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The Effect of Halothane on the Baroresponse of Adult and Baby Rabbits

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The effect of anesthesia on the baroresponse of infants is not known. Therefore, the authors studied the baroreceptor activity of adult and 10- to 14-day-old rabbits during halothane anesthesia. The arterial systolic pressure was increased 20 to 30 per cent by injecting 0.03–0.04 mg/kg of phenylephrine into the femoral or external jugular vein while recording the electrocardiogram and femoral arterial blood pressure. The slope of the R-R interval on systolic pressure (baroresponse) was determined. The studies were done in the awake, unmedicated state and at 0.5, 1.0, and 1.5 MAC halothane. Oxygen was the carrier gas. The sensitivity of the response was different in the two groups of animals. When awake, the adults' slope was greater than that of the babies. During anesthesia the slopes decreased in both groups, but the decrease was greater in the babies. At 0.5 MAC halothane, the baroresponse was reduced 80 and 54 per cent in baby and adult rabbits, respectively. Lag time (the time between the onset of the rise in systolic blood pressure and the change in R-R interval) was prolonged in both the babies and the adults. Both showed the same prolongation during anesthesia, although the percentage change in the babies was greater. (Key words: Anesthesia: pediatric. Anesthetics, volatile: halothane. Receptors: pressoreceptors.)

THE BAROREFLEX-MEDIATED heart rate responses of adult humans and animals are depressed by general anesthesia.[1–6] To our knowledge, there have been no studies to determine whether this is also true of babies. If so, the baby would have limited ability to compensate for hypotension and reduced cardiac output when anesthetized because cardiac output in babies is primarily rate-dependent.[7] In a preliminary study of 53 preterm human infants anesthetized with halothane for ligation of patent ductus arteriosus, we found no change in heart rate despite a 38 per cent increase in arterial pressure during surgery.[8] This suggested an absence of baroresponses. However, several factors might have obtunded reflex responses of these infants. They were ill, in severe congestive heart failure, and had unknown end-tidal anesthetic concentrations. To eliminate these variables and determine whether anesthetics depress the baroreflexes of the baby, we studied the effects of known end-tidal halothane concentrations on the baroreceptor responses of normal, healthy, unpremedicated 10- to 14-day-old rabbits and compared the results to those found in adult rabbits.

Methods

We did a tracheostomy and inserted catheters into the femoral artery and vein of six adult rabbits and into the femoral artery and external jugular veins of four 10- to 14-day-old New Zealand white rabbits after anesthetizing the tracheostomy and cutdown sites with 1 per cent lidocaine. The animals breathed spontaneously. The tracheostomy was connected to a Bain Circuit through which we administered halothane and oxygen. End-tidal halothane concentrations were measured with a Beckman® LB-2 infrared analyzer that was modified to accurately measure the end-tidal gas concentration in the presence of small tidal volumes and rapid respiratory rates.[10] The electrocardiogram and transduced arterial pressure were recorded continuously on a Grass polygraph and magnetic tape. The frequency response of the arterial catheter and strain gauge was flat to 10 Hz. We used the presence of a dicrotic notch in the arterial pressure wave to indicate that the arterial pressure tracing was not damped. The baroreceptor response was tested by the method of Smyth *et al.*,[2] *i.e.*, 0.03 to 0.04 mg of phenylepherine was injected to increase the arterial pressure 20–30 per cent. This rise in systolic pressure resulted in a decrease in heart rate (prolonged the R-R interval) when the baroreflexes were functioning.

The arterial pressure and heart rate data were analyzed on a PDP-11 computer which was programmed to determine the linear, least squares, best fit relationship between the R-R interval and arterial pressure. We accepted only those slopes with correlation coefficients (r) greater than 0.85. Data were sampled by the computer at 1-ms intervals. Studies were conducted in the awake animal and during 0.5, 1.0, and 1.5 MAC halothane anesthesia. MAC for halothane was determined to be 0.80 ± 0.02 per cent for the adults and 1.15 ± 0.13 for the babies in a separate group of animals (unpublished data).

