Pediatric Graduate School
Children's Hospital
Institute of Clinical Medicine
University of Helsinki
Helsinki, Finland

EFFECTS OF SIDS RISK FACTORS AND HYPOXIA ON CARDIOVASCULAR CONTROL IN INFANTS

Suvi Viskari-Lähdeoja

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in the Niilo Hallman Auditorium, Children's Hospital, on 15th of February 2013, at 12 noon

Helsinki 2013

Supervised by

Docent Turkka Kirjavainen
Children's Hospital
Helsinki University Central Hospital
Helsinki, Finland

Reviewed by

Professor Pekka Kääpä
Department of Pediatrics
University of Turku
Turku, Finland

and

Docent Jyri Toikka
Institute of Clinical Medicine
Clinical Physiology
University of Turku and Turku University Central Hospital
Turku, Finland

Opponent

Professor Hugo Lagercrantz
Karolinska Institute
Astrid Lindgren Children's Hospital
Stockholm, Sweden

Cover Design: Henri Hakkarainen

ISBN 978-952-10-8586-4 (Paperback)
ISBN 978-952-10-8587-1 (PDF)
http://ethesis.helsinki.fi
Unigrafia Oy
Helsinki 2013

To Tuomas and Hilla

TABLE OF CONTENTS

ABSTRACT

Background and aims

Sudden infant death syndrome (SIDS) is a rare lethal event occurring in 0.1 to 0.3 ‰ of infants. In Finland, 10 to 20 infants die from SIDS annually. Research has defined many risk factors for SIDS, but the cascade leading to death remains unexplained. Cardiovascular recordings of infants succumbing to SIDS, as well as animal models, suggest that the final sequelae involve cardiovascular collapse resembling hypotensive shock. There is also evidence of previous hypoxia in SIDS infants. In animal studies, vestibulo-mediated cardiovascular control has been shown to be important in hypotensive shock. Hence, we hypothetized that SIDS victims may have impaired vestibulo-mediated cardiovascular control, possibly due to previous hypoxic episodes. In this thesis, we studied cardiovascular control, and especially vestibulo-mediated cardiovascular control in infants with known risk factors for SIDS at 2 to 4 months of age when the risk for SIDS is highest.

Study subjects

A full polysomnographic recording with continuous blood pressure (BP) measurement was performed in 50 infants at 2-4 months of age: 20 control infants, nine infants with univentricular heart (UVH) suffering from chronic hypoxia, 10 infants with bronchopulmonary dysplasia (BPD) with intermittent postnatal hypoxic events, and 11 infants whose mothers had smoked during pregnancy, and thus had been exposed to intrauterine hypoxia and nicotine, were studied. In addition, 20 preterm infants were studied at the gestational age of 34-39 weeks to evaluate developmental aspects of cardiovascular control during head-up tilt test and vestibular stimulus.

Methods

Linear side motion and 45° head-up tilt tests were performed in quiet non-rapid eye movement sleep (NREM). Heart rate (HR) and BP responses were analysed from the tests without signs of subcortical or cortical arousal. In addition, HR variability during NREM sleep was assessed. As a general marker of cardiovascular reactivity, HR response to spontaneous arousal from NREM sleep was also evaluated.

Results

Side motion test. In the side motion test, control infants presented a biphasic response. First, there was a transient increase in HR and BP. This was followed by a decrease in BP to below baseline, and a return to baseline in HR. All other infant groups showed altered responses. UVH infants and preterm infants near term age had markedly reduced responses. Infants with BPD presented with variable responses: some responded similarly to controls, whereas others showed no initial increase in BP, and the following BP decrease was more prominent. Infants with intrauterine exposure to cigarette smoke showed flat initial BP responses, and the following decrease was more prominent, similarly to a subgroup of BPD infants.

Tilt test. Control infants presented with a large variability in BP responses to head-up tilting. On average, systolic BP remained, at first, close to baseline, and diastolic BP increased, after which both decreased and remained below baseline even at the end of the tilt test. On average, HR showed a biphasic response with an initial increase followed by a decrease to below and, finally, a return to baseline. UVH infants showed a similar BP response, but their HR response was tachycardic. Preterm infants with BPD presented with an even greater variability in their BP responses to head-up tilts than control infants, but the overall response

as a group did not differ from that of the controls. The tilt response of infants exposed to maternal cigarette smoking during pregnancy did not markedly differ from the control response. Preterm infants near term age showed attenuated responses in both cardiovascular measures, together with greater inter-subject variability compared to the control infants.

Discussion

In conclusion, the studied infants with SIDS risk factors showed altered vestibulo-mediated cardiovascular control during the linear side motion test and head-up tilt test. The findings support our initial hypothesis that some infants with SIDS risk factors have defective vestibulo-mediated cardiovascular control, which may lead to death in life-threatening situations.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals I-IV:

I. Kirjavainen T, Viskari S, Pitkänen O, Jokinen E. Infants with univentricular heart have reduced heart rate and blood pressure responses to side motion and altered responses to head-up tilt. J Appl Physiol 2005;98(2):518-525.

II. Viskari S, Andersson S, Hytinantti T, Kirjavainen T. Altered Cardiovascular Control in Preterm Infants with Bronchopulmonary Dysplasia. Pediatr Res. 2007;May;61(5 Pt 1):594-9.

III. Viskari-Lähdeoja S, Hytinantti T, Andersson S, Kirjavainen T. Heart rate and blood pressure control in infants exposed to maternal cigarette smoking. Acta Paediatr. 2008;Nov;97(11):1535-41.

IV. Viskari-Lähdeoja S, Hytinantti T, Andersson S, Kirjavainen T. Acute cardiovascular responses in preterm infants at 34 – 39 weeks of gestational age. Early Hum Dev. 2012 Nov;88(11):871-7.

 In addition, some unpublished results are also presented.

ABBREVIATIONS

ALTE	apparent life-threatening event
ANOVA	analysis of variance
AS	active sleep
BP	blood pressure
BPD	bronchopulmonary dysplasia
CHD	congenital heart defect
CO	carbon monoxide
CO_2	carbon dioxide
CPAP	continuous positive airway pressure
DBP	diastolic blood pressure
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyogram
EOG-L	left oculogram
EOG-R	right oculogram
$EtCO_2$	end-tidal carbon dioxide
FN	fastigial nuclei
GA	gestational age
HF	high frequency
HLHS	hypoplastic left heart syndrome
HR	heart rate
HRV	heart rate variability
HVS	high voltage slow
LF	low frequency
NREM	non-rapid eye movement
NTS	nucleus of solitary tract
PVL	periventricular leucomalacia
PMA	postmenstrual age
QS	quiet sleep
REM	rapid eye movement
RVLM	rostral ventrolateral medulla
SBP	systolic blood pressure
SD	standard deviation
SIDS	sudden infant death syndrome
SpO_2	arterial oxyhemoglobin saturation
TP	total power
UVH	univentricular heart
VLF	very low frequency

1 INTRODUCTION

Sudden infant death syndrome (SIDS) still is one of the leading causes of death of healthy infants under the age of one year (Hauck, et al. 2008,Moon, et al. 2007,Task Force on Sudden Infant Death Syndrome, et al. 2011). SIDS is defined as the sudden, unexpected death of an infant younger than one year where the fatal episode is presumed to occur during sleep, and after detailed investigation including autopsy and reviews of clinical history and circumstances of death, the cause remains unexplained (Krous, et al. 2004).

The etiology of SIDS is unknown, but epidemiological research has provided valuable information on the risk factors. Prone sleeping position has constantly been shown to constitute a major risk factor for SIDS, and highly successfull campaigns have been carried out to prevent infants from sleeping in the prone or side position, followed by a dramatic decrease in SIDS cases (American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome. 2005,American Academy of Pediatrics. Task Force on Infant Sleep Position and Sudden Infant Death Syndrome. 2000,Gilbert, et al. 2005). However, it is still not known exactly how these risk factors increase the risk, and why only a minority of infants with these risk factors – and some without any of them – succumb to SIDS. Pathology has increased our knowledge of the subtle changes in the SIDS infants, but because the death of a healthy infant is very rare, comparison to "healthy normal infants" is difficult. Thus, understanding the physiology of a normal, healthy infant and how it changes, if at all, in relation to SIDS risk factors, may provide some further information on the pathophysiology of SIDS.

It is suggested that the death in SIDS occurs during sleep. On the basis of home monitoring and population sleep studies, altered autonomic control during sleep is presumed to be one main factor in SIDS. Nevertheless, SIDS is most likely not a single-factor disease, but rather a multifactorial entity which is suggested to include certain infant characteristics such as altered serotonin pathways in the brain and altered autonomic cardiorespiratory control, unfavorable external factors such as prone sleeping position and infection, together with a vulnerable developmental time window peaking at 2-4 months of age.

To be able to understand what happens in SIDS, we must first obtain information on the normal physiology of the infant during sleep, and how SIDS risk factors may affect these functions. Thus, our aim was to try to study a possible SIDS mechanism in infants with and without SIDS risk factors by measuring some common physiological responses during sleep.

2 REVIEW OF THE LITERATURE

2.1 Sudden infant death syndrome

2.1.1 Definition

Sudden infant death syndrome (SIDS) is defined as the sudden, unexpected death of an infant under one year of age, the onset of the fatal episode apparently occurring during sleep, and remaining unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history. The diagnosis has traditionally been that of exclusion, but a recent consensus meeting agreed on also including positive criteria in the diagnosis, as well as the criterion of death occurring during sleep.(Krous, et al. 2004)

2.1.2 Incidence

The number of deaths attributed to SIDS in Finland during the last two decades has been similar to other European and North American countries. The incidence of SIDS has been about 0.10-0.30/1000 live-born children, which means 9 - 19 annually (Figures 1 and 2) (Official Statistics of Finland. Causes of death [e-publication].). Worldwide, the SIDS rates have diminished markedly since the late 1980s, with reduction rates of over 50%, as a result of risk-reduction campaigns which have mostly promoted a non-prone sleeping position (Hauck, et al. 2008). The actual SIDS rates from 2005 vary from 0.80 in New Zealand to 0.10 in the Netherlands (Hauck, et al. 2008). Despite the impressive reduction in incidence, SIDS is still the leading cause of death between one month and one year of age (Moon, et al. 2007,Task Force on Sudden Infant Death Syndrome, et al. 2011), causing an estimated 22% of all postneonatal deaths in the United States (Hauck, et al. 2008).

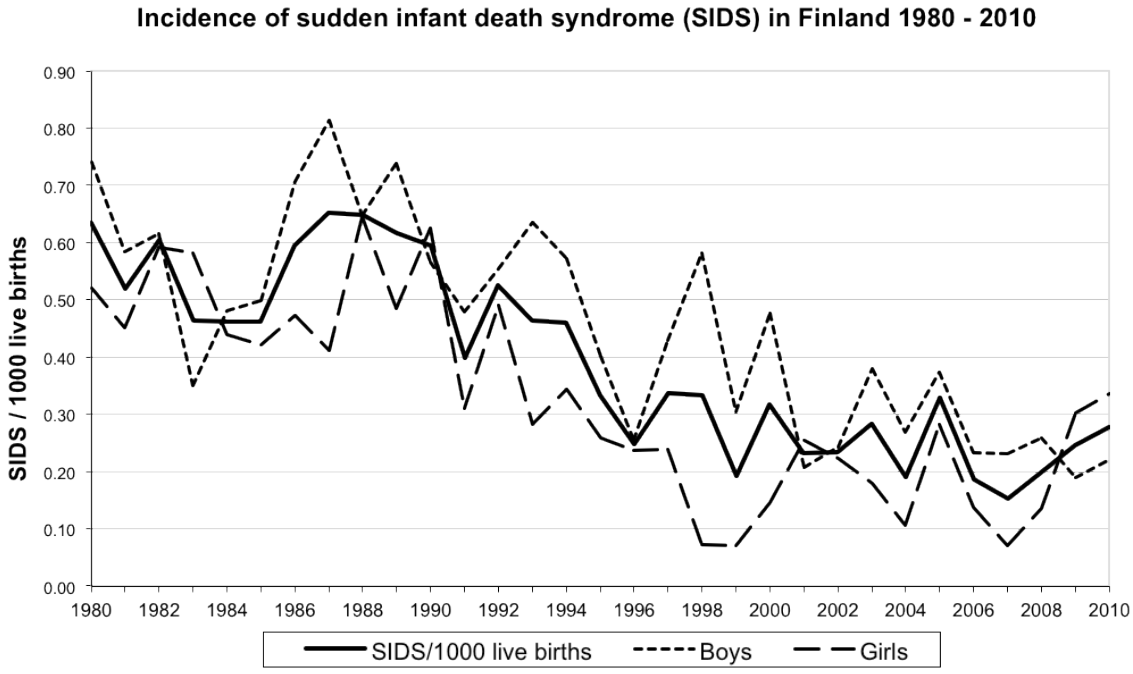

Figure 1. Incidence of sudden infant death syndrome (SIDS) in Finland 1980-2010.

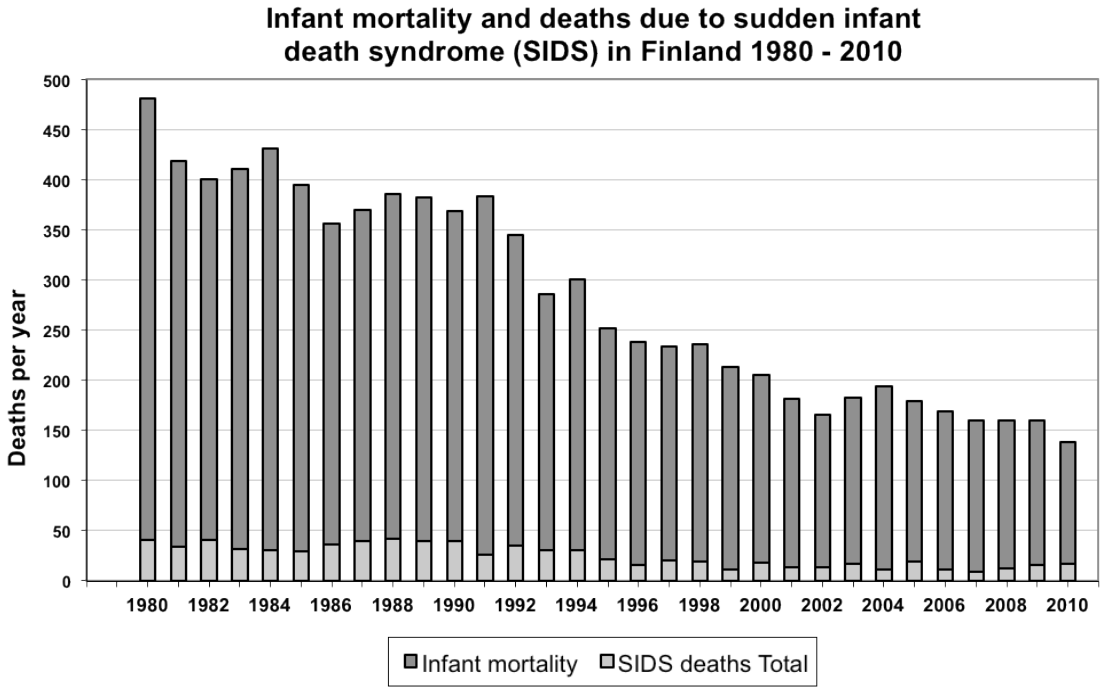

Figure 2. Infant mortality and number of deaths due to sudden infant death syndrome (SIDS) in Finland 1980-2010.

2.1.3 Risk factors

Although the ultimate cause of SIDS is unknown, there are abundant data on the prevalence, subtle clinical and autopsy findings, and risk factors. Table 1 describes risk factors for SIDS based on recent meta-analyses and review articles.

Table 1. SIDS risk factors based on systematic reviews and meta-analyses.

Risk factor	Authors	Year	Effect
General			
Gender	Moon et al.	2007	Male gender is associated with higher risk of SIDS with a ratio of 60:40.
Low birthweight	AAP	2000	The risk increases as the birth weight decreases.
Prematurity	AAP	2011	Preterm infants have increased risk of SIDS.
	AAP	2000	Preterm infants have increased risk of SIDS and the risk increases with decreasing gestational age or birth weight.
	Hunt and Hauck	2006	Prematurity is associated with younger postmenstrual age at death, but a higher postnatal age. Increased risk of infants with birth weight <2500g.
Race/Ethnicity	Moon et al.	2007	African American, American Indian, Alaska Native: increased risk of 2-3 times the national average irrespective of socioeconomic status. Risk of SIDS death in Maoris is increased 6-fold. Australian Aboriginals also have increased SIDS risk.
	AAP	2011	Non-Hispanic black, American Indian, Alaska Native: rate of SIDS is double compared with non-Hispanic white infants. Asian/Pacific Islander and Hispanic infants have nearly 50% lower SIDS risk compared with non-Hispanic white infants.
Season/climate	AAP	2011	Slightly higher SIDS rates during cold months, difference between seasons decreasing.
Mother and pregnancy			
Maternal smoking	Moon et al.	2007	Maternal smoking during pregnancy. Postnatal exposure may also increase the risk.
	AAP	2011	Maternal smoking during pregnancy is a major risk factor for SIDS and it is dose-dependent.
Alcohol and illegal drugs	AAP	2011	Increased risk of SIDS with maternal alcohol use and with illegal drug use (opiates, cocaine, or in general).

