine (2 µg/kg). The right vagus nerve was desheathed and sectioned, and platinum electrodes were placed on the proximal portion and secured with Sil-Gel. All uterine incisions were closed in two layers, the second in an imbricating fashion. Maternal incisions were closed in separate layers. All catheters were exteriorized through a subcutaneous tunnel and were placed in a cloth pouch on the ewe's flank.

Newborn and 6- to 8-wk-old lambs had femoral catheters, renal and vagal nerve electrodes, and copper grounds placed in a similar manner. Vagal loops were placed with cotton umbilical tape to allow for sectioning of the vagus nerve at the time of the experiment. Catheters were tunneled subcutaneously and were secured to the lamb's back using porous elastic bandages. Ampicillin sodium (Wyeth Laboratories) was administered to newborn and 6- to 8-wk-old lambs (1 g im) and pregnant ewes (2 g im and 2 g intra-amniotically) after surgery. Newborn lambs were housed with their mothers after surgery and were nursed adequately. Six- to eight-week-old lambs were housed in individual pens and were allowed free access to food and water. At least 24 h were allowed for recovery from surgery before experiments were performed in the newborn and 6- to 8-wk-old lambs. Fetuses were studied on the same day as the surgery due to the need for sectioning of the vagus nerve.

*Experimental protocols.* During the experiment, newborn and 6- to 8-wk-old lambs were kept immobilized standing in a sling-frame assembly while the ewes were placed in a small cart. The animals were then sedated with an intravenous bolus of diazepam (Valium, ewe 5–10 mg, lamb 0.2 mg/kg; Elkins-Sinn), given an intravenous bolus infusion of vecuronium bromide (0.1 mg/kg, Norcuron; Organon), intubated, and ventilated to maintain arterial blood gas values similar to those obtained during spontaneous respiration. Norcuron was also administered to the fetus in similar intravenous doses. The animals were then anesthetized with  $\alpha$ -chloralose

(50 mg/kg iv over 2 min). The level of anesthesia was monitored by careful observation for changes in baseline blood pressure, sympathetic nerve activity, and HR. If changes in any of these were noted, a supplemental dose of  $\alpha$ -chloralose (20 mg/kg) was intravenously administered.

During each experiment, mean arterial blood pressure (MABP) and amniotic fluid pressure (in fetuses) were recorded continuously using Statham P23 Db pressure transducers (Statham Instruments Division, Gould) and a Beckman R611 Dynograph recorder. Fetal MABP was corrected relative to concomitant amniotic pressure. HR was monitored with a cardi tachometer triggered from the arterial pressure waves. Continuous recording of RSNA was performed with the animals housed inside a Faraday cage, and the renal nerve electrodes and ground wire were attached to a high-impedance probe (HIP5S; Grass Instruments, Quincy, MA). The neural signal was amplified ( $\times 20,000$ ) and was filtered with a low-frequency cutoff at 100 Hz and a high-frequency cutoff at 1.0 kHz using a Grass band-pass amplifier (P511). The amplified and filtered signal was visually displayed on an oscilloscope (511A; Tektronix, Beaverton, OR), routed to a Grass AM8 audio monitor, and integrated using a 9873B Beckman voltage integrator (Beckman Instruments, Fullerton, CA). The integrated voltage and neurogram signals were displayed on a Beckman R611 Dynograph recorder and simultaneously recorded on-line to a Gateway 486–33 MHz computer via a Data Translation DT 2801 16-channel analog-to-digital conversion board using the software Labtech Notebook (version 4.2; Laboratory Technologies, Wilmington, MA). Vagal stimulation was performed with a Grass Stimulator using optimal parameters as determined below. This stimulator was designed to deliver the voltage at a constant resistance.

