Effect of Maturation on Heart Rate Response to Ocular Compression Test during Rapid Eye Movement Sleep in Human Infants[1]

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ABSTRACT. Thirty-three premature and full-term infants (31.5–50 wk postconceptional age) free from neurologic and cardiopulmonary disease at time of testing, underwent a standardized ocular compression test during polygraphically controlled rapid eye movement sleep. RR intervals were measured on the ECG before and during ocular compression. RR interval changes during ocular compression were compared to the preceding 60-s mean RR interval in each infant. Results were analyzed relative to gestational age, postnatal age, and postconceptional age. Baseline heart rate during REM sleep decreased with postconceptional age. During ocular compression, there was a significant negative correlation between the longest RR interval or the "latency" variable with postconceptional age. Latency is defined as the time, in milliseconds, from beginning of eyelid pressure to the first measurable RR increase compared to mean control RR + 1 SD. Our results indicate that during rapid eye movement sleep, "baseline heart rate" decreases with maturation, an effect supposedly related to increased vagal activity, whereas the heart rate response on ocular pressure stimulus, a vagally mediated reflex, is significantly influenced and blunted with maturation. (Pediatr Res 24: 477–480, 1988)

Abbreviations

REM, rapid eye movement
NREM, non-REM
GA, gestational age
PNA, postnatal age
PCA, postconceptional age
MEMA, middle ear muscle activity

Long isolated sinus pauses have been reported during systematic Holter ECG of early premature infants (1). Our knowledge of the autonomic system balance and autonomic regulation of heart rate in premature infants is incomplete. It is assumed that a prominence of vagal tone exists in premature infants (2, 3). The understanding of factors controlling heart rate is rendered more complex by the known impact of the different states of

alertness (wake, REM, and NREM sleep) on the autonomic nervous control system balance in human infants (4, 5). Observations obtained during waking hours cannot be extrapolated to explain sleep-related changes. Also it is hazardous to extrapolate from data obtained in young mammals to human infants as sleep-state maturation may be species related (6–8). Finally one must remember that full-term human newborns spend up to 70% of their total sleep time in "active" or REM sleep, and that REM sleep is even more prominent during the 24-h period in premature infants (9). To appreciate the effect of maturation on a well-known reflex involving the autonomic nervous system, we performed controlled ocular compression during polygraphically documented REM sleep to evaluate the heart rate response as a function of maturation in premature infants.

MATERIALS AND METHODS

Seventeen premature and 16 full-term infants (20 boys and 13 girls) were studied. All were free of neurologic and cardiopulmonary disease at the time of testing. Parental informed consent was obtained in each instance. GA ranged from 26.5 to 40 wk, PNA from 5 to 76 days, and PCA from 31.5 to 50 wk (see Table 1).

An ocular compression test was performed in a standardized manner, between 0900 and 1300 h, and at least 1 h after feeding. Infants were asleep on their backs. All were in active (REM) sleep just before and during the testing period as documented by polygraphic monitoring of ECG, respiration, and electroencephalogram potentials (EEG, F_{p2}–C_4, and C_4–T_4 of the 10–20 international placement system), and by continuous behavioral observation. The ECG was recorded using bipolar chest leads (DI lead). Biologic variables were monitored on an ALVAR 16 channels polygraph at 15 mm/s speed.

To perform the ocular compression, a water-filled pressure sensor (external diameter: 18 mm) was gently placed on each infant's eyelid just before testing. Each pressure sensor was connected to a pressure transducer (Hewlett-Packard Co., Palo Alto, CA) and the applied pressure to each sensor was recorded on the ALVAR polygraph simultaneously with the other variables (see Fig. 1). The mean and SD manually applied pressure recorded via the water-filled sensors was 103 ± 9 mm Hg. The pressure applied to each sensor was identical for each eye as documented by the polygraphic trace and was maintained without change during 10 s; a square wave stimulation was, thus, performed with an identical pressure applied on both eyes during a constant stimulation period (10 s) (see Fig. 1).

Polygraphic analysis and behavioral scoring were performed to affirm absence of state of alertness change during the minutes before, during, and just after testing. RR intervals were measured on the ECG recording during the minutes before and during ocular compression and after variables were collected.