	Hunt and Hauck	2006	Prenatal maternal use of illegal drugs, specially opiates, increases risk of SIDS by 2-15 -fold.
Socioeconomic factors	Spencer and Logan	2004	Low socioeconomic status (social class, low educational level, low income level, overcrowding, unemployment, young or single mother) associated with increased risk of SIDS, independent of birth weight, sleeping position or smoking status.
	AAP	2011	Lower risk of SIDS if mother has obtained regular prenatal care.
Family	Moon et al.	2006	Increased risk if a sibling has died of SIDS.
Genetic risk factors	AAP	2011	Some SIDS infants show genetic variation in serotonin system in the brain, cardiac channelopathies, and development of autonomic nervous system. Some evidence of polymorphisms or mutations in genes regulating inflammation, energy production and hypoglycemia.
	Opdal and Rognum	2011	Genetic polymorphisms in genes regulating ion channels of the heart, development of autonomic nervous system, and immune system may increase the risk of SIDS when combined with environmental risk factors.
Postnatal			
Age of death	AAP	2011	Peak at 1-4 months, 90% occur before 6 months age and uncommon after 8 months.
Position	AAP	2011	Increased risk for both prone (OR 2.3-13.1) and side sleeping position (OR 2.0)
	Gilbert et al.	2005	Increased risk for both prone (OR 4.46, 2.98-6.68) and side (OR 1.36, 1.03-1.80) sleeping positions
Bedding	AAP	2011	Soft bedding (pillows, comforters, quilts etc.) associated with 5-times increased risk of SIDS. Especially high risk if sleeping prone on soft bedding sufrace, risk increases 21-fold.
Clothing	AAP	2011	Increased risk of SIDS asssociated with overheating and the room temperature.
	Moon et al.	2007	Overheating, especially if sleeping prone.
Infection	Moon et al.	2007	Upper respiratory tract infection within 4 weeks of death.
Sleep environment	AAP	2011	Increased risk for bed sharing if under 3 months of age, on a soft surface or with soft bedding, Also increased risk for bedsharing with current smoker, if mother has smoked during pregnancy, has consumed alcohol, uses medications/substances that impair the ability to arouse, is overtired, or if multiple bed sharers or bedsharing with anyone not a parent. Decreased risk of 50% for sleeping in parents' room without bed sharing.
	Horsley et al.	2007	Bed sharing among smokers may be associated with increased risk of SIDS, data not consistent on nonsmokers. Bed sharing may be more strongly associated with SIDS in younger infants.
Head covering	Blair et al.	2008	Head covering after last sleep is associated with increased risk: pooled univariate OR 9.6 (95% CI 7.9-11.7), pooled adjusted OR 16.9 (95% CI 12.6-22.7)
Swaddling	van Sleuwen et al.	2007	Swaddling in supine position decreases the risk of SIDS whereas swaddling in prone position increase the risk of SIDS by 12-fold.
Pacifier	AAP	2011	Pacifier use decreases the risk of SIDS by 50-60%.
	Hauck et al.	2005	Pacifier use is protective, especially for the last sleep: univariate summary OR 0.47 (95% CI 0.40-0.55), multivariate summary OR 0.39 (95% CI 0.31-0.50).
Breastfeeding	Hauck et al.	2011	Breastfeeding is protective: univariable summary OR 0.4 (CI 0.35-0.44), multivariate summary OR 0.55 (95% CI 0.44-0.69).
	AAP	2011	Breastfeeding is protective of SIDS even when potential confounding factors are considered. Risk reduction is close to 50%.
Immunisations	Vennemann et al.	2007	Immunisations are associated with lower risk of SIDS: univariate summary OR 0.58 (95% CI 0.46-0.73), multivariate summary OR 0.54 (95% CI 0.39-0.76).

Definition and abbreviations: AAP = American Academy of Pediatrics; OR = odds ratio.

Triple risk factor theory

SIDS is considered a multifactorial entity. Triple risk factor theory (Filiano, et al. 1994) describes this as three separate risk clusters all of which need to coincide for the infant to succumb to SIDS: 1) vulnerable infant, 2) certain developmental timeframe, 3) the exogenous stress factor. Firstly, the vulnerability of the infant is seen as intrinsic, possibly caused by compromised intrauterine conditions or inherited properties. This could be caused by abnormalities in development of the central nervous system, genes regulating QT time of the heart or immune system, or alterations in the serotonin system of the brain (Hunt, et al. 2006,Opdal, et al. 2011). Maternal smoking during pregnancy or use of illegal drugs during pregnancy are known to affect the development and function of the central nervous system (Moon, et al.

2007,Slotkin. 1998). It is suggested that SIDS is associated with abnormalities of the autonomic nervous system (Moon, et al. 2007), especially immature cardiovascular control and immature control of breathing associated with altered propensity to arouse. Some future SIDS infants indeed show signs of altered (sympathovagal) balance of the autonomic nervous system (Franco, et al. 1998,Franco, et al. 2003), obstructive sleep apnea (Kahn, et al. 1992,Kato, et al. 2001,McNamara, et al. 2000), and cardiac rhythm disturbances (Schechtman, et al. 1988,Southall, et al. 1988). Secondly, the developmental time frame is thought to coincide with the central stages of the development of the central nervous system and development of state regulation. Although over 95% of SIDS deaths occur before 9 months of age (Krous, et al. 2004), there is a peak at 2 to 4 months, which is thought to represent this time window. Thirdly, one or more external factors, so-called exogenous stressors, are needed. These could include prone sleeping, soft bedding, or upper respiratory tract infection. Many external factors are known to increase the arousal threshold of the infant (Moon, et al. 2007), and many infants who have succumbed to SIDS have shown an increased arousal threshold in previous sleep recordings (Kahn, et al. 1992,Kato, et al. 2003,Schechtman, et al. 1992a).

Sleeping position

Prone sleeping position is a major modifiable risk factor for SIDS (American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome. 2005,Gilbert, et al. 2005,Task Force on Sudden Infant Death Syndrome, et al. 2011). Since the 1970s, studies have shown increased SIDS risk with prone sleeping position; however systematic recommendations to avoid a prone sleeping position emerged only in the beginning of the 1990s, and since then campaigns promoting supine sleeping have decreased the incidence of SIDS by 50-80% in various countries (Gilbert, et al. 2005,Hauck, et al. 2008).

A smaller, but however significant, increased risk has been observed also for the side sleeping position, which is most likely associated with the unstability of this position (Task Force on Sudden Infant Death Syndrome, et al. 2011). Concerns on increased crying, colic or inhaled vomitus (aspiration) when sleeping supine are not supported by scientific evidence (Gilbert, et al. 2005,Task Force on Sudden Infant Death Syndrome, et al. 2011).

Exposure to maternal smoking during pregnancy

Maternal smoking during pregnancy is an independent risk factor for SIDS with a dose-response relation (Alm, et al. 1998,Blair, et al. 1996,Cnattingius. 2004,Task Force on Sudden Infant Death Syndrome, et al. 2011). As prone sleeping has diminished as a result of campaigns advocating supine sleeping, the relative importance of maternal smoking during pregnancy, especially as a preventable risk factor for SIDS, has increased (Hunt, et al. 2006). It is suggested, that elimination of prenatal smoke exposure could reduce the number of SIDS deaths by one third (Moon, et al. 2007,Task Force on Sudden Infant Death Syndrome, et al. 2011).

Prematurity

Preterm infants have increased risk of SIDS (Blair, et al. 2006,Blair, et al. 2009,Halloran, et al. 2006,Malloy, et al. 1995,Malloy, et al. 2000,Task Force on Sudden Infant Death Syndrome, et al. 2011,Thompson, et al. 2006) with inverse relation of gestational age (GA) and SIDS risk (Malloy, et al. 2000). Low birth weight is also associated with increased risk of SIDS (Blair, et al. 2006,Malloy, et al. 1995,Malloy, et al. 2000,Sowter, et al. 1999,Vennemann, et al. 2005), but preterm birth and intrauterine growth restriction are independent risk factors (Vennemann, et al. 2005). In preterm infants, the risk period for SIDS is at an earlier postconceptional age than in term infants (Halloran, et al. 2006,Malloy, et al. 1995). The overall rate of SIDS in the United States decreased in 1991-95 and the decrease was similar in all preterm groups and all birth weight groups (Malloy, et al. 2000). However, a recent survey in the UK found that a third of SIDS infants were preterm infants, whereas they constitute only 5% of the age-matched control population (Blair, et al. 2006). SIDS risk factors for preterm infants have been shown to be similar to those of term infants (Malloy. 2004,Thompson, et al. 2006).

In one study (Werthammer, et al. 1982), SIDS was found to be seven times more common in preterm infants with bronchopulmonary dysplasia (BPD) than in preterm infants without BPD. However, a later study (Gray, et al. 1994) showed, contradictory results as in that study BPD infants were found to have no increased risk of SIDS or apparent life-threatening event (ALTE). In that study, many BPD infants with desaturations or apneas were discharged with supplemental oxygen and weaned from it only after normal arterial oxyhemoglobin saturations (SpO_2) without supplemental oxygen. The authors suggested that in the study by Werthammer (Werthammer, et al. 1982), the BPD infants may have suffered from clinically unrecognized periods of hypoxemia that could have contributed to their death (Gray, et al. 1994).

Prevention

Epidemiological studies have also revealed factors that seem to be protective of SIDS. These include the use of a pacifier (Hauck, et al. 2005,Task Force on Sudden Infant Death Syndrome, et al. 2011) and breastfeeding (Hauck, et al. 2011,Task Force on Sudden Infant Death Syndrome, et al. 2011), both of which have been associated with a lower arousal threshold from sleep. As for the pacifier, other possible mechanisms that reduce the risk of SIDS are a favorable modification of autonomic control during sleep, improvement in breathing through the mouth and reduction of retroposition of the tongue and thus oropharyngeal obstruction, and influence of the sleeping position (Hauck, et al. 2005,Task Force on Sudden Infant Death Syndrome, et al. 2011). According to these recommendations, a pacifier should be offered to the infant for all sleep episodes and should not be replaced if it falls out of the mouth once the infant has fallen asleep.

There is also increasing evidence that room sharing without bed sharing is associated with reduced risk of SIDS (Task Force on Sudden Infant Death Syndrome, et al. 2011). Also immunisation with diphtheria, tetanus and pertussis vaccine has been found to have a protective effect on SIDS (Vennemann, et al. 2007), although the exact mechanism is not known. Mechanisms associated with improved immunological activity and the possible role of Bordetella pertussis in SIDS are suggested, but there was also considerable diversity in the studies, and the so-called healthy vaccinee effect cannot be ruled out.

2.1.4 Pathophysiology

As the diagnosis of SIDS is set mostly by exclusion, there are no diagnostic autopsy criteria (Krous, et al. 2004), nor are there any pathognomonic autopsy findings. There are some typical findings in SIDS, such as oronasal froth, petecchiae in thymus, lungs and pericardium, as well as pulmonary congestion and edema (Valdes-Dapena. 1992). Findings of mixed inflammatory cells (lymphocytes and some eosinophils) are usually depicted as a sign of mild, subacute inflammation of the upper respiratory tract (Valdes-Dapena. 1992). Most studies mentioned below have had only a very limited number (i.e. some tens) of controls with some overlap in the findings between SIDS and control infants. In addition, many of these control infants had some acute or chronic disease making it difficult to distinguish which are “normal” postmortem changes and which are pathological findings.

Many future SIDS victims show minor alterations in autonomic control including cardiac control, sleep parameters, arousal, and breathing. These alterations in autonomic control are considered to result from immaturity, a delay in the development or congenital alterations of the brain nuclei, especially in the brainstem control areas. On normal autopsy protocol, the brains of SIDS victims look normal, but special techniques have found subtle alterations in the autonomic regions (Valdes-Dapena. 1992). Reports on the brain alterations in SIDS infants include general alterations such as astrogliosis (Kinney, et al. 1983,Matturri, et al. 2006,Naeye. 1976,Takashima, et al. 1985), delayed myelination (Kinney, et al. 1991) and general immaturity of the brainstem with increased levels of dendritic spines (Quattrochi, et al. 1985,Takashima, et al. 1985) and synapses (O'Kusky, et al. 1994). Astrogliosis and reactive astrocytes are a non-specific response to

brain injuries, seen in, e.g. hypoxic injuries, but astrogliosis is also present in many other conditions, such as congenital heart disease, congenital myopathy, and sleep apnea (Takashima, et al. 1985).

The serotonin system, including the arcuate nucleus, nucleus raphé obscurus, inferior olive, nucleus paragigantocellularis lateralis and intermediate reticular zone, in medulla oblongata is abnormal in about half of SIDS infants (Kinney, et al. 2001). Other abnormalities reported in SIDS victims are hypoplasia of nuclei related to autonomic control, such as arcuate nucleus (Filiano, et al. 1992,Kinney, et al. 1995,Matturri, et al. 2006), and hypoglossus nucleus (Matturri, et al. 2006). The levels of tyrosine hydroxylase, an enzyme involved in the biosynthesis of adrenaline and noradrenaline, is low in the locus coeruleus, a nucleus associated with cardiovascular and respiratory systems (Lavezzi, et al. 2005). In areas of the hippocampus and brainstem – including the vestibular nucleus – there is increased apoptosis in SIDS victims (Waters, et al. 1999). Also the inferior olive, which is sensitive to hypoxia, shows signs of reactive gliosis (Kinney, et al. 2001), suggesting possible hypoxic injury.

Alterations in the cerebellum include delayed myelination in cerebellar sites (Kinney, et al. 1991), gliosis in olivocerebellar fibers (Kinney, et al. 1983), and alterations in the cerebellar cortex, such as immaturity of external granular layer, apoptosis of inner granular layer, and anomalous apoptotic death of Purkinje cells (Cruz-Sanchez, et al. 1997,Matturri, et al. 2006). The cerebellar dentate nucleus also shows increased neuronal loss (Lavezzi, et al. 2006). Many of these findings are also associated with maternal smoking during pregnancy (Matturri, et al. 2006).

Infections

There is evidence of inflammation or infection at least in a subset of SIDS. Many SIDS infants have signs of respiratory infection prior to death (Valdes-Dapena. 1992), although the postmortem findings are usually so mild so that it is considered insufficient to assign the cause of death to infection. Interleukin-6, which induces fever, is increased in the cerebrospinal fluid of SIDS infants (Vege, et al. 1995), however to a lesser extent than in infants who have died of infectious causes. Hypoxanthine levels in SIDS infants and in those who had died of infectious causes were similarly elevated, whereas the levels were significantly lower in infants who had died of heart/lung diseases, or as a result of violent death (Opdal, et al. 1998). These findings suggest that there may be similarities between the mechanisms of death in SIDS and in death caused by infection. Antemortal hypoxia is suggested to be a common factor (Opdal, et al. 1998).

2.1.5 Hypoxia

In SIDS victims, there is evidence of hypoxia for some hours to days before death. Postmortem analyses include findings of increased vascular endothelial growth factor, a protein upregulated when exposed to hypoxemia, in cerebrospinal fluid (Jones, et al. 2003). Also hypoxanthine, which increases in response to hypoxemia and even more when it is intermittent (Rognum, et al. 1993), is found to be increased in the vitreous humor of SIDS infants (Opdal, et al. 1998,Rognum, et al. 1988).

Autopsy findings of SIDS infants show increased amounts of brown fat (Naeye. 1974), hepatic erythropoiesis (Naeye. 1974,Valdes-Dapena. 1992), and gliosis in the brainstem (Kinney, et al. 1983,Naeye. 1976), which may be attributed to sustained hypoxic conditions before death. Sections of brain show loss of cerebellar Purkinje cells, which are known to be sensitive to hypoxia, as well as an increased amount of reactive astrocytes, which are a non-specific response to brain injuries such as hypoxia (Lavezzi, et al. 2006). However, most of brain damage is non-specific and can be caused by different mechanisms. Thus, comparing changes in SIDS infants and infants with chronic oxygenation problems may be useful in trying to distinguish which abnormalities are caused by hypoxia and which by some other challenge. Kinney and co-workers (Kinney, et al.

2001) compared SIDS victims to acute and chronic controls, without and with oxygenation disorders, respectively. SIDS infants showed decreased 3H-quinuclidinyl benzilate binding to muscarinic receptors in the arcuate nucleus, similarly to the chronic controls, whereas acute controls without long-term hypoxic exposure did not show changes in this binding in any nuclei. This adds to the evidence suggesting that hypoxia may be an important factor in the pathogenesis of SIDS.

2.1.6 Abnormal autonomic control

The control of the autonomic nervous system in SIDS is suggested to be defective or immature (Matthews. 1992), seen as subtle abnormalities in the heart, lung and brain of SIDS infants, or altered balance of the autonomic nervous system. There are reports of altered heart rate (HR) characteristics, such as increased sinus tachycardia in SIDS victims (Meny, et al. 1994,Southall, et al. 1988) and higher HR levels in future SIDS infants (Schechtman, et al. 1988) as well as in near-miss SIDS infants (Leistner, et al. 1980). Bradycardia is also reported preceding the fatal event in some possible SIDS infants (Meny, et al. 1994,Poets, et al. 1999). Ventricular fibrillation caused by increased QT time is reported in some SIDS infants (Schwartz, et al. 1998), but there are serious concerns about the methodology and interpretation of these findings (Guntheroth, et al. 1998,Hodgman, et al. 1999,Hoffman, et al. 1999,Lucey. 1999,Martin, et al. 1999). Reports of a diminished number of body movements during sleep and increased sweating in future SIDS infants (Kahn, et al. 1992), further support the theory of deranged autonomic control.

Another method to evaluate the balance of the autonomic nervous system is to assess heart rate variability. In SIDS infants, spectral analysis showed decreased high frequency variability and increased low frequency/high frequency power rations (Franco, et al. 1998,Franco, et al. 2003). Decreased heart rate variability in SIDS victims has been found during rapid eye movement (REM) sleep and waking (Schechtman, et al. 1989,Schechtman, et al. 1992b)

There have been many theories relating SIDS to respiratory events including immature respiratory control, accidental suffocation, CO_2 intoxication or hypoxia due to rebreathing, and hypoxia caused by obstructive sleep apnea (Keens, et al. 2001,Thach. 2005). Although a purely respiratory explanation for SIDS has been found to be oversimplified, SIDS victims have been shown to have more frequently obstructive breathing (Kahn, et al. 1992,Kato, et al. 2001,McNamara, et al. 2000).

Most of the polysomnographic features of sleep are similar in both control and SIDS infants (Kahn, et al. 1992). However, future SIDS victims show less waking and more sleep compared with control infants during the last portion of the night (Schechtman, et al. 1992a) which is the presumed time of death in SIDS. The most obvious polysomnographic difference between the future SIDS victims and controls were the number of body movements in sleep: the SIDS infants moved less than controls (Kahn, et al. 1992).

2.1.7 Cardiovascular collapse and autoresuscitation

On the basis of home recordings, SIDS is suggested to resemble a hypovolemic shock (Meny, et al. 1994,Poets, et al. 1999). However, it is not clear if these cases represent “true” SIDS. In these recordings, the final sequence before death is characterized by a sudden bradycardia, which is followed by gasping. There are no sustained cardiac arrhythmias or central apneas prior to this. Cardiovascular collapse seen in home recordings is similar to extensive blood loss, where an initial compensatory response is followed by a sudden, centrally triggered inhibition, resulting in fatal hypotension and death, if the sequelae cannot be stopped (Evans, et al. 2001). It is not known why bradycardia and gasping are not followed by autoresuscitation (seen as recovered heart rate and blood pressure) or awakening. Both repetitive hypoxic exposure and prenatal nicotine are found to impair the ability of animals to autoresuscitate (Fewell. 2005), therefore some SIDS risk factors such as prone sleeping, prematurity and maternal smoking

during pregnancy may affect this protective response. In addition, arousal – another protective mechanism during sleep – is impaired in many SIDS risk groups and future SIDS victims (Franco, et al. 2010).

