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Autonomic Reflexes in Preterm Infants

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ABSTRACT. Lagercrantz, H., Edwards, D., Henderson-Smart, D., Hertzberg, T. and Jeffery H. (Department of Paediatrics, Karolinska Hospital and Institute, Nobel Institute for Neurophysiology, Karolinska Institute, Stockholm, Sweden, and Department of Perinatal Medicine, Sydney University, Sydney, NSW, Australia). Autonomic reflexes in preterm infants. Acta Paediatr Scand 79: 721, 1990.

Some autonomic nervous reflexes often tested in adult medicine have been studied in 21 preterm infants (25–37 gestational weeks). The aim was to develop such tests for preterm infants and see if there were any differences in babies with recurrent apnea and bradycardia and babies who had been exposed to sympathicolytic drugs before birth. To test sympathetic nervous activity the peripheral vascular resistance was measured before and during 45° of head-up tilting. To test parasympathetic nervous activity the degree of bradycardia was measured in response to cold face test (application of an ice-cube on the fore-head) and laryngeal stimulation with saline. Finally the heart rate changes after a sudden noise (85 dB) were studied as an indicator of both sympathetic and vagal activity. The peripheral resistance was found to be relatively low in these preterm infants, particularly in some infants tested at the postnatal age of about two months. Heart rate and mean blood pressure did not change during tilting, while the peripheral resistance increased significantly mainly due to lowered limb blood flow. The median decrease of the heart rate during the cold face test was 20.0% and during laryngeal receptor stimulation 23.7%. The sudden noise usually caused a biphasic heart rate response. An autonomic nervous reflex score was calculated and found to be negative (parasympathetic) in infants with recurrent prolonged apnea and bradycardia and positive in infants with clinical signs of increased sympathetic nervous activity. *Key words: autonomic nervous system, peripheral vascular resistance, vagal activity, reflex bradycardia, infant apnea, sudden infant death syndrome.*

Various autonomic test batteries have been developed to assess autonomic nervous functions in adult patients (1). Fairly little has been done in this field with regard to infants, who probably often suffer from a disturbance in autonomic nervous functions, for instance apnea, bradycardia and even the sudden infant death syndrome (SIDS) may be due to vagal over-activity (2, 3). Furthermore, autonomic functions can be modified by drugs given to mothers before birth, i.e. antihypertensive therapy. However, autonomic reflexes are difficult to assess in infants, since most of the tests used in adults like the Valsalva manoeuvre, the diving reflex and the hand-grip reflex require some kind of co-operation. Thus, the aims of the present study were: 1) To develop a clinical "bedside" testing of the autonomic nervous system suitable for newborn babies. 2) To evaluate developmental changes and pathological responses. 3) To learn more of the provocative factors, that lead to and sustain apnea and bradycardia, and hence provide insight for possible intervention.

Six variables of autonomic nervous functions which are easy to study in clinical practice were studied: The peripheral vascular resistance and its change during 45° of head-up tilting and the tachycardia after a sudden noise were tested as functions of the sympathetic nervous system. The cold face test, laryngeal reflex and the heart rate response after a sudden noise were tested to assess the activity of the parasympathetic nervous system. The responses were related to clinical conditions.

SUBJECTS AND METHODS

Sixteen preterm infants at the John Spence Nursery in Sydney and five infants from the neonatal ward at the Karolinska Hospital in Stockholm were studied. Clinical data are given in Table 1. The infants were divided into three groups (Table 2). 1) Infants of mothers with hypertensive disease of pregnancy (HDP) who were treated with clonidine (4) and occasionally also with alfa-methyl-dopa. 2) Infants who had persistent problems with prolonged apnea and bradycardia at the time when they were tested. Two infants of mothers with HDP were included in this group, since they were more than two weeks and apnea and bradycardia were the major symptoms. 3) Infants who had recovered from the acute phase of illness and were in stable condition.

One infant had unspecific symptoms of paleness and failure to thrive and was therefore not included in any of the three groups (baby 16). None of the infants received extra oxygen except two babies who required 23% O_2. Most of the babies had received theophylline, but the therapy was always interrupted at least two days before testing. The trials were usually performed about one hour after feeding, when the babies slept quietly. The mothers were often present during the study. We attempted to wait until the babies were in quiet or intermediate sleep according to the criteria set up by Prechtl (5). However, this was not possible in some of

Table 1. *Clinical data on 16 preterm Australian infants and 5 Swedish infants*

HDP = hypertensive disease of pregnancy, RDS = respiratory distress syndrome, PMS = pulmonary maladaption syndrome or transient tachypnea, A & B = prolonged apnea and bradycardia, SGA = small for gestational age

