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Depression of Baroreflex Control of Heart Rate by Halothane in Growing Piglets

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The purpose this study was to examine the effects of halothane on baroreflex control of heart rate in developing swine. Serial tests of baroreflex function were performed over the first 2 months of life in eight piglets in the conscious state and during anesthesia with 0.45, 0.9, and 1.35% halothane. Systemic blood pressure was increased with phenylephrine (pressor test) and decreased with nitroprusside (depressor test), and stimulus–response curves relating mean blood pressure to heart rate were constructed. Baroreflex sensitivity was determined as the slope of the linear portion of the curve. Halothane markedly depressed baroreflex sensitivity at all ages in a dose-dependent manner (conscious > 0.45% > 0.9%, 1.35%). Increasing age was accompanied by decreasing baroreflex sensitivity in both the conscious and the anesthetized states. The difference in baroreflex sensitivity between conscious and anesthetized states did not change with age for the depressor test (tachycardia response), but it did change with age for the pressor test (bradycardia response). For this test, conscious values converged toward anesthetized values at higher ages; therefore, there was relatively less depression by halothane at older ages. Halothane also decreased resting heart rate and decreased the limits and narrowed the range of the baroreflex heart rate response. Increasing age was accompanied by a decreasing resting heart rate and by decreasing limits and a narrowing range of the baroreflex response. The effect of halothane on heart rate variables was similar at all ages. Halothane decreased resting blood pressure and decreased the lower limit and widened the span of the baroreflex blood pressure range. Increasing age was accompanied by increasing resting blood pressure and increasing blood pressure limits without change in the range. The effects of halothane on blood pressure limits and range were similar at all ages, but halothane depression of resting blood pressure was greater at higher ages. We conclude that the processes of maturation alter some but not all of the depressant effects of halothane on arterial baroreflex control of heart rate in growing swine. (Key words: Anesthetics, volatile: halothane. Animals, swine: infant. Heart: Cardiovascular development. Reflexes: baroreceptor.)

ARTERIAL BAROREFLEXES maintain the stability of the circulatory system by buffering acute alterations in arterial blood pressure with adjustments in cardiac output and peripheral vascular resistance. For newborns and infants, cardiac output is regulated largely by changes in heart rate[1]; therefore, baroreflex control of heart rate may be of prime importance in maintaining circulatory stability. Halothane depresses arterial baroreflexes in adults and infants.[2–5] Under halothane anesthesia, the baroreceptor itself is more sensitive, but other components of the reflex arc (the central nervous system, sympathetic ganglion transmission, and cardiac chronotropic function) are depressed, and the net effect is inhibition of the baroreflex.[6,7]

In this study we used serial experiments that spanned the first 2 months of life to examine the effect of maturation on halothane depression of baroreflex control of heart rate in infant swine. Swine were chosen as the experimental animals because a body of work from Gootman and colleagues indicates that in this animal, developmental changes occur in arterial baroreflexes over the first weeks of life.[8–13] Baroreflex control of heart rate was examined by testing ability of the heart rate to increase and decrease in response to blood pressure perturbations. The full sigmoid relationship between heart rate and blood pressure was determined; the sensitivity of the baroreflex was quantitated; and the ranges of heart rate and blood pressure in which the baroreflexes were active were defined.

Materials and Methods

Tests of baroreflex function were performed with eight farm piglets (spotted China–Poland breed) during their first 2 months of life. This protocol was approved by the Animal Care and Use Committees of the Medical College of Wisconsin and Veterans Administration Medical Center. The sensitivity of the arterial baroreflex was quantitated using a modification of the methods of Smyth *et al.*[14] and Pickering *et al.*,[15] in which drugs are infused to increase and decrease blood pressure. Phenylephrine was infused to increase blood pressure (pressor test) and, by baroreflex, to decrease heart rate. Nitroprusside was infused to cause a decrease in blood pressure (depressor test), which unloads baroreflexes and thereby increases heart rate.

Stimulus–response curves relating mean blood pressure to heart rate were constructed for each blood pressure manipulation (fig. 1). The relationship is sigmoid: it shows threshold and saturation blood pressures and a linear midregion. Baroreflex sensitivity is defined as the slope

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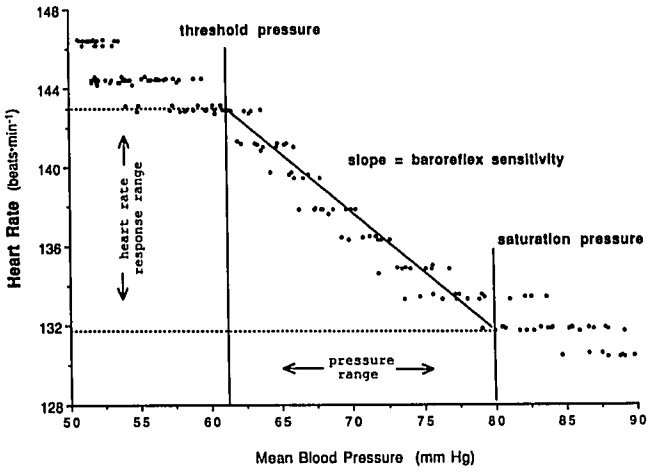