In SIDS victims, the function of fastigial and vestibulo-mediated cardiovascular pathways – which are important compensating systems during critical situations – may be altered (Harper, et al. 1998,Harper, et al. 1999,Harper, et al. 2000a,Harper. 2000,Waters, et al. 1999). Vestibular and/or fastigial input can modify blood pressure responses, and it is suggested, that they act as a compensatory mechanism similar to that of the cerebellum in locomotion (Harper. 2000). The arcuate nucleus, which is found to be hypoplastic or absent in some SIDS infants (Filiano, et al. 1992,Kinney, et al. 1995,Matturri, et al. 2006), presumably projects to the cerebellum, modifying this vestibulo- or fastigial-mediated compensatory response to hypotension (Harper, et al. 1998). The trigger for this kind of cardiovascular collapse is unknown but obstructive sleep apnea could be one possible culprit, especially as obstructive events in future SIDS infants are associated with bradycardia and desaturations (Kahn, et al. 1992). Home recording devices, however, do not register airflow, so it remains unknown whether these obstructive events truly precede the fatal event in SIDS. It is also suggested that instead of one specific type of failure mechanism, the critical issue in SIDS deaths may be the inability to recover from a life-threatening event (Harper. 2000).

In conclusion, it is suggested that different mechanisms may induce a life-threatening event in a vulnerable infant, but the main problem may be the failure to compensate for and recover from this event (Harper. 2000). This immature control of the autonomic nervous system and respiratory function, combined with defective arousal mechanisms is suggested to lead to SIDS (Moon, et al. 2007).

2.2 Cardiovascular control mechanisms

2.2.1 Blood pressure control

It is difficult to make a consistent, generalized overview of blood pressure (BP) control since the BP regulation is a complex process with a multitude of input signals improving the accuracy of the blood pressure regulation. Long-term absence of one type of signal does not seem to fundamentally alter BP control, but the short-term control may become more imprecise (Guyton. 1981,Kerman, et al. 1998,Persson. 1996,Timmers, et al. 2003,Yates, et al. 2000).

Changes in BP result from alterations in cardiac pump function, peripheral vascular resistance or volume of blood in venous capacitance vessels. The vascular tree, excluding capillaries and venules, contains smooth muscle and receives sympathetic innervation, which exerts tonic discharge to maintain vascular tone by vasoconstriction. Sympathetic vasodilator nerves also exist in resistance vessels (Ganong. 1999). Furthermore, many circulating vasodilative or vasoconstrictive hormones participate in cardiovascular control (Persson. 1996).

Central integrational mechanism of blood pressure control

The most important control sites for blood pressure are located in the brainstem, in the medulla oblongata and in the pons (bulbar region). The earlier concept of a single vasomotor center in the medulla has been replaced by increased data on cardiovascular control, and currently the cardiovascular system is proposed to be controlled by specific, interconnected neuronal groups from the cortex to the spinal cord, mostly located at the medulla. (de Burgh Daly. 1997a,Ganong. 1999)

The rostral ventrolateral medulla (RVLM) is one of the key areas in blood pressure control. It is called a pressor region since it participates in the maintaining of the vasomotor

tone, reflex control of heart rate and systemic vascular resistance. The area surrounding the nucleus ambiguus, adjacent to the RVLM, is sometimes referred to as the depressor area (de Burgh Daly. 1997a). The complex interaction between different areas participating in blood pressure control is not fully understood. Higher levels (hypothalamus and cerebral cortex) influence the circulation mostly through their action on these medullary neuronal groups. The hypothalamus and cerebral cortex are recruited during cardiovascular responses to emotions and cognitive tasks, such as anticipation of exercise.

Because of the extensive amount of data and the complex nature of cardiovascular control, only the most important nuclei concerning cardiovascular control are presented here. These important areas include the rostral and caudal ventrolateral medulla, together with the nucleus of the solitary tract and cerebellar nuclei.

Rostral ventrolateral medulla

The rostral ventrolateral medulla (RVLM) is critical for the function of the cardiovascular reflex and a major source of tonic excitatory input to cardiovascular sympathetic preganglionic fibers. Neurons in RVLM are tonically active and produce much of the resting sympathetic vasomotor activity, at least in anesthetized animals. Activation of peripheral baroreceptors decreases the firing rate of these RVML sympathetic neurons. In anesthetized animals, inhibition or destruction of RVLM neurons leads to a deep hypotension, although this hypotension is fully compensated within days. The vagal cardiac component, however, remains intact. (Dampney. 1994)

Caudal ventrolateral medulla

Stimulation of the caudal ventrolateral medulla induces the so-called depressor response, which is a result of decreased total peripheral resistance, inhibition of sympathetic vasomotor activity, and decreased cardiac contractility. Cells in this area show tonic activity similarly to the RVML area. The activity of neurons in the caudal ventrolateral medulla most likely modulates the RVLM activity. (Dampney. 1994)

Nucleus of solitary tract

The nucleus of solitary tract (NTS) mediates homeostatic cardiovascular reflexes that control blood pressure and fluid balance. It receives afferent neurons from baro- and chemoreceptors as well as from visceral and somatic receptors, and it projects via the caudal ventrolateral medulla to the RVLM. Signal transmission of NTS is possibly also modulated by the cortex, amygdala, hypothalamus, and parts of the brainstem synapse with the NTS. (Dampney. 1994)

Area Postrema

The area postrema, located on the dorsal surface of the medulla, most likely participates in cardiovascular control by connecting circulating hormones and central autonomic regulation. It is located on the dorsal surface of the medulla and because it is highly vascular, but deficient of a blood-brain barrier, it has access to circulating substances. It has extensive projections to the NTS. (Dampney. 1994)

Cerebellar nuclei

Fastigial nuclei, located in the deep cerebellum, are postulated to participate in the modulation of the cardiovascular responses, similarly to the error-correction role of the cerebellum in motion control (Harper. 2000). The role of the cerebellum in cardiovascular control is discussed in detail in the section “Vestibular and cerebellar mechanisms in cardiovascular control”.

Baroreflex control of blood pressure

Cardiovascular reactions to postural challenge are mediated by baroreflex, peripheral venous reflexes, and vestibular sympathoreflexes (Persson. 1996,Thompson, et al. 1983,Yates, et al. 1987).

Baroreflex is important in balancing blood pressure alterations caused by body position changes and in securing a sufficient blood supply to the upper part of the body and brain also during vertical body position, i.e. standing. Baroreflex responds to these challenges by exerting short-term control of arterial blood pressure, heart rate and cardiac contractility, and altering vascular tone (La Rovere, et al. 2008).

Baroreceptors maintain the vasomotor tone by firing continuously at a rate of 10-30 impulses per second and they respond to both fluctuating and stabile pressures. When distended, they increase firing, which usually occurs in pulses according to pressure pulses, with responses being greater for rising than falling pressures. Sympathetic discharge can modify baroreceptor sensitivity by affecting the vessel wall stiffness. (Ganong. 1999,Mountcastle. 1974,Scher, et al. 1963)

When baroreceptors are distended, such as during acute hypertension, they increase firing. This activation of baroreceptor afferents is conveyed to medullary vasomotor centers, mostly to the NTS (Dampney. 1994). Baroreflex activation to the heart produces both vagal activation (reflex bradycardia, decreased myocardial conductivity and contractivity, which lead to decreased cardiac output) and sympathetic withdrawal (La Rovere, et al. 2008). Baroreflex activation to vascular beds inhibits efferent sympathetic vasoconstrictor tone, producing dilatation of arterioles in most vascular beds, and decreased large vein tone. Together, these baroreflex-mediated cardiac and peripheral actions lead to decreased systemic arterial pressure (La Rovere, et al. 2008). When blood pressure decreases, a deactivation of baroreceptors leads to increased sympathetic activity and vagal inhibition.

Baroreceptor latency appears to be different for the parasympathetic and sympathetic effents, such that latency for parasympathetic activity is much shorter, i.e. 200-600 ms enabling rapid cardiovagal reactions, whereas the latency for the initiation of sympathetic activity is estimated to be around 2-3 seconds, and the maximal effect is reached even more slowly (La Rovere, et al. 2008). There is a paucity of data on the latency of baroreflex-mediated vasoconstriction during orthostatic testing, but it has been estimated to be several seconds (Gulli, et al. 2005).

Baroreceptor location

Baroreceptors located in the walls of blood vessels are sensitive to mechanical deformation and respond to mechanical stretch from intravenous blood. The carotid body comprises two of these receptors that are located in the carotid sinuses (dilatation of the internal carotid artery at its origin) and innervated by glossopharyngeal nerves. Baroreceptors of the aortic body are located at the aortic arch and innervated by the vagus nerve. (Dampney. 1994,Marshall. 1994,Timmers, et al. 2003)

Pulmonary arterial baroreceptors are located near the bifurcation of the main pulmonary artery and respond to changes in pulmonary arterial pressure similarly to carotid and aortic baroreceptors. In addition to increasing systemic arterial pressure, these receptors respond to decreases in pulmonary arterial pressure also by increasing respiratory rate and depth. (Mountcastle. 1974)

Cardiac stretch receptors reside in venoatrial junctions (atrial receptors) and ventricles (ventricular receptors). Atrial stretch receptors reside in venoatrial junctions, monitor terminal venous pressure and dynamics of ventricular filling, and activate when atrias are stretched. (Dampney. 1994,Mountcastle. 1974)

Baroreceptors in the aortic arch and carotid sinus are so-called high pressure baroreceptors, which show pulse synchronous firing. Cardiopulmonary volume receptors in atria, great veins and ventricles are so-called low pressure baroreceptors (Freeman. 2006).

Because of the multiple baroreceptor regions, the lack of one set of baroreceptor afferents does not seem to have an impact on long-term changes in blood pressure or heart rate, as the deficit can be compensated by other regions. (Persson. 1996).

Chemoreflex control of blood pressure

Central and peripheral chemoreceptors together modify breathing according to changes in oxygen and carbon dioxide (CO_2) tension and concentrations of hydrogen ion (Timmers, et al. 2003). Central chemoreceptors, which sense the changes in hydrogen ion concentration, reside in the rostral ventrolateral medulla, and adjust cardiopulmonary responses during hypercapnia and acid-base balance (Timmers, et al. 2003).

Peripheral arterial chemoreceptors are located in the aortic and carotid bodies, and induce cardiorespiratory responses during acute hypoxia. Peripheral arterial chemoreceptors primarily respond to changes in oxygen and, to a lesser extent, to changes in CO_2 tension and concentrations of hydrogen ion (Marshall. 1994,Timmers, et al. 2003). When stimulated by hypoxia, peripheral chemoreceptor activation leads to bradycardia and vasoconstriction during apnea or if ventilation remains constant. If ventilation is allowed to increase, peripheral chemoreceptor response to hypoxia leads to tachycardia and vasodilatation (Marshall. 1994,Persson. 1996).

Local cardiovascular control

Local tissue-level autoregulation with the capacity of tissues to control their blood flow, is present in most tissues, and can both increase and decrease the amount of blood flow (Guyton. 1981). The importance of local tissue-level autoregulation, however, is small in acute blood pressure control (Guyton. 1981). In autoregulation, an increase in venous transmural pressure causes vascular smooth muscle to contract, increasing peripheral resistance and decreasing the amount of tissue blood flow (Guyton. 1981,Persson. 1996).

The vascular endothelium participates in the control of blood pressure by producing local vasodilators and vasoconstrictors. Nitric oxide and prostacyclin are the most important substances in decreasing vascular smooth muscle tone whereas endothelin and thromboxane A2 are potent vasoconstrictors (Persson. 1996). In addition, hypoxia, hypercapnia, low pH, increased temperature and potassium are vasodilators, whereas injury to the vessel and cold induce vasoconstriction (Ganong. 1999).

2.2.2 Heart rate control

Heart rate (HR) is modified by both the parasympathetic and the sympathetic nervous system. Parasympathetic control exerts tonic discharge at rest, and blocking parasympathetic activity produces considerable tachycardia. The sympathetic nervous system controls cardiac function by increasing cardiac contractility and heart rate, and by inhibiting the vagal effect (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996).

The nucleus ambiguus, part of the caudal ventrolateral medulla, is the main site for cardiac vagal preganglionic neurons in most species (Dampney. 1994). The other sites, the dorsal vagal motor nucleus and the reticular formation, are also located in the medulla (de Burgh Daly. 1997a). Cardiac vagal preganglionic neurons receive mostly excitatory input from peripheral baroreceptors, although also peripheral chemoreceptors, cardiac receptors and trigeminal receptors can excitate these neurons. Baroreceptor influence is mediated by a direct pathway from the NTS. (Dampney. 1994)

2.2.3 Cardiovascular responses to hypoxia

Hypoxia has direct effects on different organs, but it also influences blood flow via reflexes. Local severe hypoxia induces vasodilatation (Daugherty, et al. 1967,Heistad, et al. 1975b), which is clearest in the coronary vessels and arteries of the brain. On the other hand, hypoxic vasodilatation has a small influence on the arteries of the extremities. This variation in the degree of vasodilatation is important in that during hypoxia more blood is directed to the vital organs, such as the heart and the brain.

The effects of short-term hypoxia on heart rate and blood pressure depend on the severity of hypoxia and differs between species (de Burgh Daly. 1997b). In cats, mild hypoxia induces mild hyperventilation, bradycardia and vasoconstriction in mesenterial and skeletal muscle vessels. Vasoconstriction increases peripheral vascular resistance thus increasing blood pressure. In dogs, mild hypoxia induces tachycardia, peripheral vasodilatation and thus a decrease in peripheral vascular resistance. Tachycardia and peripheral vasodilatation are caused by hyperventilation and activation of pulmonary stretch receptors (de Burgh Daly, et al. 1958,de Burgh Daly, et al. 1962,de Burgh Daly, et al. 1963). In humans during hypoxia, tachycardia is observed without a significant ventilatory response (Lugliani, et al. 1971).

A severe, short-term hypoxia in anesthetized animals activates brainstem defence areas, which in turn activates a visceral response. This leads to marked hyperventilation, tachycardia, mesenterial vasoconstriction, and vasodilatation in skeletal muscle vessels (Hainsworth, et al. 1973). However, in non-anesthetized animals, the threshold to activate defence areas is higher than is needed to activate a normal alert response (de Burgh Daly. 1997b).

In adult humans, mild to moderate hypoxia either does not affect or slightly increases systemic blood pressure. Vasodilatation induced by hypoxia is compensated by a reflex from the carotid body which induces vasoconstriction. In humans whose carotid bodies have been removed, blood pressure decreases significantly during hypoxia (Lugliani, et al. 1973,Wade, et al. 1970).

Although hypoxia significantly influences blood pressure, also blood pressure influences respiratory control. Baroreceptor activity changes ventilatory response to hypoxia and hypercapnia. In anesthetized dogs, hypotension increases and hypertension diminishes ventilatory response to hypoxia and hypercapnia (Heistad, et al. 1975a). By stimulating only one carotid baroreceptor, the ventilatory response induced by the contralateral carotid body diminishes. The effects of baroreceptors and chemoreceptors of carotid bodies are integrated in the central nervous system, not in the carotid body itself.

Most of the data on cardiovascular control during sustained hypoxia in humans are based on data from people living at high altitudes (Leon-Velarde, et al. 2010,Penaloza, et al. 2007). Cardiovascular changes associated with living at high altitudes include polysythemia together with increased viscosity of blood, right ventricular hypertrophy, and increased pulmonary vascular resistance and amount of smooth muscle cells in distal pulmonary arterial branches. Increased pulmonary artery pressure is associated with decreased SpO_2.

Repetitive (intermittent) hypoxia

The effects of intermittent hypoxia on human cardiovascular control are even less well known than those of chronic hypoxia; a literature search revealed no studies on infant cardiovascular control after repetitive hypoxic exposure. Animal studies, however, suggest that the effects of intermittent hypoxia are more detrimental than those of sustained hypoxia (Neubauer. 2001). It is suggested that intermittent hypoxia causes vascular disease via sympathetic nervous system overactivity, oxidative stress and endothelial dysfunction (Foster, et al. 2007). In healthy humans, intermittent nocturnal hypoxia increases BP levels, which also remains beyond the acute phase immediately after exposure (Foster, et al. 2009,Tamisier, et al. 2011). The increase in BP is mediated through sustained sympathetic activity and increased peripheral vascular tone (Gilmartin, et al. 2008,Gilmartin, et al. 2010). This increased sympathetic nervous system activity leads to

attenuated vasodilator and enhanced vasoconstrictor functions (Foster, et al. 2007). In addition, intermittent hypoxia alters cerebrovascular regulation (Foster, et al. 2009), but it seems to have no effect on the HR levels (Gilmartin, et al. 2008,Gilmartin, et al. 2010,Tamisier, et al. 2011).

2.2.4 Vestibular and cerebellar mechanisms in cardiovascular control

Traditionally, postural blood pressure control in considered to be almost entirely baroreflex driven. However, since the seventies, there have been several studies targeting the role of vestibular action; currently it has been shown that the vestibulosympathetic responses are important in cardiovascular control. The effect is additive to baroreflex and other cardiovascular reflexes (Carter, et al. 2008). In the inner ear, two otolith organs (utricle and saccule) detect linear acceleration and three semicircular canals respond to angular acceleration in the plane of the canal being stimulated (Yates. 1992).

Role of cerebellum and fastigial nucleus in cardiovascular control

The role of the cerebellum in cardiovascular control is considered to be related to the error correction and change compensation similarly to its role in motor behaviors (Harper. 2000). The cerebellum, and particularly the fastigial nuclei (FN) are important in modulating vestibulosympathetic responses, although the cerebellar action is not essential to vestibulo-mediated cardiovascular responses; also cerebellectomized animals show vestibular-elicited effects on sympathetic outflow and BP (Yates. 1992). FN activity does not participate in baseline BP or HR control, but it is important in the restoration of BP after a severe hypotensive episode (Lutherer, et al. 1983).