After a 60-min equilibration period, baseline values for MABP, HR, RSNA, and amniotic pressure were recorded. The right vagus nerve was then transected using the previously placed vagal loops. In the fetus, the right vagus nerve was cut intraoperatively. A total of 60 min was allowed for recovery after vagal sectioning before any vagal stimulation. Optimal vagal stimulation parameters were first determined in five of the 6- to 8-wk-old lambs using the following protocol. With the duration of stimulation fixed at 2.0 ms and the frequency fixed at 4 Hz, the voltage was varied between 1 and 16 V. All stimulations were maintained until a plateau was observed in the RSNA response (usually 10–15 s). For each animal, the maximum voltage response was then determined, the voltage was then fixed at that level, and frequency was fixed at 4 Hz while the duration was varied (between 1 and 10 ms). At least 5 min of recovery were allowed between all stimulations. In these five animals, the voltage and duration parameters were set at the maximum for that particular animal. Finally, the frequency was varied between 1 and 16 Hz. Once the maximum voltage and duration parameters were determined for this group of animals, these settings were used for all other vagal stimulation experiments. Therefore, in all other 6- to 8-wk-old lambs and in all fetal and newborn lambs, stimulation parameters were set at 10 V and 2 ms, and the frequency was then varied between 1 and 16 Hz. Stimulation frequencies were performed randomly. As before, all stimulations were maintained until a plateau in the RSNA response was observed, and at least 5 min were allowed between each stimulation.

Arterial blood was obtained intermittently throughout the protocol for determination of arterial pH, PCO<sub>2</sub>, and PO<sub>2</sub>. Blood was collected anaerobically in heparinized syringes, and measurements were immediately determined using a

BGM 1302 pH/blood gas analyzer (IL, Lexington, MA). At the end of the experiment, complete inhibition of nerve activity for measurement of background noise was assessed using an intravenous infusion of the ganglionic blocking agent tetraethylammonium bromide (10 mg/kg), as previously described (19, 20). Throughout the experiment, all animals (fetal, newborn, and 6- to 8-wk-old lambs) were given a continuous infusion of a solution containing 5% dextrose and 0.2% sodium chloride at a rate of  $100 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ . To test the adequacy of SAD, the RSNA response to an intravenous bolus of phenylephrine (5  $\mu\text{g}/\text{kg}$ ) was determined at the end of the experiment both before and after bilateral vagotomy.

**Computations and data analysis.** Changes in RSNA were calculated as a percent change from control levels as follows:  $\% \Delta \text{RSNA} = [(\text{RSNA}_E - \text{RSNA}_C) / \text{RSNA}_C] \times 100$ , where  $\text{RSNA}_E$  and  $\text{RSNA}_C$  refer to RSNA during experimental and control periods, respectively, and  $\Delta$  indicates change. RSNA values were calculated as the average just before each stimulation and as the plateau response with vagal stimulation.

Data analysis between different stimulation frequencies was compared by standard one-way ANOVA. If significant differences were found among the groups based on the *F* statistic, then multiple comparisons were made with the Duncan test (25) comparing a control mean with each other group mean. The unpaired *t*-test was used to compare the difference between two means from different groups of animals. For a given age group, responses to different frequencies of stimulation were compared with repeated-measures ANOVA. For all statistics,  $P < 0.05$  was considered significant. Data are expressed as means  $\pm$  SE.

## RESULTS

**Determination of optimal stimulation parameters.** In the present studies, we observed a clear difference between stimulation with high frequency/short duration and low frequency/long duration. With high-frequency/short-duration (80 Hz, 0.02 ms) stimulation, we observed a significant increase in RSNA ( $50.2 \pm 18.6\%$  increase in RSNA from control;  $n = 6$ ;  $P < 0.05$ ), whereas with low frequency/long duration, we observed a significant decrease (see data below). To determine the optimal stimulation parameters in the sheep, we performed additional studies, the results of which are depicted in Fig. 1. In a total of five 6- to 8-wk-old lambs, the optimal parameters were determined by a two-step protocol. First, with the duration of stimulation fixed at 2 ms and the frequency fixed at 4 Hz, the voltage was varied between 2 and 16 V (Fig. 1A). Efferent RSNA was observed to progressively decrease when voltage was increased from 2 to 10 V. No difference in RSNA responses was observed, however, when voltage was further increased from 10 to 16 V. To determine the optimal duration of stimulation, we next stimulated with the maximal voltage for each animal, setting the frequency to 4 Hz, and varied the duration from 1 to 10 ms. We observed no significant differences in the reflex decrease in RSNA in response to varying duration (Fig. 1B).