Case no.	Sex	Gest. age (w)	Post-natal age (w)	Birth weight (g)	Clinical condition: Perinatal	Clinical condition: Present (at the time of the test)	Autonomic score
1	F	30	5	1 575	HDP, RDS	A & B	−2.49
2	M	36	1	2 500	0	A & B	
3	M	27	9	1 233	RDS	A & B	−3.18
4	F	30	2	1 055	HDP, RDS	0	2.05
5	F	30	3	1 290	HDP, RDS	A & B	0.12
6	M	36	1	1 440	HDP, SGA, PMS	0	2.75
7	M	32	3	1 930	PMS	0	3.25
8	M	34	1	1 620	HDP, SGA	0	2.72
9	F	33	1	1 995	HDP	0	2.98
10	M	29	2	1 630	HDP	0	1.55
11	M	29	3	1 435	PMS	0	1.11
12	M	32	3	1 665	RDS	0	
13	M	30	2	1 475	RDS	0	3.47
14	M	34	3	1 900	PMS	0	2.39
15	F	36	1	1 580	SGA	0	−3.64
16	M	31	6	1 290	0	Viral infect.	5.74
17	M	32	2	2 113	HDP	0	4.55
18	M	32	2	2 199	HDP	0	0.56
19	M	27	4	1 233	RDS	A & B	−4.45
20	F	32	11	2 240	RDS, BPD	0	
21	M	25	11	799	RDS	A & B	−0.52
Median		31	3	1 575			

the cases, and therefore the tests had to be performed during active sleep. The study was approved by the Ethics Committees both in Sydney and in Stockholm and informed consent was obtained from all the mothers.

Methods. The following recording devices were applied half an hour before the study: skin electrodes for respiratory and ECG-monitoring, an oximeter probe to monitor O_2 saturation (Nelcor Hayward, Cal.); a mercury in rubber strain gauge around the calf to measure peripheral blood flow. A gavage tube (3, 5) for instillation of saline was inserted into the epipharynx through one of the nostrils. The study was performed in the incubator or in a warm room (at least 25°C).

Peripheral limb blood flow (LBF), heart rate (HR) and mean arterial blood pressure (MAP) were measured during 45° rapid head-up tilting which was performed in 2 sec. Limb blood flow was measured with occlusion plethysmography using mercury in rubber strain gauges (Parks Electronics, Beaverton, Oregon, USA), which were calibrated using a micrometer. Heart rate was recorded beat-to-beat with a heart-rate monitor (Kontron, Basle). Blood pressure was measured according to the oscillation method with a Dinamap (Criticon, Tampa, Florida). The peripheral blood flow was determined according to Whitney (6):

$$[Q=2dC\times 100\times 60/C]$$

Q = blood flow in ml/100 ml tissue/min; C = initial limb circumference in mm; dC = increase of C/sec.

The means of three recordings of LBF, HR and MAP were computed. If the baby woke up or moved during the recording, the trial was abandoned and a new measurement was performed. The peripheral vascular resistance was calculated according to the formula: PVR = MAP/LBF.

Noise response. A sudden noise was achieved by clapping a pair of castanets three times about one meter from the infant. The sound was estimated to about 85 dB. The test was initiated when the HR had been fairly stable for about 5 sec. The test was repeated three times and maximal and minimal HR during 20 sec after the stimulus were noted.

Cold face test. An ice-cube in a thin plastic bag was applied at the fore-head of the babies for 20 sec three to five times, with at least one min pause between each trial. If the baby was aroused the test was interrupted. The duration of apnea and the minimal HR during 30 sec following the initiation of the test were noted.

Laryngeal receptor reflex. Saline (0.2–0.5 ml; about 25°C was injected through the gavage tube and the apnea and HR responses recorded during the following 30 sec. Three tests were performed.

Autonomic score. To estimate the overall autonomic reflex responses an autonomic score was calculated for each baby. The peripheral vascular resistance (PVR); the change of it during tilting (dPVR) and the tachycardia response to noise (TNR) were taken as variables of sympathetic nervous activity and given positive signs, while the decrease of heart rate during cold face test (CFT), laryngeal reflex stimulation (LR), and bradycardia noise response (BNR) were taken as variables of parasympathetic function and given negative signs. The individual responses were divided with the median responses found in the whole group of infants: Thus, the autonomic score was calculated according to the formula:

PVR/median PVR + dPVR during tilting/median dPVR + TNR/median TNR − CFT/median CFT − LR/median LR − BNR/median BNR.

Statistical comparison between the groups was performed according to Mann-Whitney and correlations tested with Spearman-Rank test.

RESULTS

The results of all the tests are summarized in Table 3. *Head-up tilting* caused no change of heart rate or blood pressure while peripheral vascular resistance increased significantly (Fig. 1). Peripheral vascular resistance tended to decrease with postnatal age in these preterm babies ($r = -0.37$), but no significant correlations between the cardiovascular parameters and gestational or postnatal age could be detected.