Fastigial nuclei are part of the deep cerebellar nuclei, and they lie most medially in both sides of the deep cerebellum. FN are considered an important structure for processing vestibular signals (Siebold, et al. 2001). The majority of FN neurons receive vestibular (otolith) input, indicating that they are responsive to linear motion. The FN show extensive reciprocal connections with the vestibular nucleus (Diagne, et al. 2001,Noda, et al. 1990,Zhou, et al. 2001). Functionally, the fastigial nucleus has been divided into a rostral and a caudal region. Its caudal part shows a response to eye movements (fastigial oculomotor region) and vestibular stimulation (Noda, et al. 1990,Zhou, et al. 2001). The rostral part responds to angular and linear vestibular stimulation, and neurons in the rostral part of the fastigial nucleus are often called “vestibular only” neurons (Siebold, et al. 2001,Zhou, et al. 2001).

Stimulation of the rostral pole of the fastigial nucleus causes a sympathetic activation termed the fastigial pressor response. The fastigial pressor response includes an increase in BP, tachycardia, and inhibition of reflex bradycardia (Elisevich, et al. 1991,Giuditta, et al. 2003). Lesions involving brainstem areas of the uncinate fasciculus, the NTS, the locus coeruleus-lateral parabrachial nucleus, or rostral ventrolateral reticular nucleus result in abolished or attenuated fastigial pressor response (Giuditta, et al. 2003). Fastigial pressor response has also been described in humans (Elisevich, et al. 1991).

After transection of the vestibular nerve, i.e. the VIII cranial nerve, FN lesions do not result in any further deficit, suggesting that fastigial and vestibular pathways are part of the same reflex arc responding to orthostatic challenge (Doba, et al. 1974,Yates. 1992). There is, however, also evidence challenging the role of the FN in the fastigial pressor response. The pressor response from stimulating the FN may result from activation of passing nerve fibers in the FN, and not from excitation of intrinsic cerebellar neurons. (de Burgh Daly. 1997a,Yates. 1992)

The role of the posterior cerebellar vermis (uvula) in cardiovascular control is not clear, but stimulation of this area has been found to induce cardiovascular effects and inhibit vestibulosympathetic reflexes (Yates. 1992). Stimulation of the cerebellar uvula or nodulus alters baseline BP levels, and stimulation of the posterior vermis activates neurons in brainstem areas controlling BP (Yates, et al. 2000). Furthermore, ablation of the cerebellar uvula or nodulus

modulates BP levels during postural challenge (Holmes, et al. 2002). Thus the vestibulocerebellum (flocculus, nodulus, uvula, posterior cerebellar vermis) may play a role in the recovery of compensatory or movement-related cardiovascular responses following vestibular lesions (Yates, et al. 2005).

There are direct connections from the nodulus-uvula region via Purkinje cells to brainstem areas including the vestibular nucleus (Yates, et al. 2000). As Purkinje cells are the only efferent neurons from the cerebellar cortex, their death causes a functional lesion of the cerebellum, and thus they may present an especially vulnerable anatomic structure (Sarna, et al. 2003). Purkinje cells have been found to be sensitive to acute (Sarna, et al. 2003), intermittent (Pae, et al. 2005) and chronic hypoxia (Hutton, et al. 2007), as well as to nicotine (Abdel-Rahman, et al. 2005).

Vestibular nuclei functional anatomy

The anatomy and function of vestibular complexes are extensively reviewed by Barmack (Barmack. 2003). The two vestibular complexes are located symmetrically on both sides along the lateral wall of the fourth ventricle in the brainstem, and they consist of four subnuclei: the medial, descending (inferior), lateral and superior vestibular nucleus. In addition, several smaller nuclei in the region of classical nuclei receive vestibular primary afferents. Vestibular subnuclei have extensive connections with each other on the ipsilateral side and also with the corresponding nuclei on the contralateral side. The vestibular complex send projections to the thalamus, cerebellum (including vermis, flocculus, and fastigial nucleus), spinal cord, and regions regulating the autonomic nervous system. Primary afferent signals to vestibular nuclei come from vestibular end-organs, but also secondary afferents originate from visual, proprioceptive, and cerebellar (posterior cerebellum, uvula and nodulus) systems.

Lesions of the medial and inferior vestibular nucleus abolish vestibular-elicited sympathetic activity (Yates. 1996). These vestibular nuclei neurons project via the brainstem interneurons to the rostral ventrolateral medulla, which is an important command center for sympathetic BP regulation.

Vestibular stimulation and cardiovascular responses

The vestibular system helps to maintain homeostasis during movement and changes in posture, making rapid adjustments in BP (Carter, et al. 2008,Yates, et al. 2005). In animal models, changes in blood pressure induced by the vestibular system seem to be exerted mainly through the sympathetic nervous system (Kerman, et al. 1998,Yates, et al. 2000). The strongest influences are exerted on components of the sympathetic nervous system regulating peripheral vascular resistance (Kerman, et al. 1998). In the central nervous system, vestibular stimulation induces activity changes in brainstem neurons in BP regulation areas such as the NTS, lateral tegmental field, rostral ventrolateral medulla, and caudal medullary raphe nuclei (Yates, et al. 2000).

The action of the vestibular nucleus on cardiovascular control is not exclusively due to labyrinthine signals, and circuits involving the vestibular nuclei elicit compensatory cardiovascular responses during movements even after removal of labyrinthine signals (Yates, et al. 2000). Non-labyrinthine inputs – signals from the muscle, skin, viscera and visual cues – can modulate the firing of vestibular nucleus neurons during vertical rotations (Yates, et al. 2005).

Bilateral removal of labyrinthine inputs by cutting vestibular nerves results in unstabile control of BP in both anesthetized (Doba, et al. 1974) and awake cats when visual input is absent (Jian, et al. 1999). After vestibular damage in head-up tilt, the initial BP decrease is augmented, BP compensation is delayed, and BP does not return to the pre-test baseline values without an effect on the reflex tachycardia induced by tilt (Doba, et al. 1974). There is, however, a rapid compensation and recovery of postural BP responses within one week (Jian, et al. 1999,Yates, et al. 2005). If the cerebellar uvula is damaged together with bilateral labyrinthectomy, no recovery

occurs, at least for the observed one month period (Yates, et al. 2005). The authors suggested that plasticity of the central nervous system is responsible for the recovery after damage to the peripheral vestibular system, and that this adaptation is dependent upon the cerebellar uvula.

Acute hypotensive response in the beginning of the tilt after removal of vestibular input suggests delayed and attenuated modulation of peripheral vein resistance. Bilateral lesions in the fastigial nuclei produced similar responses indicating that fastigial and vestibular projections share a common pathway (Doba, et al. 1974). Combined bilateral fastigial nucleus lesions and baroreceptor denervation produced an augmented, hypotensive BP response that was significantly greater than baroreceptor denervation alone (Doba, et al. 1974). Thus, it was proposed that vestibular inputs contribute to baroreceptor reflexes, which regulate blood pressure and volume distribution during changes of body posture. Furthermore, nose-up head tilt in animals with extensive denervations of peripheral input to remove pulmonary, airway and cardiovascular signals that could participate in the cardiovascular response, elicited a significant blood pressure response, indicating that vestibular-elicited activity can induce BP changes alone (Woodring, et al. 1997). As no HR response was seen, the authors suggested that the vestibular-elicited BP increase was induced by changes in peripheral vasoconstriction.

Also in humans, vestibulo-mediated cardiovascular control is suggested to function to prevent hypotension (Dyckman, et al. 2007). Baroreflex-mediated activation of vascular resistance is estimated to be relatively slow, 7 – 9 seconds from tilt onset until vasoconstriction (Gulli, et al. 2005,Scher, et al. 1963,Warner. 1958), whereas the vestibulo-cardiac reflex is rather fast with a short latency of about 400-500ms (Kaufmann, et al. 2002,Radtke, et al. 2003,Yates, et al. 2005). It is therefore suggested that the vestibular action initiates the compensatory cardiovascular mechanisms at the beginning of the head-up tilt test. However, the literature search did not reveal any more recent studies or evidence targeting specifically on the speed of the baroreflex action onset.

Activation of vestibular function in humans has been shown to induce similar changes in sympathetic nerve activity and blood pressure responses to those observed in animal studies (Kaufmann, et al. 2002,Yates, et al. 2000,Yates, et al. 2005). It is, however, difficult to gain an understanding of human vestibular-autonomic control because of the rapid vestibular compensation after peripheral lesions. Reduced vascular sympathetic reactivity during orthostatic challenge has been observed to dissipate within two weeks (Yates, et al. 2005). Recovery of vestibulo-ocular and vestibulo-postural responses occurs during a time course similar to that in which deficiencies in autonomic responses resolve, suggesting a common mechanism. Furthermore, it is possible that vestibulo-mediated deficits of BP regulation only become apparent when the level of alertness is diminished (Yates, et al. 2005).

2.3 Cardiovascular tests in infants

Clinical tests of cardiovascular autonomic function include tests of cardiovagal and sympathetic adrenergic function. Cardiovagal function tests include HR variability, HR response to Valsalva maneuver, and HR response to postural change, whereas the sympathetic adrenergic function is evaluated by BP response to active standing and passive tilting, BP response to Valsalva maneuver, isometric exercise, cold pressor test, mental stress test, carotid sinus massage, and prolonged tilt-table test (Freeman. 2006,Ravits. 1997).

Peripheral vasoconstrictor function is evaluated by assessing peripheral vascular resistance or venoarterial reflex (Freeman. 2006). The most common method to evaluate peripheral vascular resistance is venous occlusion plethysmography, where an increase in the volume of a limb during the initial stage of venous occlusion is considered to reflect arterial blood flow

to the limb. The vascular resistance is then calculated as the mean arterial pressure divided by this blood flow. (Freeman. 2006,Greenfield, et al. 1963)

2.3.1 Continuous blood pressure measurement

There are only relatively few data on acute blood pressure responses in newborns and infants due to difficulties in measurement. Furthermore, comparison of the studies is difficult due to different study populations, age distributions, and study protocols. Many of the earlier studies have used an umbilical catheter to evaluate the immediate cardiovascular responses (Gupta, et al. 1965,Moss, et al. 1963,Moss, et al. 1968,Oh, et al. 1966,Shekhawat, et al. 2001,Waldman, et al. 1979,Young, et al. 1966).

Volume clamp method

Nowadays, invasive BP is hardly justified in otherwise healthy infants because of the risks associated with invasive catheters. Those infants with invasive blood pressure monitoring for clinical purposes frequently have severe cardiovascular problems, and thus they do no not represent a normal population. Oscillometric devices have not enabled continuous evaluation of blood pressure responses. Finapres®, Portapres® and Finometer® resolve these problems by measuring continuous blood pressure using the volume clamp method of Peñáz (Penaz. 1992).

In the volume clamp method, the diameter of an artery is kept constant during the beat-to-beat changes in arterial pressure (Imholz, et al. 1998,Penaz. 1992). This is managed by wrapping a cuff around the finger (or the wrist in infants (Drouin, et al. 1997a,Harrington, et al. 2001)) and measuring the changes in arterial diameter by infrared photo-plethysmograph. An inflatable air bladder with a fast pressure servo-controller opposes the changes in arterial diameter, thus keeping the arterial diameter stabile and unloaded. When unloaded, the arterial transmural pressure equals zero, and the blood pressure measured at the finger cuff equals intra-arterial blood pressure. Because the arterial tone changes following, e.g. stress, the correct unloaded diameter must be checked regularly. The Physiocal algorithm analyzes the signal from the plethysmogram at several constant pressure levels, and thus is able to find the correct unloaded diameter. This Physiocal algorithm, however, interrupts the blood pressure measurement, and thus it has to be disabled for the test periods. It can be enabled before and after the tests to ascertain reliable values for blood pressure. Finger (wrist) arterial blood pressure may differ from brachial artery blood pressure in waveform and in absolute levels. (Imholz, et al. 1998,Penaz. 1992)

The Finometer is reported to slightly underestimate the absolute BP values, but it is considered to reflect the changes in blood pressure levels reliably, especially during orthostasis and cardiovascular maneuvers (Friedman, et al. 1990,Imholz, et al. 1998,Jellema, et al. 1996). In infants, these devices can be used to measure continuous non-invasive blood pressure by wrapping a modifiable, adult XL-sized finger cuff around the wrist of the infant, and it has been shown to reliably detect BP changes (Drouin, et al. 1997a,Harrington, et al. 2001,Yiallourou, et al. 2006).

Reliable studies on changes in cardiovascular parameters require that the physiological state (awake or sleep, and sleep stage) is standardized, because in addition to different BP levels between waking and sleep, BP and HR levels also differ according to sleep stages (Horne, et al. 2010,Somers, et al. 1993). In addition, arousal threshold during non-rapid eye movement (NREM) sleep is higher compared with rapid eye movement (REM) sleep, and compared to REM and awake state, in NREM sleep, breathing is regular, there is less movement and fewer spontaneous arousals (Franco, et al. 2010,Grigg-Damberger, et al. 2007).

2.3.2 Head-up tilt test

The head-up tilt test is a common method used to evaluate cardiovascular function and control (Benditt, et al. 1996,Freeman. 2006,Weimer. 2010). When passively tilted to an upright position, the venous volume in the lower body increases, which in turn decreases venous return to the heart, reduces atrial filling and stroke volume. Together, these result in decreased cardiac output and

systolic blood pressure. Decrease in blood pressure activates aortic and pulmonary baroreceptors which rapidly reduce vagal activity, and then increase sympathetic activity, thus restoring homeostasis by increasing HR and BP. BP is restored via tachycardia (vagal inhibition) and peripheral vasoconstriction (sympathetic activation). Inhibition of vagal tone causes the initial HR increase, whereas both inhibition of vagal and increased sympathetic activity are responsible for the more gradual HR increase (Freeman. 2006).

Traditionally the head-up tilt test has been considered to evaluate baroreflex function (Carter, et al. 2008,Doba, et al. 1974). During the initial phase of the head-up tilt test, however, also vestibulo-mediated control apparently participates in the induction of the appropriate cardiovascular response (Carter, et al. 2008,Doba, et al. 1974). Furthermore, if the head-up tilt test is performed when the subject is awake, alert centers most likely participate in the response (de Burgh Daly. 1997b). This alert response may be one reason why the acute response is not considered clinically significant in adults. To eliminate the influence of these alert centers on cardiovascular reflexes, sleep may be the optimal state in which to perform the head-up tilt test.

Head-up tilt test in adults

The response to orthostatic stress has been well described in adults. Typical adult response to orthostatic stress includes an increase in HR and an initial BP decrease, followed by a restoration of BP with reduced pulse pressure from a greater increase in diastolic BP (Gabbett, et al. 2001,Sprangers, et al. 1991). Total peripheral vascular resistance is initially decreased, followed by an increase (Wieling, et al. 1998). A head-up tilt test in adults results in gradual circulatory adjustments that reach stabile levels within 30-60s (Gabbett, et al. 2001,Wieling, et al. 1998).

Tilt test methodology is not uniform and standardized. The methodology of tilt tests has been variable with regard to timing, angle of the tilt, position, age ranges, study conditions, and analysis methods. There are significant differences in the reported responses to head-up tilting in the HR and BP even in normal cohorts of healthy adults (Sprangers, et al. 1991).

In addition, it is worth noting that tilt tests in adults are commonly performed awake, which may add variability because of arousal responses. Although considerable effort has been made to exclude startle effects by familiarizing the subjects with the test, it is likely that these tests are not fully comparable with those performed on sleeping infants, as the control of blood pressure also differs during awake and sleep stages (Orem, et al. 1980,Somers, et al. 1993).

Tilt angle and length

In adults, the focus of interest in head-up tilt testing is usually on the more prolonged response (for example, in the work-up for unexplained syncope), rather than on the acute cardiovascular response (Benditt, et al. 1996,Weimer. 2010). The angle is usually between 60 and 90 degrees, and the transition from supine to upright position between 10 and 15 seconds. Regarding orthostatic intolerance, the test length of 5 to 15 minutes usually suffices (Weimer. 2010), but considerably longer test durations are also suggested (Benditt, et al. 1996).

In adults, the acute cardiovascular responses to tilt angles from 70 to 90 degrees and tilt rise time between 1.5 to 3 seconds are virtually the same (Sprangers, et al. 1991). In children and adolescents, a 30 min tilt test for syncope shows similar results between 60 and 70 degrees (Lewis, et al. 1997), but apparently, cardiovascular effects of lower tilt angles and acute responses are not well characterized. In a study using an oscillometric method to measure the BP response, HR and BP responses were found to be proportionate to the angle of the tilt up to 60 degrees (Thoresen, et al. 1991).

In animal studies, cardiovascular response to the tilt test is related to the tilt angle (Doba, et al. 1974,Jian, et al. 1999). In both anesthetized and awake animals, tilt angles of 20 to 40 degrees have elicited smaller BP changes than 60 degree tilts.

Head-up tilt test in autonomic failure

In autonomic failure showing severe orthostatic hypotension, the head-up tilt test provokes only a slow HR increase and a pronounced BP decrease due to unchanged total peripheral resistance (Wieling, et al. 1998). In addition, patients with neurogenic orthostatic hypotension have low levels of plasma noradrenaline which do not increase during orthostatic stress, further suggesting a deficit in the peripheral sympathetic nervous system (Freeman. 2006).

2.3.3 Head-up tilt test in infants

Although the tilt test is a common way to study cardiovascular control in adults, this study method is not in common use in evaluation of infants. Few data exist on the initial BP responses to tilt tests in infants, as until the volume clamp method of Penaz was adopted, continuous BP data during the tilt test was obtained only by invasive monitoring methods. A few recent studies have evaluated cardiovascular responses to tilt tests using the Finometer, or its earlier versions, Portapres and Finapres (Cohen, et al. 2008,Cohen, et al. 2010,Harrington, et al. 2001,Harrington, et al. 2002,Harrington, et al. 2003,Witcombe, et al. 2010,Yiallourou, et al. 2008).

The overall comparison between tilt test studies on infants is difficult because of differences in study methods and reporting. The reported and used tilt angles vary from 15° to 90°, the position may be supine or prone, the length of the tilt test and the assessment point for the response varies from 1 to 30 minutes, the study age varies from premature infants to close to one-year-olds, and the sleep-wake state has varied from awake to quiet sleep, and in many cases the sleep-wake state is not even mentioned (Tables 2, 3, 4, and 5). It is therefore very difficult to draw clear and uniform conclusions on infant HR and BP responses to the tilt test.