FIG. 1. Arterial baroreflex stimulus–response curve for 6-day-old piglet anesthetized with 0.9% halothane.

of the linear portion of the curve. It quantitates the change in heart rate per unit change in blood pressure and is a negative number, indicating the inverse relationship between these two parameters. A more negative slope indicates greater baroreflex sensitivity. Threshold and saturation are blood pressure limits that define the pressure range in which the reflex is active. Heart rates at threshold and saturation blood pressures define the limits of the heart rate response.

Threshold and saturation were determined by inspection of the curve. Although there is intrinsic variability (within a range of 3 or 4 beats per min) in heart rate below threshold and above saturation, this is clearly different from the steep change that occurs in the baroreflex operating range (the linear portion of the curve). Baroreflex sensitivity, the slope of the linear portion, was determined by the method of least squares linear regression, and regression coefficients were all ≥ 0.9. Because resting heart rate lies on the linear portion of the curve, the vasoactive drugs were continuously alternated in order to derive the full sigmoid relationship. Blood pressure was increased until there was no further change in heart rate, and then it was decreased until again there was no further change in heart rate. This was repeated until multiple replications (usually three) were obtained for both pressor and depressor tests. By deriving the full sigmoid relationship, the linear portion of the curve is defined clearly and the inclusion of subthreshold or supersaturation points in analysis is avoided. Multiple replications minimize the potential for bias due to acute baroreceptor resetting or due to change in background autonomic activity.

Chronic indwelling arterial and venous catheters were inserted surgically under halothane anesthesia into each animal at least 36 h before the initial baroreflex test. The left external jugular vein and right common carotid artery were cannulated (Vascular-Access-Ports, Access Technologies, Skokie, IL) and the catheters tunnelled in the dorsolateral neck as previously described.[16] This arterial site was chosen because of technical considerations in maintaining chronic catheters in these small animals. The carotid is the only artery of sufficient size that is easily accessible in piglets. The catheter in the right common carotid artery partially occluded blood flow to the right carotid sinus and thereby created a potential differential in blood pressure and baroreceptor activation between that sinus and other baroreceptors.

To prevent differential baroreceptor activation, the right carotid sinus was denervated by cutting the carotid sinus nerve and stripping the sinus and contiguous artery of adjoining tissues. Other investigators have used this approach in similar situations when one carotid sinus will not reliably be exposed to the experimental condition.[17–19] Denervating one carotid sinus potentially alters the baroreflex response by diminishing the carotid contribution to the total response. However, although there is variation among species, it is well established that in humans and animals, extracarotid baroreceptors exert a large influence on heart rate that may be greater than that exerted by the carotid baroreceptors.[20] It is preferable to have a constant condition (unilateral carotid denervation) for all experiments than to risk addition of an aberrant and unstable carotid component.

Animals were tested while conscious and while anesthetized with each of three doses of halothane: 0.45, 0.9, and 1.35%. The minimum alveolar concentration (MAC) of halothane that prevents movement in response to noxious stimuli for young piglets is 0.9%. MAC was determined from published data for 4–10-day-old piglets[21] and verified in these animals for 21–57 days of age. We used three doses of halothane that encompass MAC in order to define a dose-response relationship.

Animals were tested at weekly or biweekly intervals from the end of their 1st week of life through approximately the 8th week. These intervals were maintained in order to limit exposure to the testing procedure and to avoid conditioning the reflex. The animals were not all tested at exactly the same ages, but the series of tests for each animal spanned the first 2 months of life. For each test, the animal rested in a sling. Conscious measurements were obtained with the animal in a quiet state (*i.e.*, resting with no motor activity other than breathing). If the animal moved, the data were discarded. Resting heart rate and blood pressure variables were stable for at least 3 min and were comparable to previously published values.[22,23] For tests with halothane, anesthesia was induced by inhalation of halothane through a face mask; the trachea was intubated; and ventilation was controlled to maintain arterial carbon dioxide tension between 35 and 40 mmHg. No other anesthetic drugs were administered. Phenylephrine

was infused at a rate of 12 ± 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (mean ± standard error of the mean) for conscious tests and 18 ± 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for halothane tests. Nitroprusside was infused at 10 ± 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for conscious tests and 15 ± 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for halothane tests. Doses were titrated so that the full span of blood pressure change was achieved in 1–2 min. Rectal temperature was monitored in animals that weighed less than 10 kg and was maintained in the normal range (38°–39° C) with a radiant heater. The animals were healthy throughout the experimental period as judged by activity, feeding, and growth.[16]