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Table 1. *Subjects, age, and ocular compression test results**

Subject	GA (wk)	PNA (day)	PCA (wk)	Control RR Mean (ms)	Control RR SD (ms)	Latency (ms)	Longest RR interval (ms)	%RR maximum
1	30.5	6	31.5	398	18	2400	1733	435
2	31.0	8	32.0	440	21	440	1867	424
3	31.5	5	32.0	437	11	500	1800	412
4	26.5	46	33.0	399	17	433	1033	259
5	31.5	11	33.0	441	24	1800	1666	378
6	32.0	19	34.5	436	21	600	1866	428
7	34.0	7	35.0	446	25	2630	1233	276
8	35.0	10	36.5	392	17	1233	933	238
9	35.0	15	37.0	440	22	1833	1066	242
10	32.0	36	37.0	442	21	1633	1071	242
11	36.5	6	37.5	434	25	2000	666	153
12	30.0	52	37.5	406	24	1600	869	214
13	35.5	17	38.0	441	14	890	845	192
14	37.0	10	38.5	434	19	2160	1200	277
15	35.5	20	38.5	412	23	1200	833	202
16	29.5	70	39.5	435	7	2050	733	169
17	29.0	73	39.5	396	11	3350	666	168
18	38.5	18	41.0	430	18	2400	566	132
19	40.0	10	41.5	434	18	600	833	192
20	39.5	25	43.5	430	9	2800	1000	233
21	39.5	26	43.5	431	7	4000	700	162
22	40.0	28	44.0	430	10	3200	600	140
23	39.5	31	44.0	408	15	3150	700	172
24	40.0	35	45.0	398	7	1900	800	201
25*	39.5	36	45.0	469	10			
26*	40.5	39	45.5	430	9			
27	40.0	41	46.0	401	6	2600	666	166
28	39.5	44	46.0	498	7	2850	600	120
29	40.0	50	47.0	509	4	2200	533	105
30	40.0	56	48.0	469	9	5200	533	114
31	39.5	58	48.0	464	7	2900	666	144
32	38.5	73	49.0	471	12	4050	666	141
33	39.0	76	50.0	431	7	3700	533	124

* Control RR interval is the mean RR interval determined from measurement of each RR interval recorded during the 60 s just preceding the ocular compression test, RR interval is expressed in milliseconds (±1 SD); "latency" is latency from applied eyelid pressure to the first measurable RR interval-increase compared to mean control RR + 1 SD expressed in ms; longest RR interval is the duration of the longest RR interval in ms noted just after eyelid pressure; % RR maximum is the longest RR interval in ms just after eye-lid pressure divided by mean control RR, in ms, multiplied by 100. Subjects 25 and 26 had no response to ocular compression test, RR interval during ocular compression test was similar to control RR interval and % RR maximum was 100%.
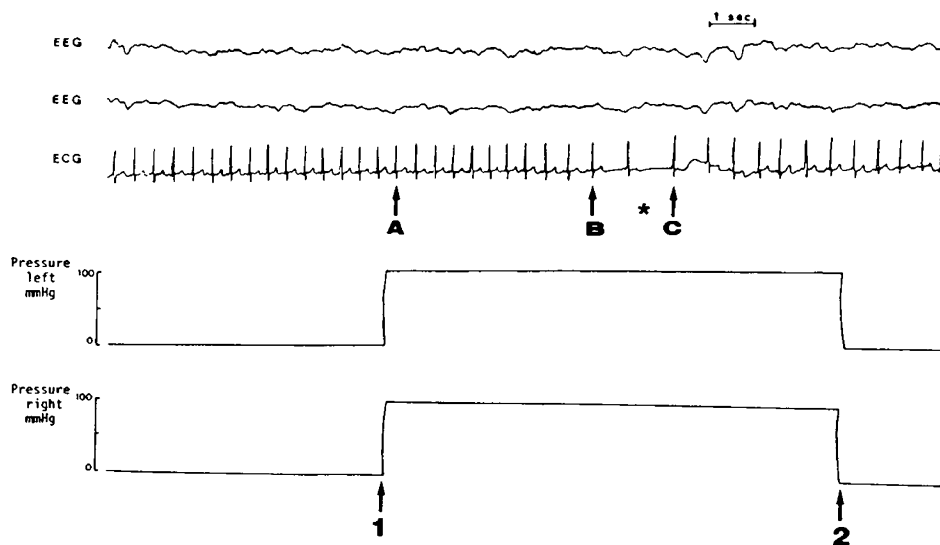

Fig. 1. Channel 1: EEG F_{p2}-C_4; channel 2: EEG C_4-T_4; channel 3: ECG DI. *1*. Control RR is defined by calculating the mean heart rate during 60 s terminating at onset of stimulation (*i.e.* point *A*). *2*. Heart rate between points *A* and *B* is defined as latency. *3*. * indicates longest RR. Channel 4 and 5: measurement of left and right eyelid pressure; pressure is applied in *arrow 1* and withdrawn in *arrow 2*. The pressure lasted for 10 s. Note the maintainance of REM sleep EEG throughout the recording. No arousal is noted with pressure onset and offset (*arrows 1* and *2*).