The importance of sleep stage during tests is underlined by the finding of more variable BP responses in active REM sleep (AS) compared with quiet NREM sleep (QS), and that many of the tests performed during AS resulted in arousal (Galland, et al. 2000a,Harrington, et al. 2001,Witcombe, et al. 2010). Thus, it is possible that some of the discrepant findings reflect an arousal response rather than a response to orthostatic challenge, as even a brief arousal causes HR (Finley, et al. 1984,Galland, et al. 2000a,Thoresen, et al. 1991) and pressor response (Horner. 1996,Trinder, et al. 2003).

Blood pressure responses to tilt test in full-term infants

Most of the tilt test studies on full-term infants have been performed during the neonatal period, but some data exist up to 1-1.5 years. The initial BP responses to the tilt test have been described as mature, adult-like biphasic responses, but no consistency exists in the BP values after stabilization in the new, head-up position (Table 2). When tilted in a prone position (Chong, et al. 2000,Thoresen, et al. 1991,Yiallourou, et al. 2008), BP decreases. Variation is commonly observed both in the tilt responses between the study subjects (Andrasyova, et al. 1996,Moss, et al. 1968,Oh, et al. 1966,Young, et al. 1966) and depending on the sleep stage and age studied (Yiallourou, et al. 2008). Some studies have reported a change in response pattern after a few days of life (Chen, et al. 1995,Hakulinen, et al. 1962,Young, et al. 1958).

Blood pressure responses to tilt test in preterm infants

Similarly to the studies on full-term infants, the study methods and analysis points differ among preterm tilt studies making comparison difficult, but in preterm infants different gestational and study ages render the evaluation even more complex. Tilt tests evaluating BP responses in preterm infants are presented in Table 3. The initial BP response to the head-up tilt test in preterm infants is mostly reported to be similar, biphasic, to that in full-term infants. After stabilization for at least 1-2 minutes in the tilted position, most studies report no change or an increase in BP levels. These findings of intact baroreceptor response have been reported in studies using both continuous and discrete BP measurements, although some authors

describe a great variability in the individual responses (Haenninen, et al. 1964,Lagercrantz, et al. 1990). The tilt responses in preterm infants are similar to those in full-term infants shortly after birth, suggesting that preterm infants have a well-developed baroreflex function already shortly after birth.

Heart rate responses to tilt test in full-term infants

In term infants, studied both shortly after birth and at 2-4 months of age, the initial HR response to the head-up tilt test when tilted supine is mostly an increase or biphasic (an increase followed by a decrease) (Table 4). Later the HR response is mostly reported to be either an increase or no change in HR level. One longitudinal study of twenty infants (Yiallourou, et al. 2008) reported a HR decrease to tilt in quiet sleep up to 2-3 months and after that a biphasic response, but this group performed tilt tests of only 15 degrees, which is a rather weak stimulus for cardiovascular control. Most studies do not report any significant differences between HR responses in different sleep stages.

When tilted prone, HR increases in the newborn period, but at a later age of 1-4 months, a biphasic response (Galland, et al. 1998,Galland, et al. 2006) or no change is reported (Fifer, et al. 1999,Grieve, et al. 2005,Myers, et al. 2006). These differences may result from tilt rise differences, since the former group perfomed the tilt test in a few seconds, whereas the latter group tilted the infants very slowly up to 30 seconds. Galland and coauthors have noted, however, that when tilted in the prone position, fewer awakenings are seen (Galland, et al. 1998,Galland, et al. 2006).

Heart rate responses to tilt test in preterm infants

Heart rate decreases with increasing age in both term and preterm infants, and from 2-4 weeks of age onwards, HR levels are found to be similar at comparable corrected ages (Witcombe, et al. 2010). Close to term age, i.e. at 40-42 weeks of postconceptional age, however, preterm infants still have higher resting HR (Cohen, et al. 2007). Cardiac function is also noted to improve with increasing age (Shekhawat, et al. 2001).

In a few-days-old preterm infants, a head-up tilt induces either tachycardic or a flat HR response (Table 5). An increasing positive HR response to tilt, however, is reported with increasing postnatal age (Mazursky, et al. 1998,Witcombe, et al. 2010). Observation of stabile HR levels at 2 to 20 minutes after initiation of head-up tilting in preterm infants suggests intact baroreflex control occurring at least on average from 32-33 weeks of GA onwards (Gronlund, et al. 1997,Schrod, et al. 2002,Shekhawat, et al. 2001). It thus seems that maturation of baroreflex control of HR occurs already before corrected term age, although this maturation may be delayed in comparison to normal term infants even after reaching full-term postmenstrual age.

Table 2. Blood pressure responses to head-up tilt tests in healthy, full-term infants

Authors	Year	Study subjects			Tilt test angle	Sleep stage	Position
		n	GA (wk)	study age			
Young et al.	1958	36 31	..	3h-3d 4d-12d	80°	QW	Su
Hakulinen et al.	1962	18	..	1-3d 4-6d	30°	..	Su
Moss et al.	1963	27	..	1-77h	70°	..	..
Young et al	1966	25	..	0.5-36.5h	80°	..(QW?)	Su
Oh et al.	1966	17	37-43	2-14h	40-45°	..	Su
Moss et al.	1968	40	..	6-52h	70°	..	Su
Picton-Warlow et al.	1970	20	..	4h-12d	70-80°	obs. QS	Su
Magrini et al.	1989	14	..	6mo, 18mo	90°	..	Su
Thoresen et al.	1991	9	..	7-24h, 5d	30°	obs. QS, AS	P
Chen et al.	1995	32	36-42	2h 24h	30°	obs. QS	Su
Andrasyova et al.	1996	83	38-42	1-7d	45°,90°	QW	Su
Browne et al	2000	26 14	..	2-3d 3mo	70°	..	Su
Chong et al.	2000	44	..	6-9wk	60°	obs. QS	S, P
Harrington et al.	2001	12	..	13±2wk	45°	SWS,REM	Su
Cohen et al.	2008	15	38-41	2d-2wk	60°	obs. QS	Su
Yiallourou et al.	2008	20	38-42	2-4wk 2-3mo 5-6mo	15°	QS,AS	Su,P
Cohen et al.	2010	13 6 17 10	39±0.5 40±0.6 39±0.4 39±1	<1wk 2-3wk 3 mo 1 year	60°	obs. QS	Su

Table 3. Blood pressure responses to head-up tilt tests in preterm infants

Authors	Year	Study subjects			Tilt test angle	Sleep stage	Position
		n	GA (wk)	study age			
Moss et al.	1963	23	..	1-77h	70°	..	..
Hänninen et al.	1964	24	28-40	2-42d	30°	..	Su
Gupta et al.	1965	43	..	0-24h	90°	..	..
Waldman et al.	1979	13	26-38	0-48h	45°	..	..
Lagercrantz et al.	1990	21	25-36	1-11wk	45°	obs. QS, AS	..
Dellagrammaticas et a	1991	23	26-34	..	45°	obs. QS	P
van Reempts et al.	1997	32	26-36	2-86d	60º	sleep	P
Shekhawat et al.	2001	25	24-35.5	7-83d	30° 60º	QW	Su
Schrod et al.	2002	36	25-35	2-12d	30°	obs. QS	Su
Cohen et al.	2008	16	27-34	PMA 40-42wk	60°	obs. QS	Su
Witcombe et al.	2010	25	28-32	2-4wk corr.age 2-3mo corr. age 5-6mo corr. age	15°	QS, AS	Su

Definition and abbreviations: corr.age = corrected age; GA = gestational age; PCA = postconceptional age; PMA = postmenstrual age; obs. = observed; P = prone; QS = quiet sleep; QW = quiet wakefulness; REM = REM sleep; Su = supine; SWS = slow wave sleep

Table 2 continued

Measurement		Blood pressure response		Heart rate response	
time from tilt onset	method	initial (0-15s)	late (>30s)	initial (0-15s)	late (>30s)
30s-2min	palpation and cuff	..	↔ (30s) ↑ (30s)	..	↑ ↑
3min	sphygmo-manometer	..	↔ (3min) ↑ (3min)	..	..
0-20s	invasive	↑ ↓ ↔	..	↑ ↓	..
..	invasive	↑	..	↑	..
0-30min	invasive	↑ ↓ or ↑ ↔	↓ or ↔ (30min)	↑ ↓	↓ (30min)
..	invasive	↓ →	..	↑	..
..	microphone + cuff	..	↓	↑	↑
5min	sphygmomanom.	..	↔ (5min)	..	↔ (5min)
30s-5min	oscillometric	..	↓ (30s-5min)	↑	↑
5min	oscillometric	..	↓ (5min) ↔ (5min)	..	↔ (5min) ↔ (5min)
1, 3, 5min	oscillometric	..	↑ (5min)	..	↑
45-75s, 104-135s	oscillometric	.. ..	↔ ↑	.. ..	↔ ↔
1,5-30min	..	..	↓ (30min)	..	Su:↔, P: ↑ (30min)
0-1min	Portapres	↑ ↓ →	↔ (30s)	↑ ↓ →	↔ (30s)
0-1min	Finometer	↓ ↑	↑ (1min)	↑	..
0-45s	Finometer	Su:↑→(QS) ↔(AS) P: →↓ (QS) ↔(AS) Su:↑↓↓(QS) ↔ (AS) P:↓↓↓ (QS) →↓↓(AS) Su:↑→↓(QS)↑→(AS) P:→↓(QS)→↓↓(AS)	..	Su:↓→(QS) ↑→(AS) P:↓→(QS) ↔(AS) Su:↓→(QS) ↑→(AS) P:↓→(QS) ↑→(AS) Su:↑↓→(QS) ↑→(AS) P:↑↓→(QS) ↑→(AS)	..
0-1min	Finometer	↑ ↓ ↑ ↓ ↑ ↓ ↑ ↓	↑ (1min) ↑ (1min) ↑ (1min) ↑ (1min)	↑ ↓ ↑ ↓ ↑ ↓ ↑ ↓	..

Table 3 continued

Measurement		Blood pressure response		Heart rate response	
time from tilt onset	method	initial (0-15s)	late (>30s)	initial (0-15s)	late (>30s)
0-20s	invasive	↑ ↓ ↔	..	↑ ↓	..
2-3min	sphygmo-manometer	..	variable (2-3min)	..	..
0-2min	invasive	..	↑ (2min)	..	..
..	invasive	↓	..	↔	.
..	oscillometric	..	↔	..	↔
1-5min	oscillometric	..	↔ (1-5min)	..	↓(30s-5min)
15s-5min	oscillometric	..	↑ ↓ ↔	↑ ↓ ↔	..
1-2min	invasive	.. ..	↔ (1-2min) ↔ (1-2min)	.. ..	↔ (1-2min) ↔ (1-2min)
5-20min	oscillometric	..	↔	↓	↔ (5-20 min)
0-1min	Finometer	↑	↑ (1min)	↑	..
0-30s	Finometer	↑→ (QS) ↔ (AS) ↑ → ↑ →	.. .. ..	↓ → ↓→ (QS) ↑↓→ (AS) ↑↓→ (QS) ↑→ (AS)	.. .. ..

Definition and abbreviations: ↔ = no change; ↑ = increase; ↓ = decrease. Those fields with data missing are marked with "..". If authors described BP and HR responses as a sequence, arrows are marked accordingly (e.g. an increase followed by a decrease is marked ↑ ↓)

Table 4. Heart rate response to head-up tilt tests in full-term infants

Authors	Year	Study subjects			Tilt test angle	Sleep stage	Position
		n	GA (wk)	study age			
Young et al.	1958	36+31	..	3h-3d, 4-12d	80°	QW	Su
Moss et al.	1963	27	..	1-77h	70°	..	..
Young et al.	1966	25	..	0.5-36.5h	80°	..(QW?)	Su
Oh et al.	1966	17	37-43	2-14h	40-45°	..	Su
Moss et al.	1968	40	..	6-52h	70°	..	Su
Picton-Warlow et al.	1970	20	..	4h-12d	70-80°	obs. QS	Su
Finley et al.	1984	19	..	1-7d	30°	QS,AS	..
Magrini et al.	1989	14	..	6mo, 18mo	90°	..	Su
Thoresen et al. .	1991	9	..	7-24h, 5d	30°	obs. QS, AS	P
Chen et al.	1995	32	36-42	2h, 24h	30°	obs. QS	Su
Andrasyova et al.	1996	83	38-42	1-7d	45°, 90°	QW	Su
Galland et al.	1998	37	..	8-17wk	60°	obs. QS, AS	Su, P
Fifer et al.	1999	114	..	1-2d,2mo,4mo	30°	sleep	P
Chong et al.	2000	44	..	6-9wk	60°	obs. QS	Su, P
Galland et al.	2000	36	35-42	1mo, 3mo	60°	obs. QS, AS	Su, P
Browne et al.	2000	26, 17	..	2-3d, 3mo	70°	..	Su
Galland et al.	2000	60	..	1mo, 3mo	60°	obs. QS, AS	Su, P
Harrington et al.	2001	12	..	13±2wk	45°	SWS,REM	Su
Massin et al.	2002	7	..	PCA 40-41	45°	sleep	Su
Grieve et al.	2005	27	35-42	12-48h,2-4mo	30°	sleep	P
Myers et al.	2006	54	..	12-48h,2-4mo	30°	sleep	P
Galland et al.	2006	50	>37	1mo, 3mo	60°	obs. QS, AS	Su, P
Yiallourou et al.	2008	20	38-42	2-4wk 2-3mo 5-6mo	15°	QS,AS	Su
Cohen et al.	2008	15	38-41	2d-2wk	60°	obs. QS	Su
Cohen et al.	2010	13	39±0.5	<1wk	60°	obs. QS	Su
		6	40±0.6	2-3wk			
		17	39±0.4	3 mo			
		10	39±1	1 year			

Table 5. Heart rate response to head-up tilt tests in preterm infants

Authors	Year	Study subjects			Tilt test angle	Sleep stage	Position
		n	GA (wk)	study age			
Moss et al.	1963	23	..	1-77h	70°	..	..
Waldman et al.	1979	13	26-38	0-48h	45°	..	..
Finley et al.	1984	11	≤37	2-19d	30°	QS,AS	..
Lagercrantz et al.	1990	21	25-36	1-11wk	45°	obs. QS,AS	..
Dellagrammaticas et al.	1991	23	26-34	..	45°	obs. QS	P
Grönlund et al.	1997	9	30-34	1d	20°	obs QS	Su
van Reempts et al.	1997	30	26-36	2-86d	60°	sleep	P
Mazursky et al.	1998	28	24-31	PCA ≤40	45°	sleep	Su
Shekhawat et al.	2001	25	24-35.5	7-83d	30° 60º	QW	Su
Massin et al.	2002	7	30-34	PCA 40-41	45°	sleep	Su
Schrod and Walter	2002	36	25-35	2-12d	30°	obs. QS	Su
Cohen et al.	2008	16	27-34	PMA 40-42wk	60°	obs. QS	Su
Witcombe et al.	2010	25	28-32	2-4wk corr.age 2-3mo corr. age 5-6mo corr. age	15°	QS, AS	Su

Definition and abbreviations: as in table 2 and 3.

Table 4 continued

Measurement	**Heart rate response**	
time from tilt onset	initial (0-15s)	late (>30s)
0-2min	..	↑
0-20s	↑↓	..
..	↑	..
0-30min	↑↓	↓ (30min)
..	↑	..
..	↑	↑
30-90s	↑	..
5min	..	↔ (5min)
30s-5min	↑	↑
5min	..	↔ (5min)
1,3,5min	..	↑
>1min	↑↓	..
0-1.5min	↑ (newborn), ↔ (2-4mo)	↑ (newborn), ↔ (2-4mo)
1,5-30min	..	Su:↔, P:↑ (30min)
..	↑↓	..
0-2min	..	↔
0-1min	↑↓→	↓(QS),↑ (AS)
0-1min	↑↓→	↔ (30s)
0-30s	↔ / ↑	
0-2min	..	↑ (newborn), ↔ (2-4mo)
0-2min	..	↑ (newborn), ↔ (2-4mo)
30-90s	↑↓	..
0-45s	Su:↓→(QS) ↑→(AS) P:↓→(QS) ↔(AS) Su:↓→(QS) ↑→(AS) P:↓→(QS) ↑→(AS) Su:↑↓→(QS) ↑→(AS) P:↑↓→(QS) ↑→(AS)	..
0-1min	↑	..
0-1min	↑↓ ↑↓ ↑↓ ↑↓	..

Table 5 continued

Measurement	**Heart rate response**	
time from the tilt onset	initial (0-15s)	late (>30s)
0-20s	↑↓	..
..	↔	..
30-90s	↑	..
..	..	↔
1-5min	..	↓ (30s-5min)
0-2min	..	↔ (2min)
15s-5min	↑↓→	..
3s-1 min	PCA 28-32wk ↔ PCA 35-39wk ↑	..
1-2min	..	↔ (1-2min)
	..	↔ (1-2min)
0-30s	↔ or ↑	..
5-20min	↓	↔ (5-20min)
0-1min	↑	..
0-30s	↓ →	..
	↓→ (QS)	..
	↑↓→ (AS)	
	↑↓→ (QS)	..
	↑→ (AS)	

Definition and abbreviations: as in table 2 and 3

Peripheral vascular resistance during head-up tilt test

Venous occlusion plethysmography is the most frequently used method to evaluate peripheral vascular resistance. It evaluates noninvasively the amount of arterial blood flow to a limb by measuring the increase of limb volume (swelling) during total venous occlusion. When arterial BP is divided by this limb blood flow, an estimate of vascular resistance is reached (Freeman. 2006,Greenfield, et al. 1963).

During a prolonged (minutes) head-up tilt test in healthy adult subjects, estimated peripheral vascular resistance briefly decreases after which it increases and remains higher compared with baseline level during the rest of the tilt (Wieling, et al. 1998). In full-term neonates, peripheral vascular resistance increases during the head-up tilt test (Picton-Warlow, et al. 1970). At 6 months of age, no change in calculated total peripheral resistance or cardiac index was found during tilt test, whereas at 18 months, the cardiac index decreased and peripheral resistance decreased when tilted (Magrini, et al. 1989).

