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Acute cardiovascular responses in preterm infants at 34–39 weeks of gestational age☆

Suvi Viskari-Lähdeoja [a,b,*], Timo Hytinantti [a], Sture Andersson [a], Turkka Kirjavainen [a]

[a] Children's Hospital, University of Helsinki and Helsinki University Central Hospital, 00029 HUS, Finland
[b] Department of Ophthalmology, University of Helsinki and Helsinki University Central Hospital, 00029 HUS, Finland

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ABSTRACT

Background: Premature infants demonstrate immature physiological control mechanisms; however their acute cardiovascular control has not yet been widely studied.
Aim: The aim of this study was to analyze heart rate (HR) and blood pressure (BP) control in preterm infants.
Subjects: Twenty preterm infants with a mean gestational age of 31 ± 2.4 (26–34) weeks at birth were evaluated at a gestational age of 36 ± 1.5 (34–39) weeks. Results were compared to twenty, healthy, full-term, control infants studied at the age of 12 ± 3 weeks.
Outcome measures: HR and BP responses to 45° head-up tilt and side motion tests during non-rapid eye movement sleep were analyzed. In addition, HR responses to spontaneous arousals from non-rapid eye movement sleep were evaluated.
Results: Preterm infants showed significantly smaller initial HR and BP responses compared with controls in head-up tilt (HR $p = 0.0005$, systolic BP $p = 0.02$, diastolic BP $p = 0.01$) and side motion tests (HR $p = 0.002$, systolic BP $p < 0.0001$, diastolic BP $p < 0.0001$). Furthermore, in tilt tests, preterm infants presented with greater intersubject variability in BP responses than controls (systolic BP $p = 0.009$, diastolic BP $p = 0005$). Preterm HR responses to spontaneous arousals were similar to controls.
Conclusions: This study indicates immature vestibulo-mediated cardiovascular control in preterm infants compared with term infants. This is seen as attenuated BP responses to side motion test and more labile acute BP control to postural challenge.

1. Introduction

Passive head-up tilting is a common way to study acute autonomic cardiovascular control [1,2]. In adults, blood pressure (BP) control during head-up tilt is consistent, and BP levels remain stable, throughout the passive tilting with an immediate increase in heart rate (HR) followed by a gradual increase in peripheral vascular resistance [2]. Some intersubject variability in immediate responses to fast head-up tilt is evident for adults, however [3,4]. In autonomic sympathetic failure, HR responses remain intact, but BP is markedly decreased, without significant increase in peripheral vascular resistance [2].

During the first few months of a full-term infant's life, the initial HR response to tilting is similar to adults. Most studies have observed a biphasic response with initial increase in HR followed by a decrease and stabilization [5–7], or simply an increase in HR [8–10]. Similar HR responses have been seen in preterm infants [6,11,12].

Although acute BP responses to the head-up tilt test are widely studied in adults, there are only a few studies on these responses in premature and term infants. Supine full-term infants typically present an initial increase in BP followed by a decrease below baseline levels or stabilization [5,10,13]; however, although not clearly stated in the previous studies, there seems to be a high variability in responses according to the given standard deviations and ranges. Acute BP responses to the head-up tilt test also follow a similar pattern in preterm infants [6,10,14]. Detailed summary tables of the published BP response results are presented in the Supplementary materials.

The aim of this study was to analyze heart rate and blood pressure control in preterm infants. The infants were studied at the gestational age (GA) of 34–39 weeks, and the results were compared to healthy control infants studied at 3 months of age. We performed 45° head-up tilt test (baroreflex and vestibular control) and side motion test (vestibular control) in quiet non-rapid eye movement (NREM) sleep. We also analyzed HR responses to spontaneous arousal (HR reactivity).

Abbreviations: BP, blood pressure; BPD, bronchopulmonary dysplasia; DBP, diastolic blood pressure; GA, gestational age; HR, heart rate; NREM, non-rapid eye movement; SBP, systolic blood pressure.