A sudden noise caused only tachycardia in three infants; only bradycardia in three infants, no response in one baby and a mixed response in the remaining babies. A pronounced response is shown in Fig. 2 with an initial tachycardia when the baby is breathing, but then a bradycardia during apnea.

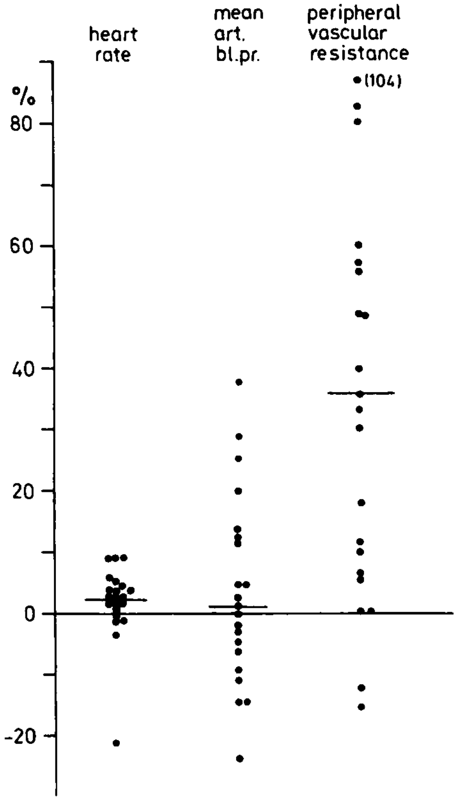

Fig. 1. Relative cardiovascular responses to 45° head-up tilting.

Cold face test led to bradycardia only when apnea occurred. A significant inverse correlation between the decrease of heart rate and duration of apnea was found ($r=-0.62$, $p<0.01$). Seven infants did not respond at all to cold face test or were aroused.

Provocation of the *laryngeal receptor reflex* resulted in bradycardia in all tested babies, although the variation was considerable. There was no significant inverse correlation between the bradycardic response and duration of apnea in this test.

An arbitrary *autonomic score* was computed based on resting peripheral resistance and the reflex responses (Table 1). In three infants one of the tests was not

Table 2. *Study groups*

		Autonomic score			
Main diagnosis	Infants	Median	Range	p	
1. Infants (<2 weeks) of mothers with hypertension	4, 6, 8, 9, 17, 18	2.7	0.6–4.5	<0.01 (1 vs 2)	NS (1 vs 3)
2. Infants with apneas and bradycardia	1, 3, 5, 19, 21	−2.5	−4.4–0.1	0.06 (2 vs 3)	
3. Infants without any major problems at the time of the test	7, 10, 11, 12 13, 14, 15, 20	2.0	−3.6–3.5		

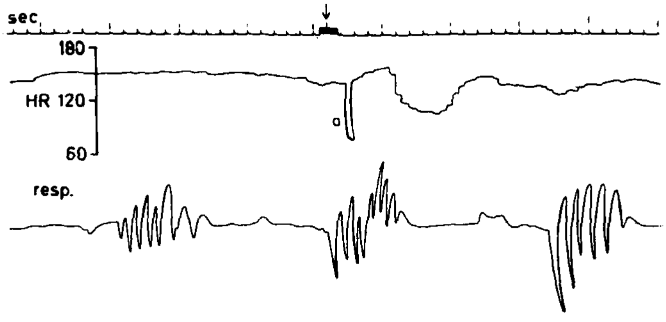

Fig. 2. Heart rate response to a sudden noise (at arrow). Note initial tachycardia and a subsequent bradycardia during apnea. a = probably an artifact. Recording from baby 15.

performed, thus a score could not be computed in these babies. Predominant sympathetic nervous responses were given positive signs, while predominant vagal responses led to a more negative score. We found no consistent relationship between the score and gestational age, but a tendency of inverse correlation between the score versus postnatal age. Young infants of mothers treated for hypertension always had a positive score, while babies with recurrent apnea and bradycardia usually had a negative score (Table 2). Baby no. 6 had an exceptionally high score possibly caused by a viral infection which was later documented.

DISCUSSION

Four tests of autonomic nervous function have been studied in preterm infants giving six variables. The present four tests were chosen since they do not require any patient co-operation and they are fairly easy to perform. Ocular compression or carotid massage as tests of vagal function were excluded because of difficulty with quantitating the stimulus. Sweating tests might be useful, but special equipment is required (7, 8).