**Effects of cardiopulmonary afferent vagal stimulation early during development.** To assess central integration of vagal afferent input, we randomly varied the frequency of stimulation (from 1 to 16 Hz) while recording

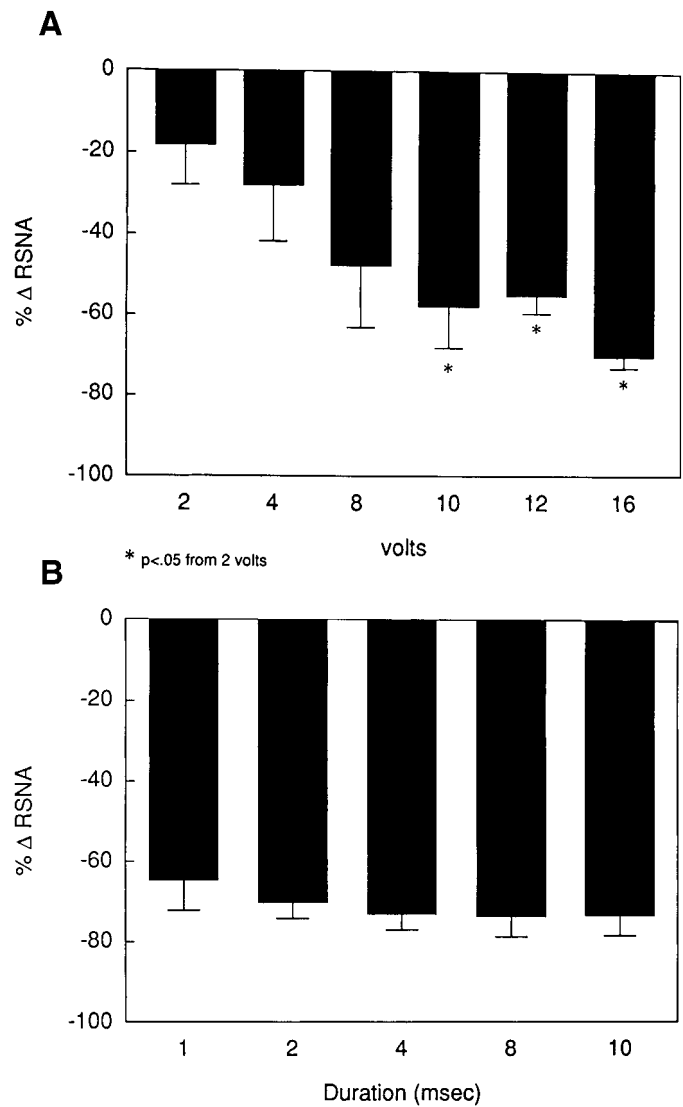


Fig. 1. A: renal sympathetic nerve activity (RSNA) responses (expressed as %changes from control) to increased voltage stimulation of vagal afferents in young adult lambs ( $n = 5$ ). Duration of stimulation was fixed at 2.0 ms, and the frequency was fixed at 4.0 Hz. \*  $P < 0.05$  from value observed at 2 V. B: RSNA response (expressed as %change from control) to increased duration of stimulation of vagal afferents in young adult lambs ( $n = 5$ ). Voltage was fixed at the maximum for each animal, and frequency was fixed at 4.0 Hz.