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* Corresponding author at: Children's Hospital, Biomedicum 2C, 6th floor, P.O. BOX 705, 00029 HUS, Finland. Tel.: +358 50 5433790.
E-mail address: suvi.viskari@helsinki.fi (S. Viskari-Lähdeoja).

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2. Materials and methods

2.1. Study subjects

Twenty preterm infants born at a mean GA of 31 ± 2.4 weeks (26–34 weeks) were studied at a mean GA of 36 ± 1.5 (34–39) weeks. Demographic data of these infants are presented in Table 1. The mean postnatal age of these infants was 4.9 ± 3.5 (0.9–13) weeks. The cardiorespiratory state of the infants was stable at the time of study. Three infants were on supplemental oxygen at the time of the study, but none was on nasal continuous positive airway pressure therapy or received vasoactive drugs. Five (25%) preterm infants received theophylline at the time of the study. All preterm infants were studied a few days before planned discharge from the children's ward. Five of these infants had a diagnosis of bronchopulmonary dysplasia (BPD) [15]. Sixteen infants had been treated with benzylpenicillin and netilmycin antimicrobial therapy for proven or suspected clinical sepsis (subject nos. 2, 5, 19 and 20 did not receive antibiotics), and one (no. 6) had also received vancomycin. All preterm infants passed an audio brainstem response test [16].

Twenty control infants were born full-term and they were studied at 12 ± 3.4 (8–19) weeks of age. They had uneventful neonatal history, no medication and were considered healthy. None of the mothers of control infants had a history of smoking. The results for control infants have been published earlier [7].

Approval of the study was obtained from the Ethics Review Committee of the Hospital for Children and Adolescents, Helsinki University Hospital, Helsinki, Finland and the parents gave written consent.

2.2. Study design

Preterm infants were studied in the children's ward during a nap mostly at evening-time. They were sleeping in a plastic cot, which was lifted up from the trolley base. Control infants slept one night in the hospital on a normal bed with a rigid-framed mat on top of the mattress. The study protocol followed that described earlier [7,17].

Polysomnographic recording included two electroencephalograms (C3/A2 and O2/A1), one or two electrooculograms, chin and diaphragm muscle surface electromyograms, ECG, nasal airflow (RSS100-HR, Hans Rudolph, Kansas City MI or Nasal Flow sensor, Compumedics, Abbotsford, Australia), respiratory movements, arterial oxyhemoglobin saturation, and a BP measurement. BP was measured from the wrist of the infant using a Finometer® (premature infants, 9 controls) or Finapres® (11 controls) (Finapres Medical Systems, Amsterdam, Netherlands) enlarged finger cuff that was modifiable to enable a good fit to each infant's wrist. This method enabled continuous non-invasive measurement of BP throughout the tests.

Data collection was performed with either an Amlab (11 controls) (Amlab Technology Pty Ltd, Sydney, Australia) or a Siesta (preterm infants and 9 controls) (Compumedics, Abbotsford, Australia) polygraphic system, both with 16-bit amplitude resolution. Data sampling varied with a maximum of 200 Hz in Amlab and 512 Hz in Siesta which were for ECG and electromyogram signals. The SpO_2 signal was collected with 1 Hz and the remainder at 100 Hz (Amlab) or 128 Hz (Siesta).

During NREM sleep, two types of cardiovascular tests were performed. In the tilt test, the position of the infant was manually changed in 2–3 s from a horizontal position to a 45° angle head-up, then held upright for 45 s, after which the infant was returned back to a horizontal position. The side motion test consisted of a back-and-forth movement with a radius of 0.5 m. A baseline of 30 s of uneventful NREM sleep was required before the tests, and the test interval was a minimum of 1 min. Because even small arousals have a clear effect on the test response [17], the infants were constantly observed during the tests for any signs of arousal.