For each test arterial blood pressure, ECG, heart rate, and halothane concentration were continuously displayed by a polygraph (model 7, Grass Instrument Co., Quincy, MA). Airway gases were sampled at the distal end of the endotracheal tube and end-tidal halothane and carbon dioxide concentrations were measured by mass spectrometry (model MGA 1100, Perkin Elmer, Pomona, CA). The blood pressure transducer (DTX, Spectramed, Inc., Oxnard, CA) was calibrated with a mercury manometer. A lead of the ECG that clearly displayed P waves was monitored, and the heart rhythm was sinus for all data analyzed. The arterial blood pressure wave and ECG were continuously displayed by an oscilloscope (model 5113, Tektronix, Beaverton, OR) and recorded on magnetic tape (model D, A. R. Vetter Co., Redersburg, PA). Mean blood pressure was determined electronically with a second-order Bessel low-pass filter with an averaging window of 2 s. The R–R interval was measured by setting a voltage threshold on the R wave of the ECG such that levels exceeding this threshold generated rectangular voltage pulses. The time between successive pulses was measured using an 8-bit counter/timer with digital-to-analog output that provided a continuous reading of the R–R interval with a resolution of 5 ms. For each blood pressure maneuver, mean blood pressure and R–R interval were sampled at 5 Hz using a computer (model 310, Hewlett-Packard Co., Palo Alto, CA) equipped with a 12-bit analog-to-digital converter (AD 200, Infotek Systems, Anaheim, CA). The R–R interval was converted to heart rate, and both signals were stored on floppy disk for later graphical and statistical analysis.

Pressor and depressor curves exhibited hysteresis of the linear portion,[15] so they were analyzed separately. We examined statistically the effects of halothane and age on baroreflex sensitivity. Comparisons were made among three doses: 0 (conscious), 0.45, and 0.9% over the age range of 6–59 days; comparisons included a fourth dose, 1.35%, for the age range of 21–59 days. Data from the conscious studies have been reported previously and are included here as controls.[24] A multivariate linear regression model with a quadratic term for age was used to test whether baroreflex sensitivity varied with age (either linearly or nonlinearly). An interaction between age and dose was included to test whether regression lines were parallel among doses and therefore whether dose affected the relationship with age (fig. 2). Within each dose, a similar regression model for test and age compared pressor and depressor tests. Significant difference is defined as $P < 0.05$.

Heart rate and blood pressure baroreflex variables (threshold, saturation, and range) were analyzed with the same multivariate regression model to determine dose and age effects.

Resting heart rate and blood pressure were analyzed for effects of age and halothane by analysis of covariance, with age as the covariate and halothane dose (conscious *vs.* 0.9% halothane) as the treatment effect. Resting values are baseline values measured prior to initiating blood pressure manipulation in the conscious pigs and in those anesthetized with 0.9% halothane.

Results

Baroreflex Sensitivity

Halothane effect: Halothane decreased baroreflex sensitivity in a dose-dependent manner: conscious > all halothane doses ($P < 0.0001$) and 0.45 > 0.9 and 1.35% ($P = 0.01$) (figs. 2 and 3). The two highest doses, 0.9 and 1.35%, were not significantly different from each other. These relationships applied over age ranges tested and for both tests (pressor and depressor).

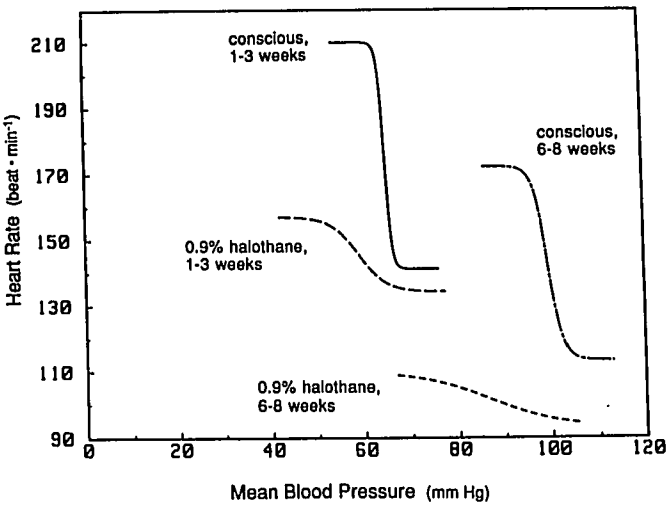

FIG. 2. The effects of age and halothane on baroreflex stimulus–response curves. These sigmoidal curves are derived from mean values for the respective groups. For both the conscious and the anesthetized state, increasing age decreased slope (baroreflex sensitivity) and shifted the curves to higher mean blood pressures and lower heart rates. For all ages, halothane decreased slope (baroreflex sensitivity) and shifted the curves to lower heart rates and lower threshold mean blood pressures.