We measured the time between the initial rise in systolic blood pressure and the onset of heart rate slowing (lag time) associated with that rise in pressure (fig. 1) to determine whether anesthesia caused a delay in the onset of heart rate slowing. The time from the onset of a rise in BP to the beginning of a HR response was called the lag time.

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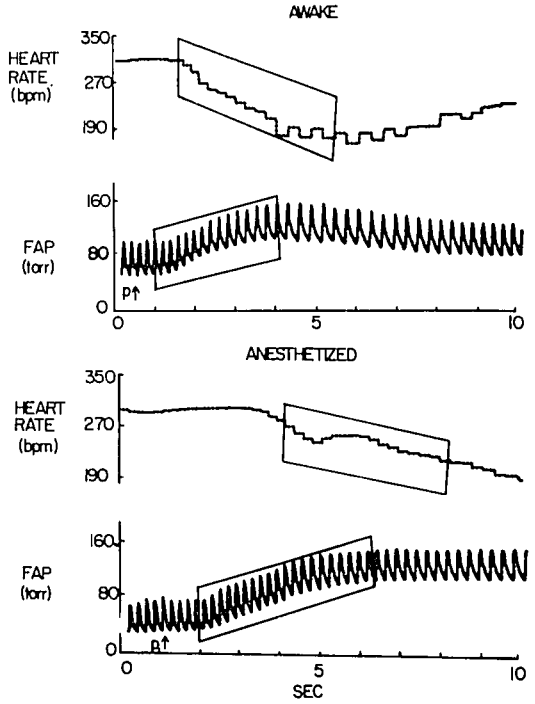

FIG. 1. This figure shows the relationship between heart rate and arterial pressure (FAP) in a baby rabbit. P ↑ indicates the point at which phenylephrine was injected. Awake, the heart rate began to decrease within three beats after the initial rise in arterial pressure. During anesthesia the decrease in heart rate occurred later (after nine beats). The time from the onset of the rise in pressure to the onset of the decrease in heart rate is defined as the lag time.

These data were tested for statistical significance by one-way analysis of variance, analysis of covariance and multiple range testing within both the adult and neonate groups, and by the unpaired *t* test between groups (adult *vs.* baby).

Results

Table 1 shows the average heart rate and systolic blood pressure awake and during anesthesia. In each instance, the neonate's resting heart rate was significantly greater than the adult's and the systolic blood pressure lower. Anesthesia decreased the systolic blood pressure of both groups. The pressures at 1.0 and 1.5 MAC were significantly lower ($P < 0.01$) than those of 0.5 MAC. Those at 1.5 MAC were also significantly different in both groups ($P < 0.001$) from those at 1.0 MAC.

Table 2 shows the relationship between halothane and the baroreceptor response. The sensitivity (slope) was greater (2.90 ± 0.41) in the adults than in the babies (1.94 ± 0.27) when awake ($P < 0.01$). It decreased progressively in both groups during anesthesia. The slope of this response was significantly lower in babies than in the adults at all anesthetic concentrations. At 0.5 MAC the babies' slopes were only 20 per cent of the awake values while the adults' slopes were still 46 per cent of control.

Anesthesia prolonged the lag time (table 3). Awake, the best correlation occurred with matching the initial rise in pressure with its associated R-R interval and with matching all subsequent R-R intervals and pressures over the rising phase of arterial BP (fig. 1). During anesthesia, the best correlation (highest *r* value) occurred, when the initial rise in systolic pressure was matched, not to the simultaneously occurring R-R interval, but with later occurring R-R intervals. The deeper the anesthetic level, the further from the initial rise in blood pressure this occurred. All lag times during anesthesia were significantly longer than awake ($P < 0.001$) and the values at 1.0 and 1.5 MAC were different from those at 0.5 MAC in the babies. The difference between the babies' and adults' lag times were not significant. The blood gases and *p*H were normal in both groups.