efferent RSNA. Reflex suppression of efferent RSNA in response to varying frequencies of cardiopulmonary vagal afferent stimulation in fetal, newborn, and young adult lambs is depicted in Fig. 2A. RSNA (expressed as a percent change from control) decreased progressively with increased frequency of stimulation in all three groups of animals ( $P < 0.05$  by 1-way ANOVA with repeated measures). When comparing the three groups at any given frequency of stimulation, reflex withdrawal of RSNA tended to be more pronounced in newborn lambs (1 Hz: newborn vs. young adult,  $P = 0.02$ ; 4 Hz: newborn vs. fetus,  $P = 0.03$ ). HR was also noted to decrease significantly with vagal afferent stimulation in each group, but no significant differences in the reflex decreases in HR were noted among

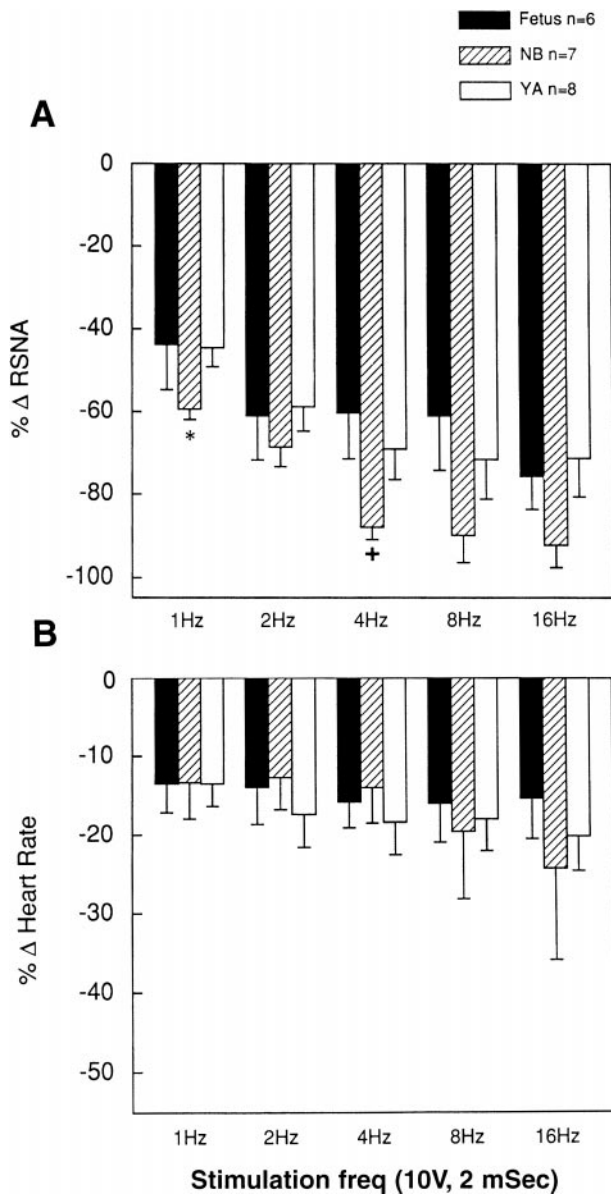


Fig. 2. A: RSNA responses (expressed as %change from control) to varying frequency of stimulation of vagal afferents in fetal, newborn (NB), and young adult (YA) sheep. \* $P < 0.05$ , NB vs. YA; + $P < 0.05$ , NB vs. fetus. B: heart rate responses (expressed as %changes from control) to varying frequency (freq) of stimulation of vagal afferents in fetal, newborn, and young adult sheep. All responses  $P < 0.05$  from control.

the three groups of animals (Fig. 2B). The effects of afferent vagal stimulation on MABP are shown in Table 1. A significant reflex decrease in MABP in response to vagal afferent stimulation was observed in all groups. The reduction in MABP, expressed as either absolute change or percent change from control, tended to be greater in older lambs, but this did not reach statistical significance ( $P = 0.08-0.18$ ). In addition, the reflex decrease in MABP did not appear to vary with increasing frequency of stimulation in any group.