2.3. Data and statistical analysis

Data were analyzed with Somnologica sleep polygraphy software (MedCare, Reykjavik, Iceland) after conversion to European Data Format. The original sampling rate was used in the analysis, and special purpose software enabled the beat-to-beat ECG and BP evaluation. Sleep was staged by the criteria introduced by the Pediatric Task Force for American Academy for Sleep Medicine [18]. The first successful tilt and side motion tests without arousal were selected for each infant.

For the statistical analysis, four time intervals for each test were selected: 20–5 s prior to the test, 0–5 s and 10–15 s from the test onset, and 25–40 s from the onset of side motion or from the end of

Table 1
Demographic data of preterm infants.

Subject	Sex (M/F)	GA (wk)	Birth weight (g)	Study age (wk)	Weight (g)	Surf (n)	Vent (d)	CPAP (d)	O_2 (GA)	BPD (+/−)	Sepsis (n)	M. smoking (+/−)	Theophylline (+/−)	Current medication
1	M	32 + 2	1560	36 + 5	2470	0	0	<1	32 + 3	−	0	−	−	
2	M	33 + 5	2320	35 + 5	2220	0	0	<1	None	−	0	−	−	
3	F	30 + 0	1300	33 + 4	1415	0	0	<1	None	−	0	+	+	Theophylline
4	M	30 + 0	1210	34 + 3	1770	0	1	2	None	−	0	+	−	
5	F	32 + 5	1470	35 + 4	1800	0	0	<1	None	−	0	−	−	
6	F	28 + 3	800	39	2435	1	2	30	None	−	0	−	−	
7	M	31 + 6	1760	35 + 6	2275	0	0	4	None	−	0	−	−	Furosemide
8	M	31 + 6	1680	36	2395	0	0	3	32 + 1	−	0	+	−	
9	F	27 + 3	770	38 + 3	2310	3	6	38	41 + 1	+	0	+	−	HCT, spironolactone
10	F	31 + 3	1965	33 + 5	2100	0	0	<1	None	−	0	−	+	Theophylline
11	F	29 + 0	1220	37 + 2	2540	4	8	24	36 + 2	+	1	−	−	HCT, spironolactone
12	M	31 + 5	1210	35 + 4	1795	0	0	6	None	−	0	+	−	
13	M	27 + 6	1090	35 + 3	1980	4	22	20	37	+	1	−	+	HCT, spironolactone, theophylline, trimethoprim
14	M	25 + 4	790	38 + 2	2615	1	14	34	37	+	0	−	+	HCT, spironolactone, theophylline
15	M	28 + 5	930	36 + 6	1865	2	8	26	37	+	2	−	−	HCT, spironolactone
16	F	32 + 1	1556	34 + 4	1795	0	0	3	32 + 4	−	0	−	−	
17	M	32 + 1	1845	34 + 4	2040	1	5	2	33 + 0	−	0	−	+	Theophylline
18	F	34 + 5	1845	35 + 4	1800	0	0	<1	None	−	0	−	−	
19	M	33 + 5	2225	35 + 5	2285	0	0	0	None	−	0	−	−	
20	M	34 + 1	2080	35 + 3	1925	0	0	<1	34 + 1	−	0	−	−	

Medication other than vitamin, iron, or electrolyte supplement is presented. One preterm infant had bilateral intraventricular hemorrhages that resolved spontaneously (subject no. 9), with a normal MRI at term age; another had suspicion of mild periventricular leukomalacia and a small hypodensic area possibly resulting from a small hemorrhagic insult (subject no. 14) at term age by MRI. BPD = bronchopulmonary dysplasia; CPAP = continuous positive airway pressure; d = days; F = female; g = grams; GA = gestational age; HCT = hydrochlorothiatzide; M = male; M. smoking = maternal smoking during pregnancy; Surf = surfactant (Curosurf®, Chiesi, Parma, Italy); Theophylline = currently on theophylline; Vent = ventilatory support; wk = week. O_2 = oxygen supply.