Studies on preterm infants suggest some immaturity in their ability to control peripheral vascular resistance (Lagercrantz, et al. 1990,Waldman, et al. 1979). Waldman (Waldman, et al. 1979) described increased vascular resistance during head-up tilt in healthy preterm infants aged 0 – 48 hours, whereas preterm infants with respiratory distress showed decreased peripheral vascular resistance. It is of note that in some infants showing this decreased vascular resistance, the resting vascular tone was already high. A study by Lagercrantz (Lagercrantz, et al. 1990) on preterm infants aged 1 – 11 weeks found, in general, increased peripheral resistance during the head-up tilt test, but the variation was marked from -15.3% to +104%, further supporting this variable ability of preterm infants to control peripheral vascular resistance.

Cardiovascular responses to tilt test in infants with apparent life-threatening event

Few studies have evaluated infants with a preceding apparent life-threatening event (ALTE) using the head-up tilt test (Fox, et al. 1989,Harrington, et al. 2002). In the first report, Fox and Matthews (Fox, et al. 1989) performed a 90° head-up tilt during quiet NREM sleep in 30 ALTE infants, 24 SIDS siblings, 8 infants with cyanotic attacks and 17 controls. The sleep position was not controlled. The authors do not report all responses, but the proportion that was abnormal. None of the control infants showed abnormal HR response such as a slow decline or a slow increase in HR, but this was seen in several ALTE infants and in only 1 SIDS sibling. Postural hypotension was also much more common in the ALTE group than in controls or other infants. The same authors later published a case report on one of these ALTE infants, who died in hospital after completion of the sleep study (Ledwidge, et al. 1998). This infant had shown no apnea, nor bradycardia episodes during the sleep study. The autonomic function of the infant was, however, abnormal during sleep, seen as reduced heart rate variability (HRV), and abnormal responses to the tilt test. This infant showed postural hypotension associated with bradycardia during the tilt test, and the authors suggest that this type of cardiovascular response may be associated with death in SIDS.

Edner et al. (Edner, et al. 1997) compared HR responses in 18 ALTE and 12 control infants to a 45 degree head-up tilt test while asleep. Of the control infants, 83% showed biphasic HR response, whereas only 22% of ALTE infants showed this type of response. ALTE infants predominantly showed sustained HR increase, but the responses were overall more variable. In addition, 28% of the ALTE infants showed constant HR decrease or no change, whereas none of the controls showed these types of responses.

Harrington et al. (Harrington, et al. 2002) found that at 3 months of age, ALTE infants with obstructive sleep apnea showed abnormal cardiovascular control compared with 5 ALTE infants without obstructive sleep apnea and 12 healthy controls. Infants with obstructive sleep apnea showed reduced HRV and increased arousal threshold in REM sleep. Their HR responses were attenuated, and 3 out of 5 also showed postural hypotension, with the

remaining two having abnormal BP response compared with controls. A later study by the same group (Harrington, et al. 2003) showed that the abnormal cardiovascular responses and arousal thresholds in infants with obstructive sleep apnea improved after nasal continuous positive airway pressure (CPAP) treatment.

Cardiovascular responses to tilt test in infants exposed to maternal smoking during pregnancy

A couple of studies have evaluated HR and BP responses to the head-up tilt test in infants exposed to maternal smoking during pregnancy. Subcortical arousals, which may interfere with the results, were not considered in the analysis except in the study by Galland et al. (Galland, et al. 2000a).

Cohen and co-workers (Cohen, et al. 2008) compared full-term infants with and without exposure to maternal smoking during pregnancy. A supine 60° head-up tilt test performed at 2 days-2 weeks after birth caused a transient HR increase and a systolic blood pressure (SBP) decrease, followed by a gradual BP increase during the rest of the 1-min tilt in 29 infants who had not been exposed to maternal smoking during pregnancy. Infants with intrauterine smoke exposure showed a similar HR response, but a prolonged and exaggerated BP response.

Browne and associates (Browne, et al. 2000) studied cardiovascular responses to a supine 70° head-up tilt lasting for 3 minutes in full-term infants exposed to maternal smoking during pregnancy. The infants were studied at 2 – 3 days and at 3 months of age. BP was measured by the oschillometric technique, which enabled the BP measurement only 45 to 75s after the tilt onset. Reported HR responses were averaged over the 2-min tilt period. Compared with infants without maternal smoking exposure, infants with intrauterine smoke exposure showed higher resting SBP at both ages. During the tilt test at 2 – 3 days of age, SBP decreased in antenatally smoke-exposed infants, whereas it remained at the pretilt level in non-exposed infants. At 3 months of age, SBP did not change during the tilt in antenatally smoke-exposed infants, but it increased in non-exposed infants. Mean HR and HRV values remained at pre-tilt levels in both groups at both study ages.

Galland et al. (Galland, et al. 2000a) studied HR responses to a 60° head-up tilt test in control infants and infants exposed to maternal smoking during pregnancy at the age of one and three months. In both groups, a similar biphasic HR response was observed.

A recent study by Cohen et al (Cohen, et al. 2010) assessed longitudinally BP and HR responses to the head-up tilt test in infants exposed to maternal smoking during pregnancy and in control infants from term up to one year of age. They found biphasic HR and BP responses in both groups, but infants with intrauterine smoke exposure presented with an increased HR response compared to controls from 3 months onwards. At the age of one week, the BP values of these antenatally smoke-exposed infants were higher than those observed in the controls at the end of a 1-min tilt, whereas at the age of one year, antenatally smoke-exposed infants had lower BP values compared with the controls.

2.3.4 Vestibular tests

Head-down rotation

Head-down rotation is a well-studied method to evaluate how stimulation of otolith organs influences sympathetic neural traffic (Carter, et al. 2008). This method requires considerable cooperation as the subject is lying prone with chin or forehead supported, and the head is passively lowered until the chin touches the chest. Characteristics of vestibulosympathetic reflex have recently been reviewed by Carter and Ray (Carter, et al. 2008). The vestibulosympathetic response is a reflex system designed to respond to acute hypotensive challenges, and it is a separate entity from other cardiovascular reflexes; baroreflex, visual

input, neck afferents and central command do not affect the reflex activity. In addition, the vestibulosympathetic reflex is capable of increasing muscle sympathetic nerve activity also during arterial hypotension, and during baroreflex unloading by nitroprusside infusion (Dyckman, et al. 2007).

Linear acceleration

Horizontal linear acceleration is an alternative method to activate the sympathovestibular reflex instead of head rotation (Yates, et al. 1999). By using a linear motion, the baroreflex activation may be prevented. Yates et al (Yates, et al. 1999) have used eight different stimulus conditions: linear forward (head straight, forward, and back), linear back (head straight, forward, and back), right and left acceleration (head straight). In adult control subjects, HR increased shortly after the onset of linear acceleration, and slowed within 6 s to below the pre-test HR level. The initial acceleration response was immediate, and seen within the first heartbeats. The largest alteration in HR was produced by forward acceleration with head upright. Systolic and diastolic BP increased during acceleration and decreased back within 10s (max in 3-6s). The responses to each stimulus condition were, however, variable among the subjects. As all head positions were able to induce cardiovascular responses, both saccular and utricular inputs (otolith) are suggested to contribute to vestibulo-cardiovascular reflexes in humans. In three patients with profound bilateral reduction in vestibular inputs, the linear accelerations were unpleasant and BP responses were significantly dampened compared to normal controls.

2.3.5 Heart rate variability

Heart rate and blood pressure show constant beat-to-beat fluctuations, and the measurement of heart rate variability (HRV) is used to evaluate the balance between sympathetic and parasympathetic autonomic nervous system input to the heart (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996). The most important mechanisms affecting HRV are breathing, baroreflex, and thermoregulation. Vagal tone is prominent in the resting state (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996). For HRV analysis, deep NREM sleep (N3) is the optimal condition, as respiration is regular, there are only few body movements, and external disturbances are minimized (Brandenberger, et al. 2005).

Either of two approaches – time-domain and frequency domain – are generally used to evaluate HRV. Time domain measures, featuring R-R intervals (interval between QRS complexes), are more useful in the evaluation of long-term HRV changes, whereas in short-term HRV analysis, frequency domain methods are more suitable. In frequency domain method, changes in R-R interval spectral components are categorised as very low frequency variability (VLF), low frequency variability (LF), and high frequency variability (HF). There is no clear consensus on the exact frequency band limits, especially in infants, but in adults most often the VLF band is defined as changes between 0 – 0.04Hz, the LF band as 0.04-0.15Hz, and the HF band as variability between 0.15 – 0.4Hz (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996). In infants, the upper level of the HF band is recommended to be set higher because of more rapid heart rate and breathing (Rosenstock, et al. 1999). The HRV is calculated from 2-5-minute time intervals. VLF analysis requires long periods of uninterrupted data, and it is not reliably detected in epochs under five minutes (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996).

LF and HF components can be presented as absolute power (ms^2), but comparing these values can be misleading if the total power has changed at the same time. Thus, normalized units (n.u.) converted from the absolute power values are often used (Task Force of the European Society

of Cardiology and the North American Society of Pacing and Electrophysiology. 1996). The normalized units represent the relative value of each power component in proportion to the total power (VLF excluded).

The quality of the analyzed electrocardiogram has several requirements for a reliable analysis: the signal should be stabile, the optimal sampling rate would have to be 250-500Hz unless interpolation is used, baseline and trend removal should be used cautiously, and the recording should have minimal noise and missing data (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996). Deep NREM sleep (N3, slow wave sleep) is considered the optimal condition because of the stabile characteristics of this state (Brandenberger, et al. 2005).

Interpretation of spectral components

The interpretation of physiological correlates of HRV components is based on animal research and studies with medical interventions in human subjects (Akselrod, et al. 1985,Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996). The interpretation of HRV is not straightforward, but roughly, HF power is considered to represent mostly parasympathetic vagal balance, whereas LF power is considered to be jointly mediated by the parasympathetic and sympathetic nervous systems. The ratio of LF/HF is used as a marker of sympathovagal balance (Akselrod, et al. 1985,Malliani, et al. 1991,Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996). Respiratory variability affects HRV; the peak power of the HF component shifts with changes in respiratory rate. LF variability of HR is related to the frequency response of the baroreflex, and to compensation of BP fluctuations. The peak component of VLF is suggested to be related to peripheral vascular resistance fluctuations caused by thermoregulation (Rosenstock, et al. 1999).

Either the LF or HF power of HRV can increase depending on the physiological state; LF power increases during head-up tilt, standing, mental stress, and exercise, whereas an increase in HF power is observed during controlled respiration, cold facial stimulation, and rotational stimuli (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996). Normally, the power of the LF component is greater than the HF, with the LF/HF ratio remaining above 1 (Malliani, et al. 1991).

Heart rate variability in infants

The use and findings of HRV analysis in infants is reviewed by Rosenstock et al. (Rosenstock, et al. 1999). HRV analysis in infants is not as thoroughly and widely studied as in adults. Infants have much higher breathing frequency and baseline HR levels than adults, and thus, the HRV frequency bands are different. If a VLF band is excluded, the LF band usually starts at 0.02 Hz, the cut-off point between LF and HF bands is usually set at 0.2 Hz, and the upper limit of the HF band has varied between 0.5 and 2.0 Hz depending on the study. HRV depends greatly on the behavioral state of the infant; in REM sleep, LF and VLF indices are higher and the HF component lower than in quiet NREM sleep.

In infants, HRV increases with age as the baseline HR and respiratory rate decrease (Rosenstock, et al. 1999). This age dependency is seen already in preterm infants. In term infants, there is a transient decrease in HRV at 1-2 months of age, after which the variability again continues to increase (Rosenstock, et al. 1999). Preterm infants show lower HF variability and thus a lower vagal tone compared with term infants (Hunt. 2006,Rosenstock, et al. 1999). This is also seen at the comparable postconceptional age. Respiratory distress syndrome, intraventricular hemorrhage, and being born small for gestational age are also associated with decreased HRV (Rosenstock, et al. 1999).

2.3.6 Baroreflex sensitivity

The traditional method to evaluate baroreflex is to to measure HR change in response to BP distortion induced by vasoactive drugs (Freeman. 2006,La Rovere, et al. 2008). In this method, BP is increased with intravenous phenylephrine, and subsequent R-R interval changes are compared to preceding SBP changes. Other methods to study baroreflex include lower body negative pressure, Valsalva maneuver, neck suction and pressure, and analysis of spontaneous oscillations in BP and HR (Freeman. 2006,La Rovere, et al. 2008).

The evaluation of spontaneous oscillations of BP and HR provide an easy and noninvasive method to asses baroreflex sensitivity even in small children. In the sequence method, spontaneous beat-to-beat changes in SBP are compared with simultaneous, opposite changes in HR (Drouin, et al. 1997b,La Rovere, et al. 2008). The baroreflex sensitivity is calculated as the slope of this regression line. The spectral method evaluates oscillations in the R-R interval that are elicited by spontaneous BP oscillations (La Rovere, et al. 2008). These oscillations of the R-R interval are in the same frequency as in BP, and usually two main bands, LF and HF, as defined above for adults, are considered.

In spite of these two different methodological approaches for analyzing spontaneous baroreflex sensitivity, baroreflex sensitivity in infants has been found to increase with age, and to be lower in preterm infants compared with term infants at similar postconceptional ages (Andriessen, et al. 2004,Andriessen, et al. 2005,Drouin, et al. 1997b,Gournay, et al. 2002,Yiallourou, et al. 2010). In infants, baroreflex sensitivity increases with increasing GA, postnatal and postmenstural age, suggesting an increase in reflex vagal activity with increasing age (Andriessen, et al. 2005,Gournay, et al. 2002,Yiallourou, et al. 2010). Supporting this conclusion, Andriessen et al (Andriessen, et al. 2005) found a similar increase in HRV and baroreflex sensitivity with increasing postmenstrual age (PMA).

2.4 Sleep

2.4.1 Sleep architecture in neonate and infant

The time spent in sleep decreases with age. Newborn infants sleep around 16-18 hours per day, and no circadian sleep-wake rhythm is present. During the first year, the sleep-wake state organization develops, and the time spent in sleep is concentrated on the night time. (Ferber, et al. 1995).

The sleep characteristics are thoroughly reviewed in the American Sleep Association committee statement of new sleep stage criteria in humans (Grigg-Damberger, et al. 2007). Sleep constitutes two major stages, rapid-eye-movement sleep (REM) and non-rapid-eye-movement sleep (NREM). After the appearance of K-complexes and sleep spindles in electroencephalogram (EEG) signals during between two to four months of age, three stages of NREM sleep may be observed, N1 to N3 (Grigg-Damberger, et al. 2007). The sleep architecture in preterm infants and full-term newborns differs qualitatively and quantitatively from that of adults. Sleep architecture and polysomnographic features of infant sleep undergo considerable changes during the first six months of life, but no major changes are noted after one year of age (Darnall, et al. 2006,Grigg-Damberger, et al. 2007,Lehtonen, et al. 2004).

In young infants, the EEG reflects the maturation of the brain. Thus, evaluation of the polysomnography of the preterm neonate or infant must be based on PMA or equivalent rather than postnatal age (Grigg-Damberger, et al. 2007). Because of the immature EEG in young infants, infant sleep has been traditionally scored as active-REM sleep (AS), intermediate (IS), and quiet sleep (QS) (Grigg-Damberger, et al. 2007). However, all the major characteristics of REM sleep are noted already in term infants. Therefore, the new consensus statement notes

that infant sleep may be scored as REM and NREM sleep similarly to adults (Grigg-Damberger, et al. 2007). Respiratory regularity and other behavioral criteria may be useful additional markers of sleep stage in young infants as there is a lack of specific EEG characteristics of NREM sleep such as K-complexes, spindles, and high voltage slow activity in deep quiet sleep. In very preterm infants, REM and NREM sleep stages are not easily distinguished, but a limited number of sleep studies in preterm infants have been carried out (Darnall, et al. 2006,Hunt. 2006,Lehtonen, et al. 2004).

Clearly defined, EEG-based AS-REM and QS-NREM sleep first appear around 34 weeks, and by 36 weeks of PMA, all the EEG and behavioral correlates of wakefulness, AS and QS are seen, although indeterminate sleep still accounts for a large portion of sleep (Grigg-Damberger, et al. 2007). QS is further divided into tracé alternans and high voltage slow (HVS) sleep. Tracé alternans is a distinct infant sleep pattern seen from the 28th gestational week, but is evident in its mature form from around the 36th gestational week (Ferber, et al. 1995). In tracé alternans, EEG shows 3-8 second bursts of moderate to high voltage 0.5-3.0 Hz slow waves intermixed with 2-4 Hz sharply contoured waves that are alternated with mixed frequency EEG activity lasting 4-8 seconds (Grigg-Damberger, et al. 2007). HVS, in contrast, is a continuous rhythmic slow activity of 50-150μV and 0.5-4 Hz, which is considered to be a more mature pattern of QS in infants. The relative proportions of tracé alternans and HVS change during the early post-term period from mostly tracé alternans at term age to exclusively HVS by 46 weeks of age (Grigg-Damberger, et al. 2007).

The amount and distribution of REM sleep dramatically changes with increasing age. In premature infants, REM sleep occupies us much as 60-80% of the time spent in sleep, while with increasing age, the amount of REM sleep rapidly declines reaching a pleateau of 25-30% by the age of nine months (Hunt. 2006,Darnall, et al. 2006).

As a physiological state, wakefulness, REM sleep and NREM sleep are different. This is seen especially in the control of breathing. During deep NREM sleep, the breathing is chemodriven, i.e. controlled by blood carbon dioxide and oxygen contents, whereas during wakefulness and REM sleep the respiration is much more state-driven (Dempsey. 2005,Phillipson. 1978). In infants, breathing is more irregular than later in life; this is seen especially in REM sleep (Grigg-Damberger, et al. 2007,Lehtonen, et al. 2004).

2.4.2 Cardiovascular control during sleep

The most extensive evidence of cardiovascular control mechanisms during sleep is from animal studies, especially from studies performed in cats. When compared to wakefulness, in NREM sleep, there is a minor decrease in blood pressure, which is the result of a reduction in cardiac output and a decrease in HR in association with a small decrease in peripheral vasoconstriction. More prominent changes are seen in REM sleep. Cardiac output and HR are significantly decreased, and peripheral vasculature shows vasodilatation. These mechanisms together result in marked hypotension during REM sleep. There are no changes in regional circulation in NREM sleep, but in REM sleep, vasodilatation is evident in the renal and mesenteric beds, whereas vasoconstriction is seen in red tonic muscles. Phasic events, twitches or REMs during REM sleep, are associated with an additional decrease in blood flow to the skeletal muscle circulation, which causes transient increases in BP. (Orem, et al. 1980).