Discussion

Cardiac output in babies is rate-dependent, *i.e.*, the baby alters cardiac output by altering heart rate.[11] One mechanism by which heart rate is altered is through the baroreceptors. Shinebourne *et al.*[12] demonstrated that the baroresponses were present by mid-gestation in the sheep fetus, but that their sensitivity was reduced. They also showed an increasing sensitivity with increasing gestational age. Others have shown the response to be less active at birth than it is later in life.[13] Brady and Tooley thought the response was present and active in human neonates.[14] Bloor thought it absent in newborn rabbits anesthetized with barbiturates but present and fully active by 10 days of age.[15] Vatner and Manders found the baroresponses of unanesthetized rabbits present at birth, but less active than later in life.[13] In the present study, the baroresponses of our awake, unmedicated 10- to 14-day-old rabbits were present but only 67 per cent as

TABLE 1. The Relationship between MAC and Vital Signs

	Baby		Adult	
	Heart Rate (Beats/Min)	Systolic Pressure (mmHg)	Heart Rate (Beats/Min)	Systolic Pressure (mmHg)
Awake	309 ± 35	96 ± 10	230 ± 23	123 ± 13
0.5 MAC	299 ± 26	76 ± 5*‡	249 ± 22	113 ± 12*
1.0 MAC	285 ± 42	61 ± 2*†	262 ± 26	109 ± 12*
1.5 MAC	270 ± 44	52 ± 8*†‡	258 ± 25	102 ± 25*‡

Values are means ± 1 SD.
* Significantly different from that while awake ($P < 0.01$).
† Significantly different from that while anesthetized with 0.5 MAC halothane ($P < 0.001$).
‡ Significantly different from that while anesthetized with 1.0 MAC halothane ($P < 0.001$).

TABLE 2. The Relationship between Halothane and Baroreceptor Response

	Slope of Heart Rate *vs.* Systolic Pressure (ms/mmHg)	
	Baby	Adult
Awake	1.94 ± 0.27	2.90 ± 0.41
0.5 MAC	0.40 ± 0.21*	1.33 ± 0.28*
1.0 MAC	0.23 ± 0.08*	1.05 ± 0.35*
1.5 MAC	0.07 ± 0.08*†	0.60 ± 0.20*†

Values are means ± 1 SD.

* Significantly different from values obtained when animals were awake ($P < 0.001$).

† Significantly different from values obtained at 0.5 MAC halothane ($P < 0.005$).

active as the adults. Our animals were unmedicated, normoxic and had normal *p*H values. Their heart rates and arterial pressures were normal when awake.[16]

Our technique of measuring the baroresponse tests the entire integrated baroresponse and has several advantages that make it useful. These include ease of performance, lack of dependence on a specific drug dose, small infusion volumes (each injection was 0.1–0.2 ml), and the return of arterial pressure to baseline between attempts to stimulate the reflex.

Anesthesia was associated with a decrease in the baroreflex sensitivity (slope). This was more marked in the babies. For example, at 0.5 MAC the decrease in slope was two times greater in the baby rabbits than in the adults and the decrease at 1.5 MAC was five times greater. The reasons why baby rabbits have more baroreflex depression during anesthesia is unknown, but may relate to differences in the autonomic nervous system. Young animals have significant amounts of norepinephrine in their adrenergic nerve terminals,[17] but the nerves fail to arborize and incompletely penetrate the myocardium. The response to directly injected vasopressors is also less in the neonate than in the adult.[18] Roizen *et al.*[19] suggested, based on a measured decrease in plasma catecholamines during increases in arterial pressure, that the baroresponse included a reduction in sympathetic outflow. Since the neonate's sympathetic nervous system is inadequately developed, the rise in systolic pressure may not reduce sympathetic activity and, therefore, may not permit the heart rate to decrease as much. The parasympathetic nervous system on the other hand is very active in the newborn[20] and may well be functioning at a high level already.