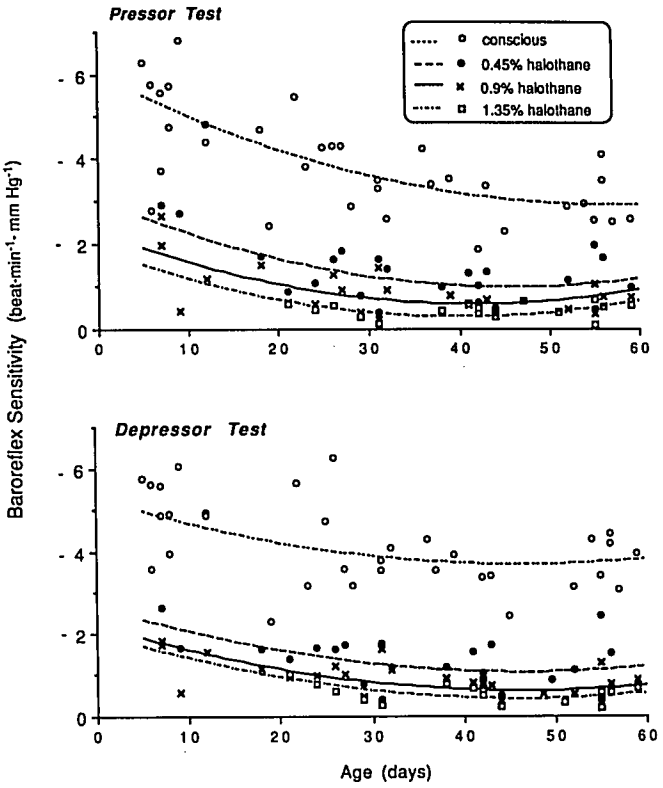

FIG. 3. Curvilinear regression models relating baroreflex sensitivity to age for each dose of halothane for pressor and depressor tests. Baroreflex sensitivity decreased with increasing age ($P \leq 0.0001$), and halothane decreased baroreflex sensitivity in a dose-dependent manner up to 0.9% ($P \leq 0.01$).

Age effect: With increasing age, baroreflex sensitivity decreased for all doses and in both tests (pressor and depressor) ($P < 0.0001$) (figs. 2 and 3).

Halothane interaction with age: For the halothane doses (0.45, 0.9, and 1.35%), the curvilinear relationships between baroreflex sensitivity and age were parallel over common regions of age, and there were no differences between pressor and depressor tests (figs. 3 and 4). Therefore, among the halothane doses, the relative effect of dose did not vary with age.

In examining the effect of halothane anesthesia compared to the conscious state, there was dissimilarity between pressor and depressor tests due to dissimilarity between tests in the conscious state. In the conscious state, pressor baroreflex sensitivity was less than depressor sensitivity at higher ages ($P < 0.05$) (fig. 4). For the pressor test, conscious values converged toward halothane values with increasing age, and therefore, with increasing age there was less depression by halothane relative to conscious ($P < 0.01$) (figs. 3 and 4). In the depressor test, the curvilinear relationships were parallel between conscious and halothane doses, and therefore, the relative effect of halothane anesthesia compared to the conscious state was similar at all ages (figs. 3 and 4).

Baroreflex Heart Rate Variables

Halothane effect: Halothane decreased heart rate at threshold (conscious > all halothane doses, $P < 0.001$) and at saturation blood pressures (conscious > all halothane doses, $P < 0.05$), and narrowed the heart rate response range (conscious > 0.45 > 0.9 and 1.35%; $P < 0.001$) (figs. 5 and 6). The effect was greatest on heart rate at threshold (peak heart rate).

Age effect: With increasing age, heart rates at threshold and saturation blood pressure decreased ($P < 0.01$), and the heart rate response range narrowed for all doses ($P < 0.001$) (figs. 5 and 6).

Halothane interaction with age: The effect of halothane did not vary with age.

Baroreflex Blood Pressure Variables

Halothane effect: Halothane decreased threshold blood pressure (conscious > all halothane doses; $P < 0.05$), and widened the blood pressure range in which the reflex was active (conscious < all halothane doses; $P < 0.05$) (figs. 7 and 8). Halothane had no significant effect on saturation pressure.

