THE EFFECT OF NITROUS OXIDE ON BARORECEPTOR FUNCTION IN NEWBORN AND ADULT RABBITS

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ABSTRACT

The baroreceptor response was evaluated in newborn and adult rabbits by the pressor test of Smyth during the administration of oxygen and nitrous oxide. Newborn rabbits were found to have an attenuated baroreceptor reflex in comparison to adults. In addition, their reflex was more susceptible to the depressant effect of nitrous oxide. The newborn may be particularly at risk of cardiovascular compromise during anaesthesia and acute stress due to the dependence of cardiac output on heart rate.

KEY WORDS: RECEPTORS, baroreceptor function; Nitrous oxide.

NORMAL AWAKE adult subjects offset changes in blood pressure by altering heart rate, cardiac contractility, and systemic vascular resistance.[1] These homeostatic reflexes may be disturbed by the presence of anaesthetic drugs.[2] If so, the ability to tolerate surgical blood loss and other insults may be adversely affected.

It has been suggested that hypotension is common during surgery in infants and small children, regardless of the type of anaesthetic employed.[3] It has further been suggested that children do not respond to the sudden increase in systemic vascular resistance and blood pressure associated with ligation of the patent ductus arteriosus with appropriate reduction in heart rate.[3] Since nitrous oxide (with or without supplementation) is the most commonly used anaesthetic in paediatric practise we sought to determine its influence on baroreceptor function in newborn and adult subjects.

METHODS

Adult and newborn rabbits were studied using the pressor test described by Smyth.[4] In essence the test involves pharmacological elevation of systolic blood pressure by a single bolus injection of phenylephrine and examining the relationship between the electrocardiogram and the resulting intra-arterial pressure. The degree of prolongation of the R-R interval is expressed as a function of the elevation of systolic arterial pressure, and the slope of this line is proportional to the overall sensitivity of the baroreceptor reflex arc.

The animals were prepared under local anaesthesia (1% lidocaine) with external jugular and femoral artery cannulae (22 gauge medicut) and occlusive tracheotomy. Blood loss and irrigation fluid administration were closely monitored to avoid changes in blood volumes. After surgery the animals were restrained in the prone position and breathed 100 per cent oxygen through a Bain circuit. Inspired oxygen concentrations were monitored constantly throughout the experiment. Nitrous oxide concentrations were the difference between 100 per cent and the measured oxygen concentration. The accuracy of the oxygen analyser was ± 1% and was not affected by nitrous oxide. Arterial blood gas analyses before and after each experiment were within normal limits.

Four adult and five neonatal (11–17 days old) animals were studied. The dose of phenylephrine was titrated for each animal to that necessary for a 20–30 per cent rise in systolic blood pressure (usual range 30–50 μg). The baroresponse was elicited three times at each inspired gas concentration. The heart rate and blood pressure were allowed to return to base line after each test. Baroreceptor function was tested before and after nitrous oxide administration while breathing 100 per cent oxygen and during administration of 40, 60, and 75 per cent nitrous oxide. Equilibration to new inspired gas mixtures was

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assumed complete after twenty minutes of spontaneous ventilation.

The electrocardiogram and arterial blood pressures were recorded on magnetic tape for later analysis by computer.[16] We determined the slope of the R-R interval vs systolic blood pressure (baroreceptor response) using the R-R interval which best correlated with the rise in pressure. Data were statistically assessed using analysis of variance.

Results

The condition of the animals was remarkably stable throughout the experimental period. There were no significant changes in temperature or blood gas status. Heart rate (Table I) and systolic blood pressure (Table II) were stable before the pressor response determination and were not significantly different from control at any nitrous oxide concentration.

The control baroreceptor response of the newborn animals was significantly less than that of the adults. (Table III). In addition, the response of the newborn animals was progressively diminished by increasing nitrous oxide concentrations. The changes were significantly different when compared both to control values in infants ($p \leq 0.05$) and the comparable nitrous oxide concentration in adults. The slopes obtained in adult animals were progressively diminished by nitrous oxide, although this change was not statistically significant.