The differences in baroresponse during anesthesia are probably not related to the initial arterial pressure or heart rate (R-R interval) since Mittler and Wade[2] were unable to alter the response by raising the arterial pressure to pre-anesthesia levels with a continuous infusion of phenylephrine or angiotensin. To test whether the changes in baroresponse were the result of changes in the resting heart rates and systolic pressures between the awake and anesthetized state, we examined the relationship between the baroresponse (slope of the heart rate *vs.* systolic pressure) (table 2) and the resting heart rate (table 1), and also the baroresponse and the resting systolic pressures (table 1) by analysis of covariance in both the awake and anesthesized states. If the changes in baroresponse were due to differences in resting heart rate and/or systolic pressure, there should be differences in the slope of the line of baroresponse *vs.* heart rate and/or blood pressure. If there were no effect of either heart rate or blood pressure then the slopes would be parallel, but the y-intercept would be significantly different. In both the adults and the babies the slopes resulting from plotting baroresponse *vs.* heart rate and baroresponse *vs.* systolic pressure were not significantly different between the awake and anesthetized states, but the y-intercepts were very different ($P < 0.0005$). Therefore, we conclude that the changes in resting heart rate and systolic pressure between the awake and anesthetized states were not responsible for the depressed baroresponse, but that these changes were due to other effects of anesthesia.

To examine whether the difference in baroresponse between adults and newborns was due to differences in initial resting heart rate and blood pressure when these animals were awake, we again analyzed the relationship between the baroresponse and both the resting heart rate and systolic pressure. We found no significant difference in either the resultant slopes or the y-intercepts ($P > 0.25$). Therefore, we conclude that the differences in baroresponse between the adult and the newborn while awake may be due to differences in the resting heart rate and systolic pressure.

It should be emphasized that even light levels of anesthesia effectively abolished the baroresponses of baby rabbits. At 1.0 MAC halothane, their slope of 0.2 ms/mmHg indicates that the response is effectively absent in any practical sense. If the baby's arterial pressure fell from 100 to 50 mmHg, the heart rate would only increase 20 per cent, *i.e.*, 80 per cent of the blood pressure reduction would remain uncompensated. Conversely, in the

TABLE 3. The Effects of Halothane on Lag Time

	Lag Time (s)	
	Baby	Adult
Awake	0.67 ± 0.25	0.75 ± 0.67
0.5 MAC	1.11 ± 0.26*†	1.19 ± 0.61*
1.0 MAC	1.75 ± 0.51*	1.50 ± 0.63*†
1.5 MAC	2.44 ± 0.44*†	1.87 ± 0.30*†

* Significantly different from values obtained when animals were awake ($P < 0.001$).

† Significantly different from values obtained at 0.5 MAC halothane ($P < 0.001$).

adult, most of the decrease in pressure would be compensated for by an increase in heart rate.

Smyth *et al.*[7] suggested that the best correlation between heart rate (R-R interval) and arterial pressure occurred when they related the R-R interval associated with each pressure wave to that arterial pressure. When they tried to relate the R-R interval occurring prior to or after the pressure wave, the *r* value decreased. This was also true in our awake animals (fig. 1, table 3). However, it was not true during anesthesia. The pressure wave no longer correlated best with its associated R-R interval but with an R-R interval occurring sometime later, *i.e.*, the reflex response was delayed. This is shown in figure 1 where in the awake baby rabbit the decrease in heart rate began within three beats of the onset of the blood pressure rise. During anesthesia the heart rate did not begin to decrease until the ninth beat. This may represent a delay in afferent or efferent transmission of impulses or in control of processing signals. While the lag times (ms) were of approximately the same duration in both the neonates and adults, the prolongation as a per cent of control was different. It is unclear what this means, but it may indicate a more profound effect of anesthetics in the babies at whatever level the block is occurring. This requires further investigation.

The same levels of anesthesia (MAC) produced a greater reduction in arterial pressure in baby rabbits than in the adults (table 2). This may reflect a lack of reflex sensitivity or a decreased ability of the baby's vessels to respond to catecholamines,[20] or a greater decrease in cardiac output than can be compensated for by a maximum vasoconstrictor baroresponse.

In summary, these data show a progressive decrease in arterial pressure with induction and deepening of anesthesia in both baby and adult rabbits. The adult's resting heart rate increased and the baby's decreased. Awake, the baroresponse was similar in both groups. During halothane anesthesia it decreased. These changes would limit the animal's ability to compensate for hypotension.

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