In humans, however, BP levels react somewhat differently to different sleep stages; blood pressure and heart rate levels are at the lowest during deep NREM sleep, whereas BP or HR are higher and generally more variable during REM sleep (Harrington, et al. 2001,Horne, et al. 2010). It is argued that these apparently higher BP and HR levels during REM sleep in humans may result from more frequent and intensive phasic REM bursts compared with cats (Orem, et al. 1980).

In adults, there is a reduction in BP and HR, as well as peripheral vascular resistance, during deep NREM sleep, whereas in REM sleep, transient BP increases are seen associated

with increases in HR and increased sympathetic vasoconstriction in muscle (Somers, et al. 1993). This hypotension, bradycardia, and lower sympathetic nerve activity during NREM sleep suggests a modulation of baroreflex activity during sleep (Somers, et al. 1993).

Cardiovascular control during sleep in infancy has recently been reviewed by Horne et al (Horne, et al. 2010). This review concluded that despite some variability in the findings, most studies have shown lower BP in quiet NREM compared with REM sleep in preterm and term infants during the first six months of corrected age. These state differences in BP have been found both in supine and prone sleeping position. State differences in HR are reported from a few weeks of age onwards in term infants, but in preterm infants, these differences are not seen until 5-6 months of age. Similarly to adults, infants' HR is lower during NREM compared with REM sleep, and shows increased HRV variability in REM sleep compared with quiet NREM.

2.4.3 Arousal

An arousal is a transient wakefulness during the sleep period, and when prolonged, it becomes an awakening. Arousals are a significant part of normal sleep, and, for example, in normal infants, the arousals occur regularly between the changes in sleep stages (Darnall, et al. 2006,International Paediatric Work Group on Arousals. 2005). Furthermore, the arousals from sleep are suggested to be an important protective response during dangerous endogenous or exogenous conditions that restores wakefulness, and thus enables escape from dangerous and potentially even lethal situations (Darnall, et al. 2006). Arousals from sleep are seen as a continuum from spinal to brainstem, and finally to cortical arousals, with habituation especially of cortical arousals (Franco, et al. 2010). However, arousals may be restricted to subcortical levels without cortical activation (McNamara, et al. 1998).

In 2005, the International Pediatric Work Group on Arousals published a consensus-based definition and scoring rules for arousals in infants aged 1-6 months (International Paediatric Work Group on Arousals. 2005). To score an arousal, the event should be preceded by at least 30s of sleep, and there should be at least ten seconds of uninterrupted sleep between the two cortical arousals. A definition of subcortical arousal is met when there is no EEG activation, but ≥ 2 of the following: 1) gross body movement including startles, 2) >10% increase in HR from baseline, 3) in NREM breathing frequency or amplitude changes, including a single augmented breath, and in REM an increase in chin electromyogram (EMG) not associated with sucking. In addition to the above-mentioned criteria, cortical arousal criteria are fulfilled when a sudden shift in EEG activity of a minimum of 1Hz for >3s is seen. Awakening is defined as changes in cortical arousal persisting for >1 min, or cortical arousal followed by wakefulness according to the Anders criteria (Grigg-Damberger, et al. 2007). The Pediatric Task Force, however, in their consensus and review paper, recommended adherence to a 3-second duration of EEG arousal also in infants, and did not include scoring subcortical arousals because of lack of evidence (Grigg-Damberger, et al. 2007).

In addition to different arousal definitions during REM sleep and quiet NREM sleep, arousal thresholds to various stimuli are higher in quiet NREM than in REM sleep, and spontaneous arousals are more frequent in REM compared with NREM (Franco, et al. 2010,Grigg-Damberger, et al. 2007,Harrington, et al. 2001). Arousal responses are associated with a brisk cardiovascular response (Horner. 1996,Trinder, et al. 2003). The BP control during arousal may significantly differ from BP control during sleep as, for example, blood pressure controlling defence areas may be involved (de Burgh Daly. 1997b). However, there are no studies addressing this issue. Nevertheless, these factors underline the importance of controlling the sleep state and subcortical arousals during cardiovascular tests. Inadvertent recruitment of arousal or alert mechanisms during tests can modify cardiovascular responses and mask more subtle variations in the cardiovascular control during sleep.

As arousals are considered an important safety mechanism during sleep, SIDS research has analyzed arousal thresholds in SIDS risk groups. Many SIDS risk factors, such as maternal smoking during pregnancy, overheating, and prone sleeping position are associated with an increased arousal threshold to both spontaneous and induced arousals. In contrast, factors suggested to protect from SIDS are associated with a decreased arousal threshold. Although different methods to induce arousals show some variance in the arousability, the final arousal pathway is suggested to be the same in all types of arousals (Franco, et al. 2010).

2.5 Univentricular heart

2.5.1 Definition and prevalence

Congenital heart diseases (CHD) are found in 0.8% of newborn children (Moons, et al. 2009). A heart condition with single ventricle anatomy is present annually in approximately 15 live-born infants in Finland. Anatomically, there are several structural heart defects behind univentricular heart (UVH), i.e. only one functional ventricle pumping blood to both systemic and pulmonary circulations (Khairy, et al. 2007). Univentricular heart can be functionally subtyped to left and right ventricle conditions, or alternatively, to a condition where both atrioventricular connections are directed to one major ventricle.

During the first years, the functionally univentricular heart is palliated by at least three staged operations that eventually aim to direct the systemic venous return to the pulmonary circulation (Connor, et al. 2007,Khairy, et al. 2007). The initial surgical palliation is modified individually according to the single ventricle anatomy. Sometimes, as in the hypoplastic left heart syndrome (HLHS), the initial approach demands reconstruction of the source for the systemic arterial circulation using the pulmonary valve and the main pulmonary artery to constitute a neo-aorta (Barron, et al. 2009,Khairy, et al. 2007). This Norwood procedure also enables recruitment of the original sub-pulmonary pumping ventricle to supply the neo-aorta. Even though the initial approach needs to be individualized in different forms of the single ventricle anatomy, the aim of the staged Fontan-palliation is to redirect the systemic venous return to flow passively through the pulmonary circulation (Barron, et al. 2009,Khairy, et al. 2007,Stumper. 2010). This entails that the central venous pressure of the patients remains higher than normal.

Hypoplastic left heart syndrome

Hypoplastic left heart syndrome (HLHS) is a single ventricle condition occurring in 0.016-0.036% of all live births (Connor, et al. 2007,Stumper. 2010). Boys seem to have HLHS somewhat more often than girls. Pregnancy is usually uneventful, and the infants with HLHS are normally born at term and have a normal birth weight (Stumper. 2010). No single gene responsible for HLHS has been found, but increased risk for HLHS has been described in over 30 syndromes including the Turner syndrome (Barron, et al. 2009).

In HLHS the aortic arch is hypoplastic due to aortic or mitral valve atresia, or both. Also, the left ventricle does not grow and will not reach the cardiac apex due to the absent shear and volume stress of blood otherwise running through the left-sided heart structures. The systemic venous return will reach the systemic circulation through the right-sided ventricle if the ductus arteriosus remains patent. However, there are slightly different morphological variations to HLHS (Barron, et al. 2009).

Infants with HLHS are usually born full-term and initially appear healthy. When the ductus arteriosus closes, the systemic circulation drastically diminishes causing hypoxemia, acidosis, and shock (Connor, et al. 2007). In order to re-establish peripheral perfusion, an infusion of a prostaglandin analogue must be instituted in order to open and maintain the ductus

arteriosus (Barron, et al. 2009,Stumper. 2010). Before the Norwood operation the infants may also need, at least temporarily, appropriate inotropic and ventilator therapy during resuscitation to maintain adequate minute volume and peripheral perfusion. Accordingly, antenatal diagnosis is extremely useful in planning the optimal delivery of the baby and expedient hemodynamic stabilization (Barron, et al. 2009).

2.5.2 Surgical palliation

Infants with functionally univentricular hearts need surgery during the neonatal period because of ductus arteriosus -dependent systemic circulation. The treatment options are three-staged univentricular palliation (Fontan track) or primary cardiac transplantation (Barron, et al. 2009,Connor, et al. 2007).

The first procedure, the Norwood operation, is performed during the neonatal period in infants with HLHS. In the Norwood operation, the right ventricle is harnessed for the systemic circulation 1) by creating a neo-aorta by augmenting and connecting the hypoplastic aortic arch to the main pulmonary artery after its disconnection from the pulmonary arterial branches, 2) the pulmonary arterial blood flow is maintained by introducing a short tubing, i.e. a shunt, from the systemic circulation (subclavian arteries, aorta or right ventricle) to the confluent main pulmonary branches, and 3) an adequate atrial mixing must be ensured by atrial septectomy (Barron, et al. 2009,Stumper. 2010). The shunts providing the pulmonary circulation may vary. In the modified Blalock-Taussig shunt, a non-valved tubing of Gore-Tex is implanted between the right-sided neck vessel and the right pulmonary artery. In the Sano modification, the shunt is implanted from the right ventricle directly to the pulmonary artery allowing a pulsatile pulmonary perfusion (Barron, et al. 2009,Stumper. 2010). After the Norwood operation, infants suffer from chronic hypoxemia due to free intraventricular mixing of the arterial and venous blood, and the haemoglobin saturations remain around 80% (Barron, et al. 2009).

The second operation, the bi-directional Glenn procedure is performed at 4-6 months of age when pulmonary resistance has decreased (Barron, et al. 2009,Stumper. 2010). A cardiac catheterisation or CT angiography is usually performed before the operation to confirm suitable anatomy and hemodynamic state (Barron, et al. 2009,Stumper. 2010). In the bi-directional Glenn (the cavopulmonary shunt), the superior vena cava is anastomosed to the right pulmonary artery, and at the same time the systemic-to-pulmonary shunt is disconnected. After the operation, blood from the upper body flows passively to the lungs and systemic saturation is usually around 85-90% (Stumper. 2010).

Proceeding to the third and final stage of palliation (total cavopulmonary connection) is individualized according to neurological development, cyanosis, and exercise tolerance, and takes place usually between 2 and 4 years of life (Barron, et al. 2009,Stumper. 2010). In this operation, the inferior vena cava is connected to the pulmonary arteries through an extracardiac conduit. After total cavopulmonary connection, the single ventricle pumps blood into the systemic circulation, and the systemic venous return is propelled through the pulmonary circulation by the central vein pressure and a slight “suction” during filling of the atria. It is of note that the central vein pressure is considerably higher than in the biventricular circulation. In this way, the systemic and pulmonary circulations are now in direct series (Barron, et al. 2009), no mixing of the systemic and pulmonary venous blood occurs, and the SpO_2 returns close to normal (Barron, et al. 2009,Stumper. 2010).

2.5.3 General and neurological outcomes in children with univentricular heart

Despite common antenatal diagnosis and advanced therapy, infants with HLHS still show considerable early mortality of 15%, and survival rates at 1, 5 and 10 years remain around

75%, 65-70%, and 55-65%, respectively (Barron, et al. 2009,Stumper. 2010). Patients with systemic-to-pulmonary shunts for CHD, as are extremely common in the case of the single ventricle palliation path, are another important group of patients recognized to succumb unexpectedly: 33% of autopsies (5 of 15) were non-diagnostic (Fenton, et al. 2003). In addition to the fatal complications, neurological and functional incapacities in patients with a single ventricle are common as outlined below.

At the age of one year, infants with HLHS have lower developmental results (Sarajuuri, et al. 2009,Tabbutt, et al. 2008), and more neurological abnormalities than normal controls (Sarajuuri, et al. 2009). Infants with UVH at one year of age show lower developmental results in gross motor skills than controls, but no differerences in overall development (Sarajuuri, et al. 2009). In the study of Sarajuuri et al. (Sarajuuri, et al. 2009), head growth was slower in UVH infants than controls, but the height and weight gain were normal, suggesting that growth of the brain was reduced. The reason for neurological impairment is not exactly known, but several candidate explanations can be presented, such as brain hypoperfusion during anaesthesia, and sustained hypoxia occurring in these children during the first few years of life. The duration of the cardiopulmonary bypass, the nature of cardiovascular support and the use of hypothermia during surgery did not correlate with neurological outcome (Sarajuuri, et al. 2009,Tabbutt, et al. 2008).

Besides being quite commonly observed postoperatively in infants with a congenital heart disease, mild preoperative ischemic lesions can be found already in preoperative scans of infants with complicated CHD like HLHS (Mahle, et al. 2002). In addition, a systematic review on cognition has demonstrated that congenital heart defects have an adverse effect on cognition, and that the cyanotic nature of the condition further accentuates the difference from normal (Bass, et al. 2004). In a study focusing on children with single ventricle hemodynamics, early childhood (at the mean age of 2.5 years) psychomotor development was delayed in both HLHS and other UVH infants compared with the control infants, whereas mental development was significantly poorer only in HLHS infants (Sarajuuri, et al. 2010). However, at the age of 5-7 years, both HLHS and other UVH patients have an intelligence quotient below the population mean (Sarajuuri, et al. 2007). Consistent with the clinical signs, brain imaging demonstrated ischemic changes, infarcts and atrophy in the majority of patients that underwent the Norwood procedure (Sarajuuri, et al. 2007).

In summary, long-term functional and cognitive results are strongly related to the initial condition at diagnosis, regardless of the chosen surgical approach, staged surgical reconstruction, or heart transplantation (Connor, et al. 2007).

2.5.4 Cardiovascular control in infants with univentricular heart

In general, there are only few studies concerning the blood pressure and heart rate control in UVH children. In a hallmark study by Ohuchi et al. (Ohuchi, et al. 2001), UVH infants and children were shown to have attenuated BP both at rest and during exercise, and their HRV was decreased when compared with control children and young adults

In another study, three-month-old infants with left-to-right shunting and clinical signs of heart failure despite pharmacological therapy showed reduced HRV in all frequency bands (VLF, LF, and HF), but normal total power (TP) and LF/HF ratio compared with healthy control infants. Propranolol treatment normalised HRV, and only VLF power remained reduced when compared to controls (Buchhorn, et al. 2002). Similar findings with decreased HRV and decreased baroreflex sensitivity have been observed in older children and adults after Fontan procedure (Davos, et al. 2003,Ohuchi, et al. 2001). In these children (Ohuchi, et al. 2001), none of the cardiac autonomic nervous activity indices was associated with the age at Fontan operation, the length of follow-up, or the number of operations. This suggests that not only surgery-related damage is associated with impaired cardiac autonomic nervous activity, but also Fontan circulation itself may impair it. Accordingly, impaired cardiac autonomic nervous

activity was suggested to be induced by the following three circumstances: 1) surgery-related direct damage, 2) heart failure, and 3) preoperative hypoxia (Ohuchi, et al. 2001).

2.5.5 Univentricular heart and sleep

Cyanotic CHD infants spend more time awake compared with their peers with healthy hearts or an acyanotic CHD, but otherwise sleep architecture or arousals do not differ between the study groups (Ykeda, et al. 2009). Although SpO_2 during sleep was lower in cyanotic infants, the majority of infants with any CHD showed in excess episodes of apnea and hypopnea with most of the apneas being of central origin. However, some of the detected differences may be explained by the fact that the CHD infants were studied at a mean age of 7 months, and control infants at a mean age of 10 months.

In another study, infants with HLHS showed decreased quiet sleep and increased amounts of indeterminate sleep compared with infants with other, mostly cyanotic, CHD, or control infants without heart defects (Olson, et al. 1989). The infants with HLHS also showed an abnormally discontinuous EEG signal in active and indeterminate sleep. Abnormal sleep characteristics were evident from the day of birth, but the follow-up EEG studies suggested that the amount of quiet sleep increases and indeterminate sleep decreases during advancing postnatal age.

2.6 Prematurity

2.6.1 Definitions and prevalence

A full-term infant is generally considered to be born at 37 weeks of gestation or later. Infants born before that time are thus born preterm. Those born before 32 weeks of GA are regarded as very preterm, and those born before the 28th week of gestation extremely preterm. Birth weight classifications are usually used as low birth weight being < 2500g, very low birth weight < 1500g, and extremely low birth weight < 1000g.

Over 500 000 preterm infants are estimated to be born yearly in the US (Chess, et al. 2006). Ten percent of these have a birth weight under 1500g and 20 000 under 1000g. In Finland, in 2010, 3568 infants were born preterm, which accounts for 5.8% of the total number of 61,191 live births. There were 499 (0.8%) infants born weighing < 1500g, and 221 (0.4%) weighing < 1000g (Official Statistics of Finland. Statistical Report 42/2011. Newborns 2010.).

Premature infants commonly have respiratory problems after birth due to premature lung development, impaired surfactant production and function, and impaired liquid transport in the lungs. Both disrupted lung development and the early surfactant-related lung disease (respiratory distress syndrome) often lead to at least some degree of chronic neonatal lung disease (bronchopulmonary dyplasia, BPD) in extremely preterm infants (Gien, et al. 2011). There are some difficulties in the estimation of the incidence of BPD due to its different definitions. The incidence is reported to range from 77% of infants with birth weight under 1000g and postmenstrual age of under 32 weeks (Chess, et al. 2006) to 30% of infants with birth weight < 1000g and the need for supplemental oxygen at 36 weeks of postmenstrual age (Bhandari, et al. 2006). The smaller birth weight and earlier GA at birth, the greater the risk of developing BPD (Bhandari, et al. 2006), but the severity has decreased with our increasing knowledge of the pathogenesis of BPD and more sophisticated treatment methods.

2.6.2 Bronchopulmonary dysplasia

BPD leads to a chronic neonatal lung disease in premature infants. The classical definition of BPD has been based on 28 days of oxygen therapy combined with radiographic lung changes. The definition of BPD was reviewed in 2000 (Table 6) (Jobe, et al. 2001). According to the new definition, no specific radiographic findings are required.

Table 6. Definition of bronchopulmonary dysplasia (modified from Jobe, et al. 2001)

	GA <32 weeks	**GA >32 weeks**
Time of assessment (TA)	36 weeks of PMA or discharge home, whichever comes first	>28 d but < 56 d of age, or discharge home, whichever comes first
Severity	**Criteria**	
	supplemental oxygen for ≥ 28 d **and**	
Mild	no supplemental oxygen needed (breathing room air) at TA	
Moderate	need for < 30% oxygen at TA	
Severe	need for ≥ 30% oxygen and/or nasal CPAP or positive-pressure ventilation at TA	

Definition and abbreviations: CPAP = continuous positive airway pressure; d = days; GA = gestational age; PMA = postmenstrual age.