The state of the baby is probably important when performing these tests. However, the aim of this study was to develop a "bedside" test possible to accomplish in a limited time. To wait for quiet sleep, in order to perform every test was found to be very time consuming, although we tried to do the tests when the baby was asleep. The laryngeal reflex has actually not been found to be different during quiet versus

Table 3. *Test results*

	Median	Range	*n*
Peripheral vascular resistance, mmHg·ml^{-1}·100 ml·min	13.2	5.0–43.5	21
Tilting 45° head-up			
dPVR %	+17.4	−15.3–104.0	21
Noise response			
dHR max	+7.0	0–27.2	20
dHR min	−8.2	0–30.8	20
Cold face test			
dHR min	−20.0	0−(−66.0)	21
Laryngeal reflex			
dHR min	−23.7	− 6.7−(−56.5)	18
Autonomic score	1.8	− 4.4−5.7	18

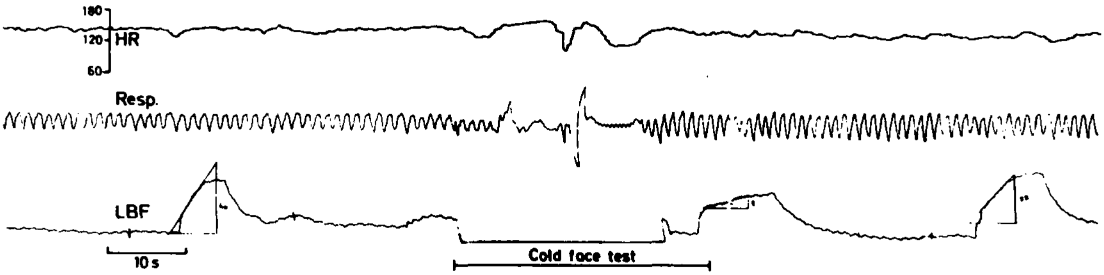

Fig. 3. Heart rate (HR); respiratory movements (Resp) and limb blood flow (LBF) before, during and after a cold face test in baby 3. Note the bradycardia and the low LBF during and after apnea. LBF is recovered slowly after the test.

active sleep in lambs (9). Whether the other reflexes are affected by sleep state is not known.

Limb blood flow was measured with mercury in rubber strain gauges, which are easier to handle than occlusion plethysmograph with latex cuffs or water chamber (10, 11). The values found in this study are comparable with those reported previously for preterm infants (12). Most of the infants responded to head-up tilting which decreased limb blood flow, while heart rate and mean blood pressure were not significantly affected in agreement with previous studies (12).

A sudden noise almost always produces tachycardia in the adult (1) and is thus interpreted as a sign of sympathetic nervous response. The preterm baby apparently responds differently; often with a biphasic response or only with a bradycardic response (three cases). The type of response might be dependent on the occurrence of a simultaneous apnea. The bradycardic response to a sudden noise might be a part of the fear or paralysis reflex which is typical for the infant animal (2). This reflex has actually been proposed to be responsible for sudden death in some animals in connection to jet bangs etc. and also to SIDS in human infants (2). However, the cold face test and laryngeal stimulation seemed to be much more potent in eliciting bradycardia.

The cold face test is a kind of simulated diving reflex testing the trigeminal-brainstem-vagal function. Stimulation of the upper branch of the trigeminal nerve, i.e. of the fore-head seems to produce the most pronounced effects (13). (The mean reduction of the heart rate in healthy adult volunteers was found to be 28%, which is higher than the median value in the present study. One reason may be that adults are always able to hold their breath voluntarily.) We found a significant correlation between the duration of apnea and bradycardiac response. A possible explanation for this finding is that breathing inhibits the vagal bradycardia by gating at a central level (14).

The responses to the laryngeal chemoreceptor test were similar as for the cold face test, although the number of positive responses was higher. Apnea was often produced by the instillation of saline in the epipharynx. This reflex has earlier been reported to be elicited only by water or milk from another species (9, 15), suggesting that it originates from chemical receptors. The present findings suggest that the reflex also can be triggered by an isotonic solution. This reflex has recently been reported to be markedly potentiated during mild hypoxia particularly in one infant who later succumbed in SIDS (16).

To quantitate the overall autonomic nervous responses an arbitrary autonomic score was computed for each baby. The balance between the different variables constituting the score is difficult to estimate. We have chosen to express the individual responses related to the median responses in the whole group.

The autonomic score was found to be negative (i.e. parasympathetic) in most of the infants with recurrent apnea and bradycardia. The highest positive scores were found in some babies of mothers with hypertensive disease of pregnancy when tested a couple of weeks after birth. This could possibly be due to some rebound effect of the material clonidine treatment (17), although this was not found in a previous study (4). There was a tendency for more parasympathetic than sympathetic responses in older infants than in younger ones, although the material was too small to draw more definite conclusions about maturation of the autonomic nervous system.

In conclusion, the present study shows that autonomic functions can be tested in preterm infants, although it is more complicated than in adults due to lack of co-operation.

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