Age effect: Threshold and saturation blood pressures increased with increasing age for all doses including con-

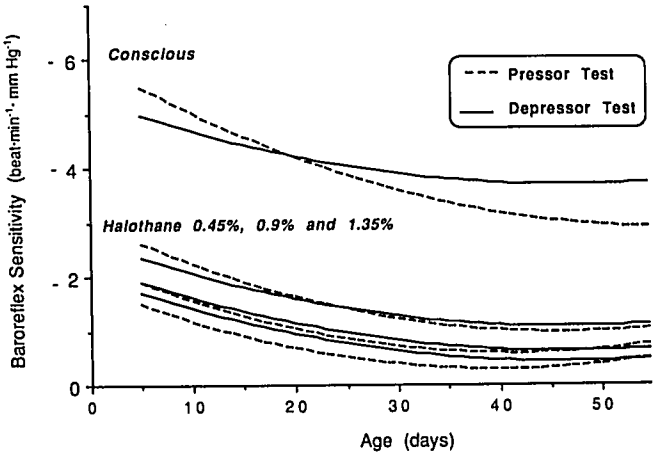

FIG. 4. Comparison of pressor and depressor tests (see fig. 3). For halothane groups, depressor and pressor values were similar. For the conscious group, pressor values were less than depressor values at higher ages ($P < 0.05$). For the depressor test, the conscious and halothane curves were parallel; therefore, the relative effect of halothane was similar at all ages. For the pressor test, the conscious and halothane curves were not parallel but converged with increasing age ($P \leq 0.01$); therefore, there was less depression from conscious by halothane at higher ages.

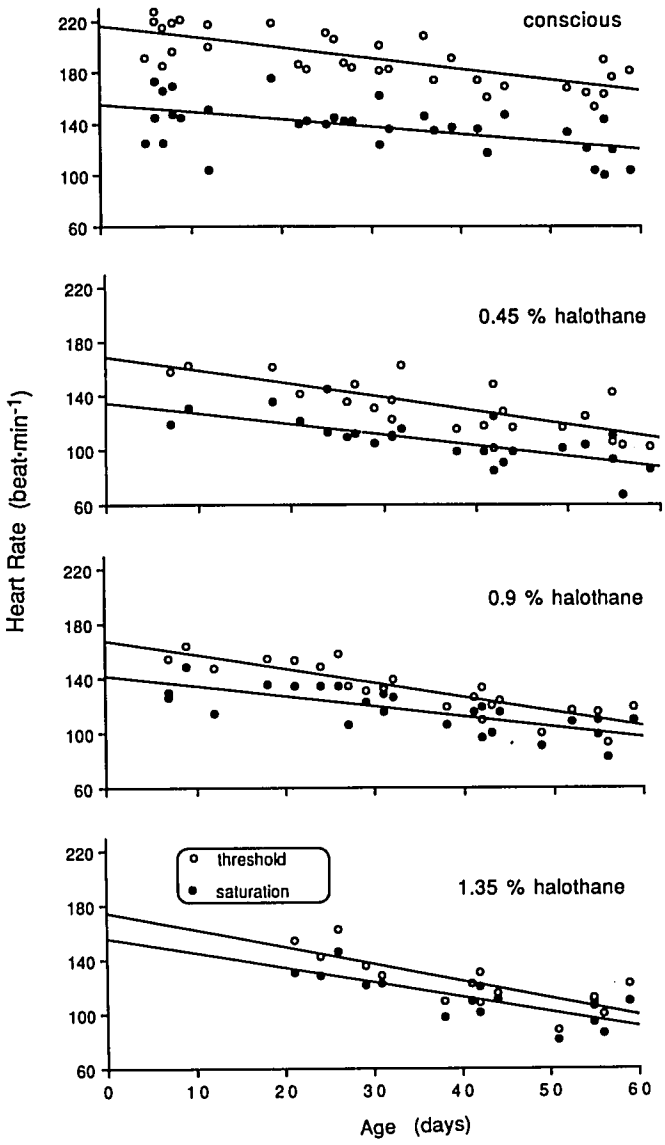

FIG. 5. Heart rates at threshold and saturation blood pressures for conscious and anesthetized states. These delineate the range of the heart rate response elicited by the baroreflex. Halothane decreased heart rates at threshold and saturation blood pressures and narrowed the heart rate response range ($P < 0.05$). With increasing age, heart rates at threshold and saturation decreased and the response range narrowed ($P < 0.01$).

scious ($P < 0.05$). The span of the blood pressure range did not change with age (figs. 7 and 8).

Halothane interaction with age: The effect of halothane did not vary with age.

RESTING HEART RATE

Halothane effect: Halothane decreased resting heart rate (conscious > 0.9% halothane; $P < 0.05$) (fig. 9).

Age effect: Resting heart rate decreased with increasing age for both conscious and 0.9% halothane ($P < 0.001$) (fig. 9).