The intervals were: *1*) the control RR interval defined as the mean RR interval determined from measurement of each RR interval recorded during the 60 s before the ocular compression; *2*) the longest RR interval, in milliseconds noted just after eyelid pressure, the percent RR maximum was defined as the longest RR interval in milliseconds just after eyelid pressure divided by mean control RR, in milliseconds, multiplied by 100, *i.e.* % RR maximum; *3*) the latency from applied eyelid pressure to the first measurable RR interval increase compared to mean control RR + 1 SD, expressed in milliseconds.

A Pearson coefficient correlation analysis was performed to establish independence of specific variables. Correlations between age (postconceptional age) and measured variables were performed using linear and/or multiplicative regression. Multiple and stepwise linear regression analyses were performed with gestational and postnatal ages selected as independent variables. The "dbase III" statistical package was used to perform statistical computation.

RESULTS

All variables were measured during uninterrupted REM (active) sleep, but no dissociation between "phasic" and "tonic" REM sleep was attempted (see Fig. 1 which illustrates a typical tracing). Any record where a sleep state change occurred or where the persistance of the REM sleep state was questioned during application of ocular pressure, was eliminated from the analysis. Less than 5% of the total number of challenge tests were discarded. Data obtained in each infant are summarized in Table 1. Two of the full-term infants had no response (nos. 25 and 26) to our mild stimulus and most full-term infants had only a mild to moderate RR interval lengthening in response to the ocular pressure at the preselected setting.

There was a clear effect of maturation on mean control RR, on the longest RR interval secondary to ocular compression, and on the latency variables. When multiplicative analyses were performed for these variables relative to postconceptional age, mean control RR, longest RR interval, and latency were significantly influenced by postconceptional age (see Table 2). Not too surprisingly "% RR maximum" which had a high correlation coefficient with longest RR interval, was also statistically influenced by postconceptional age (Table 2; and Fig. 2).

Stepwise linear regression analyses performed after determination of the statistical independence of the selected variables confirmed the effect of maturation on the ocular compression variables (Table 3). With longest RR interval or % RR maximum as dependent variables and GA and PNA as independent variables, the stepwise regression for longest RR interval gave a R^2 for the full regression of 0.64 ($p < 0.0001$, F = 18.46) (longest RR interval = 2398 − 61.4 GA + 10.1 PNA + 2.5 control RR). A similar analysis performed with % RR maximum indicated a R^2 for the full regression of 0.69 ($p < 0.0001$, F = 31.4) (% RR maximum = 790 − 13.8 GA + 2.4 PNA). With latency as the dependent variable, the R^2 for the full regression was 0.51 ($p < 0.0002$, F = 9.41) (latency = − 3197 + 138 GA + 25.9 PNA) (Table 3).

COMMENTS

In 1908, Aschner (10) and Dagnini (11) published early descriptions of the oculocardiac reflex and reported cardiac rhythm

Table 2. *Results of multiplicative analyses**

Effect of maturation (PCA) on:	F	*p*
Control RR	5.75	<0.03
Longest RR interval	78.14	<0.0001
%RR maximum	94.68	<0.0001
Latency	25.05	<0.0001

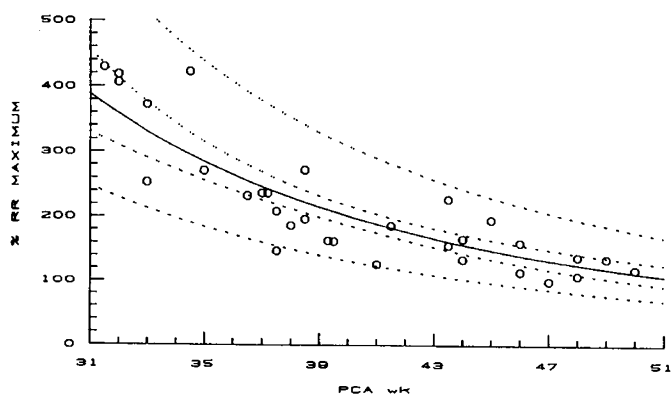* Variables were significantly influenced by PCA.