TABLE I
Resting Heart Rate Before Nitrous Oxide Pressor Test

	Heart Rate (±S.E.M.)	
	Infant	Adult
Control	297 ± 12	214 ± 8
40% N_2O	301 ± 8	220 ± 6
60% N_2O	288 ± 7	231 ± 7
75% N_2O	298 ± 7	237 ± 8
Return to Control	279 ± 5	209 ± 10

TABLE II
Resting Systolic Blood Pressure Before Nitrous Oxide/Pressor Test

	Systolic B.P. (±S.E.M.)	
	Infant	Adult
Control	91 ± 3	130 ± 5
40% N_2O	87 ± 4	131 ± 6
60% N_2O	86 ± 3	133 ± 6
75% N_2O	78 ± 4	133 ± 6
Return to Control	84 ± 3	130 ± 7

TABLE III
The Effect of Nitrous Oxide on Baroreceptor Response

	Peak Slope (±S.E.M.)	
	Infant	Adult
Control	4.9 ± 1.0*	15.3 ± 5.9
40% N_2O	1.8 ± 0.33*†	10.6 ± 2.9
60% N_2O	1.4 ± 0.29*†	10.0 ± 3.4
75% N_2O	1.2 ± 0.23*†	7.6 ± 2.7
Return to Control	3.2 ± 0.47*	20.5 ± 6.1

*$p \leq 0.001$ vs Adult value.
†$p \leq 0.05$ vs Infant control value.

Discussion

The baroreceptor reflex is recognized as one of the major homeostatic mechanisms promoting stability of the circulation during sudden alterations in arterial blood pressure. When the pressure receptors of the carotid sinus sense a decrease in arterial pressure, this reflex causes tachycardia, an increase in cardiac contractility and elevation of systemic vascular resistance.[2] An increase in pressure causes the opposite effects. Since these changes assist in returning arterial pressure to normal, they have been considered the major compensatory mechanism during acute circulatory stress. Defective modulation of circulatory insults have been demonstrated in patients with carotid artery disease,[5] hypertension,[6] advancing age,[7] and cardiac disease,[8] as well as in animals with experimental cardiac hypertrophy.[9] The latter study further demonstrated that other systemic and regional circulatory adjustments are attenuated consequent to baroreceptor derangement.

The newborn animal is markedly constrained in its ability to modify its cardiac output. In comparison to adult hearts, there is a reduced number of sarcomeres per unit mass of myocardium, less organization in the cellular structure and an increased amount of aveolar tissues between cells.[10] The compliance of the heart is therefore diminished and the force-velocity relationship (Frank-Starling mechanism) is impaired. Stroke volume is relatively fixed and cardiac outout is dependent upon heart rate. In addition, incomplete anatomic innervation of the newborn heart by the sympathetic nervous system may

minimize autonomic regulation of cardiac output.[10] Inability to modify heart rate in times of stress may therefore be disastrous to small infants.

Anaesthetics have long been known to modify baroreceptor function in man. Volatile drugs such as halothane,[11] narcotics[12] and barbiturates[13] all depress the response in adult subjects. The precise site of action of anaesthetics on the baroreceptor reflex is yet unknown.[11] The effect is not necessarily related to their anaesthetic properties, for methoxyflurane at equi-anaesthetic doses does not have the same depressant effect on the reflex as halothane.[14] Nitrous oxide by itself has not been evaluated in man due to technical difficulties with obtaining stable recordings through the excitement period seen with this drug. Nitrous oxide did not cause an excitement phase in our restrained rabbits. Our results in adult rabbits suggest that nitrous oxide may have a modest depressant effect on the pressor reflex, although the changes are not statistically significant when compared to control values.

Our data indicate that newborn animals are more susceptible to the effect of nitrous oxide than adults. This is all the more remarkable when one considers that the newborn's anaesthetic requirement is considerably greater than the adult's.[15] A similar effect has been demonstrated with halothane, where 0.5 MAC resulted in loss of 80 per cent of the reflex in 10–14 day old rabbits but only 32 per cent in adults.[16] In our present study 0.5 MAC nitrous oxide (75 per cent inspired in infants, 50 per cent in adults) obliterated the baroreflex to the same degree as reported for halothane. The precise mechanism for this newborn susceptibility to anaesthetic effect remains unknown.

In summary, we have demonstrated that newborn rabbits have an attenuated baroreceptor reflex in comparison to adults, and that their reflex is more susceptible to the depressant effects of nitrous oxide. These findings may explain the high incidence of hypotension in infants and children during surgery, and suggest that anaesthetic cardiac depression is not necessarily a function of anaesthetic potency.

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RÉSUMÉ

On a évalué la sensibilité du réflexe barorécepteur du lapin nouveau-né et adulte par l'épreuve de Smyth pendant l'administration d'oxygène et de protoxyde d'azote. Comparativement aux lapins adultes on a trouvé que les nouveaux-nés avaient un réflexe barorécepteur atténué. De plus ce réflexe était plus sensible à l'effet dépresseur du protoxyde d'azote. Le nouveau-né peut donc être plus particulièrement en danger de collapsus cardio-vasculaire pendant l'anesthésie et le stress à cause de la dépendance de son débit cardiaque sur la fréquence cardiaque.