Halothane interaction with age: The regression lines for heart rate and age were parallel for conscious and 0.9% halothane (fig. 9). Therefore, the effect of halothane on resting heart rate did not change with age.

RESTING MEAN BLOOD PRESSURE

Halothane effect: Halothane decreased resting blood pressure (conscious > 0.9% halothane; $P < 0.001$) (fig. 9).

Age effect: Resting blood pressure increased with increasing age for both conscious and 0.9% halothane ($P < 0.05$) (fig. 9).

Halothane interaction with age: Regressions for mean blood pressure and age were not parallel for conscious and 0.9% halothane but diverged with increasing age because of less rise with halothane (fig. 9). Therefore, the effect of halothane changed with age, and there was relatively more depression with increasing age ($P < 0.001$).

Discussion

Halothane markedly depressed arterial baroreflex control of heart rate in young swine. The depression was dose-dependent for doses up to 0.9%: 0.45% halothane reduced baroreflex sensitivity by approximately 66%, and 0.9 and 1.35% halothane reduced baroreflex sensitivity by approximately 80–90% of conscious values. Increasing age was accompanied by decreasing baroreflex sensitivity. The effect of maturation on halothane depression of baroreflex sensitivity is best described in two parts. First, comparing the three halothane doses, the relationship between dose and baroreflex sensitivity was constant over the ages tested whether the mechanisms tested were those that increase or decrease heart rate. Second, in the com-

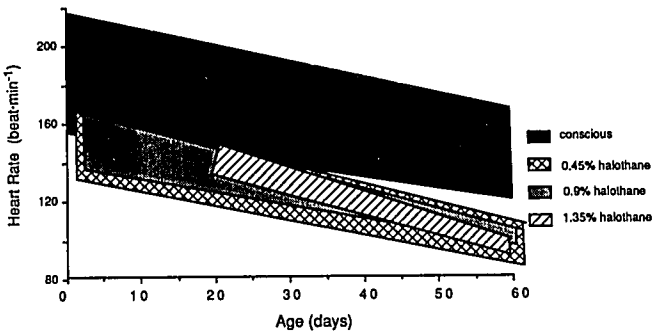

FIG. 6. The effect of halothane and age on the heart rate response range. The shaded and hatched areas represent the heart rate response ranges (see fig. 5).