**DISCUSSION**

In a previous study (10), we demonstrated that cardiopulmonary reflex control of RSNA in response to volume expansion is impaired in the newborn period and increases with maturation. The present study was designed to test the hypothesis that this delayed maturation of cardiopulmonary reflex-mediated changes in sympathetic activity is secondary to incomplete central integration of vagal afferent input. The findings of the present study suggest that central integration of cardiopulmonary vagal afferent input is fully functional in both late-gestation fetal and newborn lambs. In these studies, we utilized the technique of central vagal afferent stimulation to assess central integration. The voltage and duration parameters utilized have previously been shown in rats and cats to selectively activate the predominantly nonmyelinated cardiac vagal afferent (12, 13). To ensure that optimal stimulation parameters were utilized in this sheep model, we initially performed a series of studies involving variations in stimulation voltage and duration. After determination of the optimal parameters, stimulation of the central end of the right vagus nerve with increasing frequencies was used to provide a standardized stimulus for the activation of vagal afferent fibers. This technique enabled us to evaluate the efferent response to a standardized input in the central nervous system in fetal, newborn, and young adult sheep. The advantage of this approach is that it eliminates the confounding effects associated with volume expansion, such as dilutional effects and changes in various hormones such as arginine vasopressin (AVP), ANG II, and atrial natriuretic peptide (ANP). One potential confounding factor in the present study would be the percentage of myelinated vs. unmyelinated fibers in the vagus nerve at

Table 1. Effect of vagal stimulation on mean arterial blood pressure

	Vagal Stimulation				
	1 Hz	2 Hz	4 Hz	8 Hz	16 Hz
$\Delta$ MABP, mmHg					
F	-4.0 ± 1.3	-6.0 ± 0.8	-5.8 ± 1.4	-4.5 ± 0.9	-4.4 ± 1.2
NB	-8.6 ± 2.8	-9.4 ± 3.3	-6.6 ± 2.1	-8.0 ± 3.6	-9.0 ± 5.3
YA	-16.1 ± 5.9	-19.3 ± 7.5	-18.9 ± 6.9	-18.4 ± 8.2	-20.1 ± 8.5
MAP, %change					
F	-7.5 ± 2.1	-11.0 ± 0.7	-10.7 ± 2.0	-8.6 ± 2.0	-7.9 ± 1.8
NB	-12.8 ± 3.9	-13.8 ± 4.4	-10.6 ± 3.4	-10.9 ± 4.6	-11.4 ± 6.7
YA	-16.2 ± 5.2	-19.1 ± 6.0	-20.2 ± 5.7	-18.3 ± 6.6	-20.6 ± 7.3

Values are means ± SE. MABP, mean arterial blood pressure; F, fetus; NB, newborn; YA, young adult; Δ, change.

different points during development. It should be noted that Hasan et al. (4) have shown that the percentage of myelinated vs. unmyelinated fibers in the ovine vagus reach adult values by 100 days of gestation, whereas the youngest animals we studied were 135 days gestation. Nonetheless, it is possible that structural and functional differences in the afferent vagal fibers at the different stages in development we studied could confound our results.

Another limitation of the technique of vagal stimulation used in this study is that the right cervical vagus and not a cardiac branch of the vagus nerve was stimulated. In addition, although we used parameters that had previously been demonstrated to activate unmyelinated C-fibers (12), we did not record afferent nerve traffic at a proximal site to identify conduction velocity of the nerve fiber component activated. We did, however, observe an increase as opposed to a decrease in RSNA when the vagus was stimulated with high-frequency/short-duration impulses (presumably secondary to activation of myelinated A-fibers), as has previously been reported (12).

One potential confounding variable in the present study is the recovery time from surgery. The initial surgery was performed 24 h before the experiments in newborn and 6- to 8-wk-old lambs, whereas fetuses were studied on the same day as the surgery. As explained in METHODS, fetuses were studied on the same day as the surgery due to the need for sectioning the vagus nerve. Although the recovery time from surgery and thus from SAD was different, all other experimental conditions were the same for all three groups (all were given diazepam, Norcuron, and  $\alpha$ -chloralose).