Fig. 2. Abscissa: PCA in weeks; ordinate: % RR maximum, *i.e.* longest RR interval in ms divided by mean control RR in ms multiplied by 100. Longest RR interval values were obtained after onset of eyelid pressure, during polygraphically controlled REM sleep (see text). There is a significant % RR maximum decrease ($p < 0.0001$) with increasing PCA (%RR maximum = 2.75^{10} PCA$^{-2.58}$).

Table 3. *Results of stepwise regression for general measured variables**

Independent variables	Dependent variables	Partial coefficients	Partial R^2	*p*
Longest RR	GA	55.3	0.35	<0.0001
	PNA	10.2	0.30	<0.0001
%RR maximum	GA	114	0.38	<0.001
	PNA	2.4	0.31	<0.001
Latency	GA	136	0.28	<0.002
	PNA	25.8	0.23	<0.001

* Variables were significantly influenced by PNA and GA.

slowing secondary to eyeball pressure on humans and experimental animals. This reflex involves an afferent pathway through the ophthalmic branch of the trigeminal nerve and an efferent pathway involving the motor nucleus of the vagus nerve and its cardiac efferents. Several authors (12-15) proposed assessing cardiac reactivity to vagal stimuli by evaluation of the amplitude of the cardiac response to ocular pressure, and Philips *et al.* (16) showed that such pressure evoked severe cardiac slowing in premature infants.

In our study we assessed the effect of maturation on response to ocular pressure in well-controlled conditions. Premature infants spend most of their time in REM sleep, and we paid great attention to define the state of alertness of infants during the entire testing procedure. We avoided heart rate changes related to crying, feeding, fear, and probably other emotional stresses associated with wake behavior (17-19). We could not dissociate tonic from phasic REM sleep. Even with the monitoring of MEMA, the best human indication of phasic events of REM sleep, this dissociation is never certain, as ponto-geniculo-occipital waves cannot be monitored in humans.

Our investigation clearly demonstrates a relationship between significant cardiac slowing and postconceptional age after vagal stimulation by ocular pressure. As a general rule the more premature the infant, the shorter was the latency from beginning of the pressure stimulus to the first prolonged RR interval, and the more important was the amplitude of the cardiac response assessed by the longest RR interval and % RR maximum. However, full-term infants had a very limited response, and the response was completely lacking in two infants. This limited response can be related to the mildness of the stimulation (eyelid pressure = 103 ± 9 mm Hg) (15), but this is not a sufficient explanation considering the amplitude of the response in more premature infants. A better parasympathetic-sympathetic interaction can be evoked as an associated factor. Probably it is too

simple to attribute the blunting of the oculo-cardiac reflex to maturation of sympathetic activity. A more complex modulation of each arm of the autonomic nervous system by the other must occur with maturation. As several synapses can be identified on this arc reflex, one can imagine that maturation may lead to more complex controls at each synaptic relay.

Ocular compression allowed us to demonstrate the maturation of a certain autonomic balance when premature infants were submitted to specific challenges, and this autonomic balance implies enhanced sympathetic activity or decrease in vagal reactivity. The simultaneous slowing of baseline heart rate (*i.e.* "control RR interval") with postconceptional age during REM sleep must also be emphasized. This decrease is well known in infants (4) and kittens (7). Egbert and Katona (7) have shown in the kitten that, even if heart rate is higher during REM sleep than during quiet (NREM) sleep, there is development of a parasympathetic dominance with age during normal, unchallenged sleep. A possible effect of the maturation of the cardiac pacemaker itself cannot be well addressed from our study as it was cross-sectional and has rarely, if ever, been resolved in animal models (20). However, studies of pharmacologically denervated hearts in kittens or other mammals have shown that the intrinsic rate changes are species dependent and can be associated with an heart rate increase (7, 21–23). Even if this pacemaker maturation exists in humans, and plays a role in the baseline heart rate slowing as well as the decreased responsiveness to ocular pressure, it is usually accepted that a part of the heart rate reduction seen with sleep is linked to increased vagal control (5).

Finally, the stepwise regression analyses show that the ocular stimulus variables influenced by maturation (longest RR interval and % RR maximum or the latency) are dependent on both gestational and postnatal ages (which are included under the label "postconceptional age"). This finding that developmental changes in cardiac rate controls are functions both of gestational and postnatal ages is similar to what has been noted in investigations of cardiac control in full-term and preterm infants during sleep (5).

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