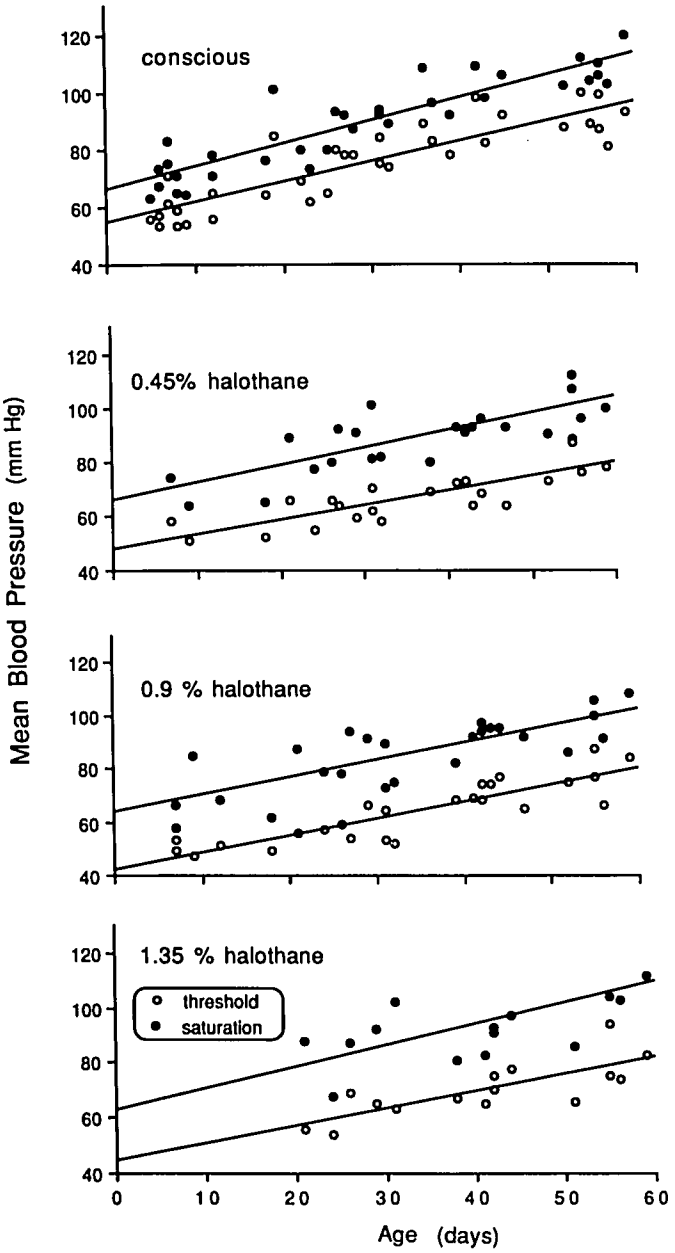

FIG. 7. Blood pressure threshold and saturation for conscious and anesthetized states. Threshold and saturation delineate the blood pressure range in which the heart rate reflexly changed. Halothane had no effect on saturation blood pressure but decreased threshold blood pressure, thereby widening the blood pressure range. With increasing age, threshold and saturation blood pressures increased ($P < 0.05$), but the span of the range did not change.

parison of halothane to conscious values, the relationship was constant with age for mechanisms that increase heart rate (depressor test), but was not constant for mechanisms that decrease heart rate (pressor test). In the pressor test, conscious values declined with age at a greater rate than did halothane values, so that at higher ages the values

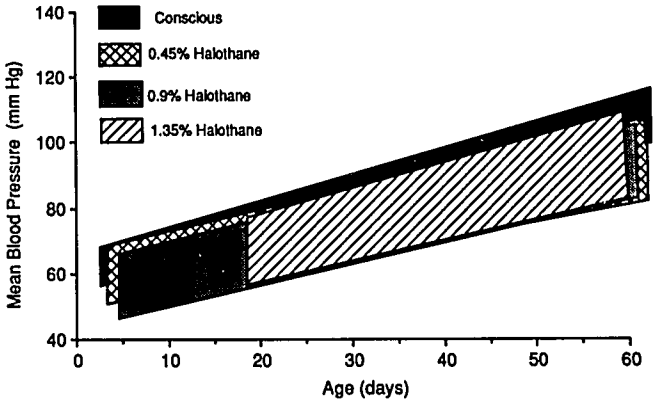

FIG. 8. The effect of halothane and age on blood pressure range. The shaded and hatched areas represent the ranges between threshold and saturation blood pressures (see fig. 7).

converged and the depression from conscious values by halothane was relatively less.

This difference in the halothane effect, relative to con-

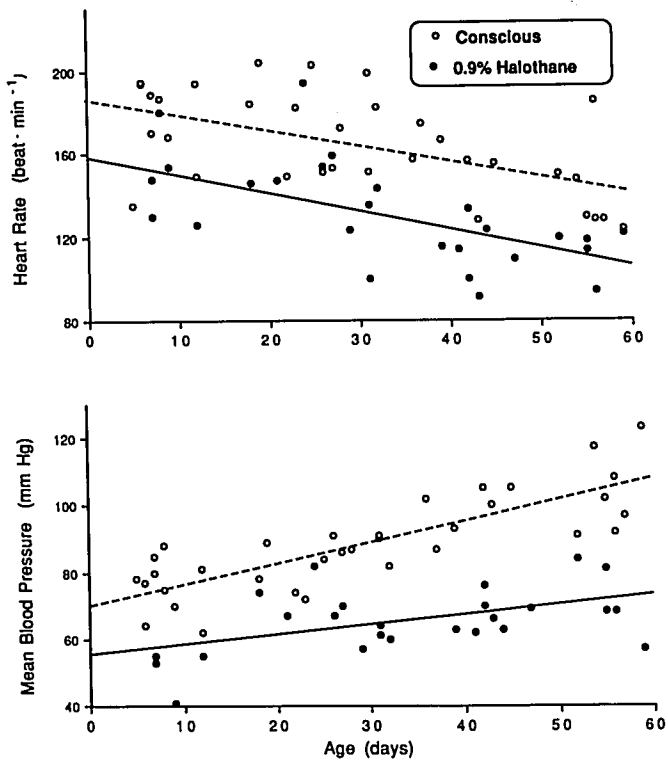

FIG. 9. Resting heart rates and blood pressures for conscious and anesthetized animals. Halothane decreased both resting heart rate and resting blood pressure ($P < 0.05$). With increasing age, resting heart rate decreased and resting blood pressure increased ($P < 0.05$). For resting heart rate, conscious and halothane regression lines were parallel; therefore, the relative effect of halothane was similar at all ages. For resting blood pressure, conscious and halothane regression lines diverged with increasing age; therefore, halothane produced relatively greater depression at higher ages ($P < 0.001$).

scious values, between pressor and depressor tests is attributable to dissimilarities between tests in the conscious state. For conscious animals, pressor values were less than depressor values at higher ages, whereas with halothane, pressor and depressor values were similar at all ages. This differential between pressor and depressor sensitivities has previously been reported in mature conscious swine.[25] The divergence with increasing age may be due to differential maturation of mechanisms responsible for baroreflex responses. Decreasing heart rate in the pressor test is mediated by a vagal mechanism, whereas increasing heart rate in the depressor test is mediated by both vagal and sympathetic mechanisms.[20]