It is important to point out that, in the present studies, efferent responses were only recorded in the kidney. Certainly, different results may have been obtained if sympathetic responses from other vascular beds were recorded. Furthermore, there may be differences in the cardiac output responses (despite the fact that there was no difference in HR), and different degrees of sympathetic withdrawal in various vascular beds may lead to significant differences in MABP responses. In the present studies, mean arterial pressure tended (but not significantly) to decrease to a greater extent in older lambs in response to vagal stimulation. In the present study, we concentrated on RSNA due to the fact that, in our previous studies (10), we observed significant differences in the RSNA response to volume expansion early in development.

If not secondary to immaturity of central integration pathways, what then may be responsible for the impaired cardiopulmonary reflex response to volume expansion observed early in development (10)? One may speculate that the differences observed may be due to factors acting at the level of the atrial mechanoreceptor. On the basis of the Laplace Law (tension = pressure  $\times$  radius), the tension generated by the atrial wall, in which the receptor is imbedded, for a given atrial pressure is directly related to the radius of the atrium. Therefore, one may postulate that the sensitivity of the atrial receptor discharge per change in atrial

pressure is less in the fetus or newborn with small atria than in older lambs with larger atrial volumes. In favor of this hypothesis, studies in adults (9) have shown that atrial receptor sensitivity increases with the size of the animals. Alterations in neuroendocrine control of cardiopulmonary reflex activity also remain as possible explanations for the attenuated RSNA and HR responses to volume expansion in SAD newborn lambs, because both ANP and AVP have been reported to regulate sympathetic activity by central mechanisms (1, 3, 5, 18). We have observed a significantly greater rise in plasma ANP levels with volume expansion in older lambs compared with newborns (10). Therefore, one may suggest that the greater sympathoinhibition observed with volume expansion in SAD older lambs compared with SAD newborn animals (10) may have been due to a greater sensitivity to the central actions of ANP, a consequence of the larger increase in circulating ANP concentration in older lambs, or both.

Another possible mechanism mediating impairment of the cardiopulmonary reflex during development is an alteration in the interaction between mechanosensitive and chemosensitive cardiopulmonary reflexes (14). It has recently been reported (24) in adult rats that subthreshold infusion (at a rate that did not alter baseline arterial pressure, HR, or RSNA) of the serotonin type 3-receptor-agonist phenyl biguanide significantly impaired the sympathoinhibition response to volume expansion. The possibility, however, that serotonin regulates sympathetic activity early during development is speculative and has not been systematically investigated.

The cardiopulmonary reflex is known to be an important regulator of fluid volume and electrolytes in the adult (3). Increases or decreases in vascular volume are sensed by cardiac receptors that in turn result in reflex changes in sympathetic outflow and vasopressin secretion. The function of the cardiopulmonary reflex early during development has recently been characterized (10, 21, 22). We have recently reported (10) that cardiopulmonary reflex-mediated changes in RSNA in response to volume expansion are significantly impaired early in the newborn period. The present study suggests that the impairment does not involve a lack of or delayed maturation of central integration pathways.

Understanding the mechanisms regulating sympathetic tone and baroreflex function is of particular significance to fetal and neonatal development. Abundant evidence suggests that the sympathetic nervous system is of vital importance in the regulation of blood pressure and circulatory function in the developing fetus and infant and in the physiological changes occurring at birth. Failure to regulate arterial pressure, peripheral resistance, and blood volume may lead to significant variations in organ blood flow and substrate delivery, resulting in ischemic or hemorrhagic complications. A more complete understanding of the ontogeny of neural control of cardiovascular function could potentially result in the development of new therapeutic strategies to prevent perinatal complications that are thought to be associated with alterations

in blood pressure, such as intraventricular hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis.

In summary, the present study provides evidence that central integration of cardiopulmonary vagal afferent input is fully functional in the term fetal and newborn sheep. The mechanism(s) mediating the impairment of cardiopulmonary baroreflex during the newborn period remain to be elucidated but may involve either intrinsic alterations in baroreceptor function (at the level of the atria) and/or altered neurohormonal control.

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