Asynchronous maturation of the sympathetic and parasympathetic branches of the autonomic nervous system may account for divergence of the two tests with increasing age. Parasympathetic innervation of the heart precedes sympathetic innervation.[10] With postnatal maturation, sympathetic responses increase and may account for the greater degree of tachycardia than bradycardia in the response in older animals. Because pressor and depressor values were similar with halothane, the factors responsible for the divergence in the conscious state were not functional with halothane anesthesia. Depression of the autonomic nervous system by halothane may mitigate the differential responses of the sympathetic and parasympathetic branches.

During the first 2 months of life, the sensitivity of baroreflex control of heart rate decreased with increasing age in both conscious and anesthetized states. This pattern in conscious animals has been the subject of a previous publication.[24] It may be due to changes in mechanical properties of the arterial vasculature, alterations in autonomic influences on the sinus node, or other mechanisms. It coincides with the maturation of other systems, namely, peripheral vascular resistance mechanisms, and may reflect less dependence on heart-rate changes for blood pressure control. An important new finding of this study is that this pattern of decreasing baroreflex sensitivity with increasing age is demonstrated with halothane; this implies that the factors responsible for this developmental pattern remain functional with halothane anesthesia.

Halothane decreased resting heart rate and shifted the baroreflex heart rate response to a narrower range at lower heart rates. The depression was greatest for heart rate at threshold pressure (peak heart rate). With increasing age, resting heart rate decreased, and the heart rate response range narrowed and shifted to lower heart rates. Age did not alter the magnitude of halothane depression of heart rate variables. Halothane has direct chronotropic depressant effects on the heart and also depresses autonomic function.[26,27] Decreasing heart rate with age occurs concurrently with other developmental changes in the cardiovascular system, such as decreasing oxygen consumption and cardiac output.[28] Although the mechanism for this change is not known, it is not mediated by β-adrenergic or muscarinic autonomic mechanisms.[29] The results of the current study demonstrate that the effects of halothane on these resting and reflexly mediated heart rate variables are not altered by maturation.

Halothane decreased resting mean blood pressure and threshold mean blood pressure and widened the blood pressure response range. (The "blood pressure response range" refers to the range of blood pressure over which the heart rate response is active. This study did not test the ability to regulate blood pressure.) With increasing age, resting mean blood pressure increased and the baroreflex blood pressure range reset to higher pressures. Age did not alter the magnitude of halothane depression of baroreflex blood pressure variables. Resting mean blood pressure increased with age in both the conscious and the anesthetized states, but there was relatively more depression from conscious values by halothane at older ages. Increase of resting blood pressure with age is due to increase of peripheral resistance.[30] Halothane, acting both directly and by depression of sympathetic activity, depresses blood pressure by depressing cardiac output and peripheral resistance.[27]

Our results confirm those of other findings that halothane depresses arterial baroreflex control of heart rate.[2,6,31] Depression occurs at multiple levels of the reflex—at central nervous system centers, autonomic ganglia, and the heart. Our results also confirm those of Wear *et al.*, who found that halothane is more depressant in younger than in older rabbits when phenylephrine is injected to reflexly decrease heart rate.[4] However, these investigators did not find a decrease in baroreflex sensitivity with age. Several differences exist between our study and that of Wear *et al.* and may account for the different findings. For example, our subjects were piglets whereas theirs were rabbits; maturation rates and patterns may vary between species. Also, we chose heart rate, a clinical measure, rather than the R–R interval, to measure the cardiac cycle. Because heart rate has a hyperbolic relationship to the R–R interval, changes are not directly proportional. We used a longitudinal design to study conscious and anesthetized animals. Replicated experiments and a repeated-measures design through the first 2 months of life increased the precision of the study.

Halothane alters baseline function and reflex regulation of the cardiovascular system by affecting both neural (central and autonomic systems) and effector-organ (heart and blood vessels) components. In developing organisms, maturation of components also affects function and regulation of the cardiovascular system. We have shown that some developmental patterns of baroreflex control of

heart rate—such as the decrease in baroreflex sensitivity with increasing age—are not affected by halothane, and that other developmental patterns—such as divergence of pressor and depressor responses with increasing age—are affected by halothane. We have shown that some cardiovascular effects of halothane—such as depression of resting and reflexly mediated heart rate variables—are constant with age, and that other effects of halothane—such as depression of resting blood pressure—are not constant with age. Further studies to elucidate the mechanisms for the changes we have described will enhance our knowledge both of the actions of halothane and of the processes of maturation.

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