Its pathogenesis is not fully understood, but BPD is considered to be mainly caused by the immature lungs of the preterm infant, impaired vascular development, and damage caused by mechanical ventilation. Infections, both pre- and postpartum, may also cause severe lung damage. Nutritional and inflammatory factors, hypoxia, patent ductus arteriosus, and supplemental oxygen may also contribute to the damage. The structure of premature lungs shows decreased alveolization and impaired vascular development. In severe PBD, there is also pulmonary hypertension and abnormal vascular development (Jobe, et al. 2001). Risk factors for BPD include prematurity (especially under 30 weeks of postconceptional age), mechanical ventilation, oxygen therapy, and respiratory distress syndrome of the infant. Colonization of the chorioamnion and the amniotic fluid, and neonatal infections increase the risk of BPD, as does patent ductus arteriosus. (Chess, et al. 2006,Gien, et al. 2011,Jobe, et al. 2001)

As infants with BPD suffer from apneas and repeated, intermittent hypoxic episodes, they are treated with supplemental oxygen and with ventilatory assistance including nasal CPAP, noninvasive positive-pressure ventilation, and invasive mechanical ventilation. An effort is made to avoid volutrauma. If oxygen and ventilation therapy are insufficient, corticosteroids, fluid restriction, diuretics, or methylxantines may be added to therapy. Inhaled nitric oxide has been used to decrease pulmonary vascular resistance and to increase pulmonary blood flow to prevent shunting. As undernutrition is related to increased risk of oxidant-induced lung injury, adequate nutrition, with the emphasis on protein intake, is considered important in preventing BPD. Many infants with BPD develop obstructive pulmonary disease later in life (Gien, et al. 2011,Jobe, et al. 2001,Schulzke, et al. 2010).

2.6.3 General effects of prematurity

Infants born prematurely are faced with many medical problems already early in life, the earlier GA at birth, generally the more numerous and more severe the possible sequelae; the most common being periventricular leucomalacia and intraventricular hemorrhage, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, and neurodevelopmental deficits. During recent years, an increasing understanding has also accumulated on the long-term consequences of prematurity, although most of the data are concentrated on the most extremely young or low birth weight part of the preterm population (Doyle, et al. 2010,Hack. 2009). These adverse effects of prematurity include hypertension, adverse

metabolic profile, altered growth, neurocongitive problems, and increased amount of respiratory illnesses (Doyle, et al. 2010,Hack. 2009,Hovi, et al. 2007,Hovi, et al. 2010).

2.6.4 Effects of prematurity on cardiovascular control

Close to term age, preterm infants show higher resting HR (Cohen, et al. 2007). From 2-4 weeks of age, the HR levels are similar at comparable postconceptional weeks to those of full-term infants up to six months of age (Witcombe, et al. 2008). Overall, HR decreases with increasing age.

During the neonatal period, both SBP and diastolic blood pressure (DBP) are positively correlated with gestational age (Georgieff, et al. 1996,Northern Neonatal Nursing Initiative. 1999). BP levels show a tendency to increase with increasing age up the to postconceptional age of 44-48 weeks, after which BP levels reach a stabile plateau (Northern Neonatal Nursing Initiative. 1999,Rankova. 1989). Compared with full-term infants, BP levels are lower in the preterm group (Rankova. 1989,Witcombe, et al. 2008).

The cardiovascular responses to the head-up tilt test in preterm infants have been described in detail in section 2.3.2 (especially Tables 3 and 5).

2.6.5 Prematurity and sleep

There are only limited data concerning sleep stage maturation and organization of sleep in preterm infants. Sleep organization is already well-defined after 27 weeks of GA with a clear sleep-wake pattern, sleep cycles, and behavioral sleep states (Curzi-Dascalova, et al. 1993,Stephan-Blanchard, et al. 2008). However, as the cortical EEG activity is highly immature, a large proportion of their sleep is considered as indeterminate sleep with a difficulty to define the sleep stage. The amount of intermediate sleep decreases with increasing PMA (Darnall, et al. 2006). Late preterm infants spend most of their time – that is 60-80% - of total sleep time in REM sleep, whereas in full-term infants, this amount has decreased to around 50% (Hunt. 2006,Darnall, et al. 2006). The amount of quiet NREM sleep increases from 32 GA onwards (Darnall, et al. 2006). In addition to changes in absolute amounts of AS and QS, when the sleep architecture of preterm infants is compared with that of term infants, preterm infants present with more trace alternans, less low-voltage irregular sleep (type of AS), and fewer arousals (Scher, et al. 1992).

2.6.6 Prematurity and breathing

Control of breathing is somewhat different in newborn infants than later in life. Most of the differences arise from different sleep state architecture, such as the high percentage of REM sleep (Darnall, et al. 2006). The control of breathing is highly dependent on the sleep stage (Dempsey. 2005,Phillipson. 1978) and unlike in NREM, the breathing in REM is not chemodriven. The premature infants show decreased ventilatory response to CO_2, which makes them susceptible to periodic breathing and the appearance of regular central apneas in NREM sleep (Darnall, et al. 2006). This periodicity of breathing is effectively treated with respiratory stimulants such as caffeine and theophylline (Henderson-Smart, et al. 2010a,Henderson-Smart, et al. 2010b,Henderson-Smart, et al. 2010c). Recurrent apneas, especially during REM sleep, lead to marked intermittent hypoxia in very premature infants (Henderson-Smart, et al. 2010a,Henderson-Smart, et al. 2010b,Poets, et al. 1994,Schmidt, et al. 2006,Schmidt, et al. 2007). The apnea of prematurity usually resolves at 37-40 weeks of postconceptional age (Darnall, et al. 2006,Poets, et al. 1994).

2.6.7 Brain development in preterm infants

Neurological abnormalities – cerebral palsy, attention-deficit/hyperactivity disorder, visual and hearing impairments – are relatively common in preterm infants (Korvenranta, et al. 2009). In general, lower GA at birth is associated with increased morbidity.

Most of the human brain growth occurs during the first and second trimester of gestation, but the major neuronal brain development continues well beyond term age with continuing myelination, and generally progresses from a caudal to a rostral pattern (Darnall, et al. 2006). The developing brain is vulnerable to hypoxic insults and these hypoxic insults are considered to be the most important factor causing adverse effects on brain function in preterms (Rees, et al. 2005).

Hypoxia and brain damage in preterm infants

The brain damage of preterm infants is suggested to be mediated by distinct pathways, although the primary causes may differ. One pathway is suggested to be ischemic, where apoptosis is seen as a result of ischemia, although this model does not explain the site-specific brain damage of preterm infants compared with term infants or adults. The another pathway is suggested to be inflammatory where brain damage and preterm birth are caused by microbial infection of fetal membranes and secondary inflammatory response of mother and fetus, cytokines acting as inflammatory mediators. There may well also be an interplay of these pathways (Arpino, et al. 2005).

Hypoxic-ischemic events cause regionally different brain damage according to the maturity of the infant. In term infants, hypoxia-ischemia has caused neuronal damage in the hippocampus, cerebellar Purkinje neurons, and deep cerebellar cortex. In preterm infants, the damage is preferentially localized to cerebral white matter seen as periventricular leucomalacia (PVL). PVL consists of focal cystic infarcts adjacent to lateral ventricles and more diffuse gliosis in cerebral white matter (Rees, et al. 2005).

MRI studies of brain damage in preterm infants at term have found somewhat contradictory results. Studies of preterm infants without brain injury showed no decrease in gray matter volume, and a moderate or no decrease in white matter volumes when compared at term age with full-term control infants (Mewes, et al. 2006,Zacharia, et al. 2006). In studies that included preterm infants with intrauterine growth restriction and brain damage, cerebral cortical and deep nuclear gray matter volumes were found to be reduced; this reduction was related to cerebral white matter injury, GA or intrauterine growth restriction (Inder, et al. 2005,Thompson, et al. 2007). In addition, the brain volumes of BPD infants have been shown to be globally reduced in comparison with full-term infants (Thompson, et al. 2007).

Brainstem

Preterm infants with BPD show impared auditory brainstem responses at the postconceptional age of 37-42 weeks compared with term infants of a similar age. The brainstem auditory-evoked click-rate responses in BPD infants were impaired, and this was suggested by the authors to be caused by delayed myelination and impaired synaptic transmission (Wilkinson, et al. 2007).

Cerebellum

MRI studies of the cerebellum show rapid growth during the last trimester, faster than in cerebral hemispheres from GA 28 week to term age (Limperopoulos, et al. 2005). The analysis of cerebellar volume has given contradictory results, with evidence of a smaller cerebellum in ex-preterm infants at term (Limperopoulos, et al. 2005) and with evidence of no difference in the volume of the cerebellum between preterm infants at term and term infants (Shah, et al. 2006). White matter injury is associated with reduction in cerebellar volume (Limperopoulos, et al. 2005,Shah, et al. 2006).

2.7 Effects of maternal smoking during pregnancy

2.7.1 Prevalence of maternal smoking during pregnancy

The prevalence of maternal smoking during pregnancy varies according to the classification method, e.g. whether only those who smoked during the whole pregnancy or those who smoked at any stage of the pregnancy are counted. In Finland, according to the medical birth register of The National Institute for Health and Welfare (Official Statistics of Finland. Statistical Report 42/2011. Newborns 2010.), 14.3-16.7% of pregnant women reported smoking during pregnancy in 1992-2010, and 9.8-14.9% reported smoking after the first trimester (Figure 3). Especially the percentage of women continuing smoking after the first trimester has fallen during recent years (Figure 3). This decline in prevalence of maternal smoking during pregnancy is similar to reports from Sweden, Denmark, and the United States (Cnattingius. 2004).

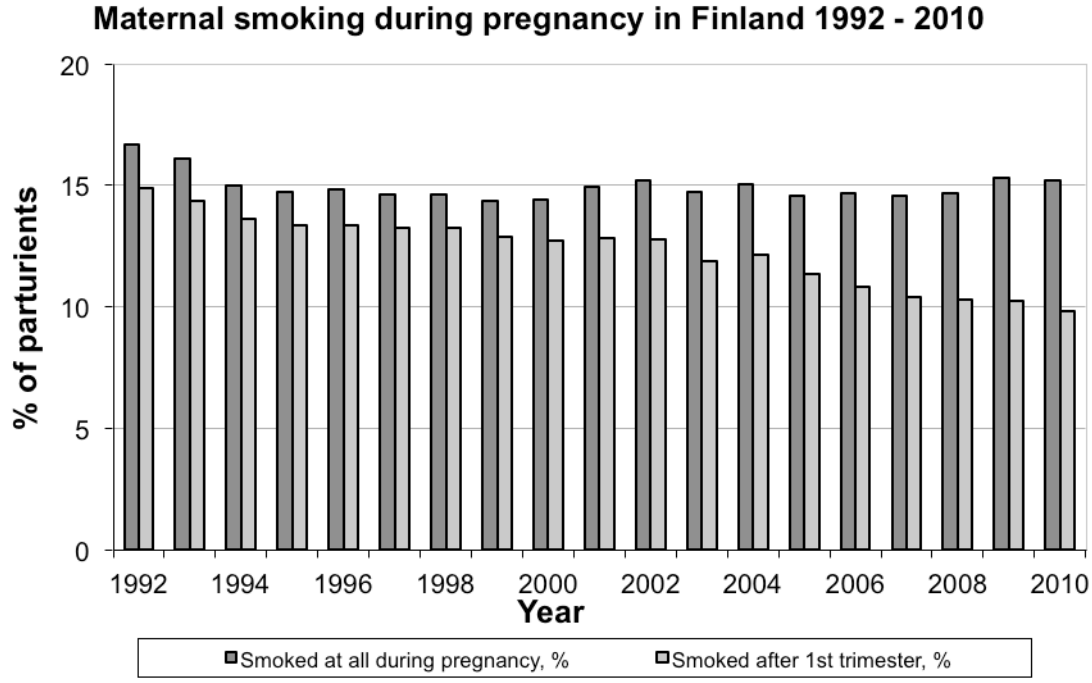

Figure 3. Maternal smoking during pregnancy in Finland 1992 – 2010 (Official Statistics of Finland. Statistical Report 42/2011. Newborns 2010.).

2.7.2 Reporting of smoking

Russell and co-workers have reviewed different ways to evaluate maternal smoking during pregnancy (Russell, et al. 2004). 1) Self-reports are a cheap and easy way to assess smoking, but they are subject to deception bias if the subjects are unwilling to reveal the information. Recall bias is also a potential problem, although Kesmodel (Kesmodel, et al. 1999) reported that retrospective data collection is reliable up to three years. 2) Cotinine is a metabolite of nicotine, with a circulatory half-life of 12-18 hours. Cotinine is currently considered as a most reliable measure of daily tobacco consumption. However, the method is expensive. It is possible to measure the cotinine levels from plasma, saliva or urine. 3) Carbon monoxide (CO) is absorbed into the blood circulation from inhaled gas while smoking. The measurement of carbon monoxide can be made from expired-air CO or carboxyhemoglobin. Expired CO is a cheap and reliable measure of tobacco consumption, but its short half-life of only 2-5 hours restricts its use in the assessment of long-term tobacco exposure. 4) A longer plasma half-life of 10-14 days is reported for thiocyanate. Thiocyanate is a metabolite of

hydrogen cyanide which is released when smoking tobacco. Evaluation of the thiocyanate content of body fluids (serum, urine or saliva) is an easy and relatively cheap method, but the results are confounded by certain foods affecting the thiocyanate levels (nuts, beer, and green leafy vegetables).

Several studies have evaluated the reporting of maternal smoking during pregnancy with conflicting results. The conclusion of some studies from the US, the UK and Sweden was that self-reported smoking status is reliable when obtained by interview or questionnaire. In these studies, self-reports were compared to cotinine level measurements (George, et al. 2006,Klebanoff, et al. 1998,Peacock, et al. 1998) or exhaled carbion monoxide levels (Christensen, et al. 2004). Other studies carried out in these same countries and one review (Boyd, et al. 1998,Lindqvist, et al. 2002,Owen, et al. 2001,Russell, et al. 2004), however, found that mothers significantly underreported smoking status during pregnancy; the misclassification rate ranged from 3% to 26%. The misclassification usually, however, is to underreport smoking status and not vice versa. The studies on smoking prevalence rely on biochemical markers with differing cut-off levels to group study subjects into smokers and non-smokers, and the self-reported smoking status is compared to the levels of this marker. The detection of a biochemical marker may also lead to a false positive finding in a non-smoking mother if there is high exposure to environmental tobacco smoke.

2.7.3 Nicotine and carbon monoxide

The harmful effects of maternal smoking during pregnancy have been attributed mostly to nicotine, while many other factors may also be important (Slotkin. 2004). Tobacco smoke contains hundreds of known harmful chemicals, and smoking also causes increased circulatory carboxyhemoglobin levels causing hypoxia (Longo. 1977).

Nicotine crosses the placenta and it is found in the fetus at 15% higher concentrations compared with maternal nicotine levels (Lambers, et al. 1996). Cotinine levels in the fetus are 88% of that of the mother (Lambers, et al. 1996). The effect of nicotine on the offspring has been studied by giving nicotine to pregnant animals in injections, infusions via osmotic minipumps and nicotine pellets resembling nicotine patches in humans (Slotkin. 1998). A method most closely resembling human cigarette smoking that has been used is a nose-only cigarette smoke exposure in rodents (Hasan, et al. 2001).

Nicotine directly stimulates acetylcholine receptors located in the autonomic ganglion, adrenal medulla and neuromuscular junctions which release vasoactive catecholamines and peptides (Lambers, et al. 1996). Prenatal exposure to nicotine in experimental animals causes upregulation of nicotinic cholinergic receptor binding sites (Navarro, et al. 1989,Slotkin. 1998). General effects on the brain include a premature switch from cell replication to differentiation (Slotkin. 1998), increased cell loss, inhibited cell division, and alterations in neural activity and signaling mechanisms (Slotkin. 1998,Slotkin. 2004). Thus, nicotine has been regarded as a fetal neuroteratogen (Slotkin. 2004). Even in doses that do not affect fetal growth, prenatal nicotine causes delays in cell maturation, decreased cell number in the cerebellum, and impairment of development of peripheral noradrenergic projections in rats (Navarro, et al. 1989). Prenatal nicotine in rats is also associated with increases in dying neurons and decreases in surviving cells in the hippocampus area CA1 (Abdel-Rahman, et al. 2005). The effects of prenatal nicotine on the cerebellum include a decrease in Purkinje cell numbers, and an increase in glial fibrillary acidic protein immunostaining (Abdel-Rahman, et al. 2005). However, another study failed to find any differences in the number or the size of Purkinje cells, granule cells, or hippocampal pyramidal cells in adult rats, exposed to pre- and perinatal nicotine (Chen, et al. 2006). Prenatal exposure to cigarette smoke reduces the immunoactivity of certain protein kinase C isoforms and neuronal nitric oxide synthase in rat pups' brainstem (Hasan, et al. 2001). Protein kinase C isoforms and nitric oxide synthase are known to participate in the maintenance of ventilatory

responses, especially during hypoxia. The effects of nicotine on cardiorespiratory function are extensively reviewed by Hafström (Hafstrom, et al. 2005). This review, concludes that in animals, prenatal nicotine alters ventilatory responses to hypoxia, impairs hypoxic arousal responses and sympathetic activation, and impairs autoresuscitation mechanisms.

Cigarette smoking increases carboxyhemoglobin levels in the blood. Smoking 1-2 packs of cigarettes per day is reported to result in carboxyhemoglobin levels of 5-10% in the blood (Longo. 1976). Fetal carboxyhemoglobin concentrations are reported to range from 10 to 15 percent higher compared with maternal carboxyhemoglobin concentrations. Because carboxyhemoglobin displaces oxygen from the hemoglobin and shifts the oxyhemoglobin saturation curve to the left, it impairs the oxygenation of tissues, thus contributing to the hypoxemia. This is exaggerated in the fetal tissues, where the oxygen dissociation curve is already shifted to the left and the oxygen tensions are lower compared with adult tissues (Longo. 1976). Thus, maternal smoking during pregnancy is presumed to lead to increased hypoxemia in the fetus (Longo. 1977). In fact, in pregnant animals, exposure to CO leads to decreased fetal partial oxygen pressures (Longo. 1976) as well as decreases in birth weight, and increases in neonatal mortality (Longo. 1977).

2.7.4 General effects of maternal smoking during pregnancy

Maternal smoking during pregnancy is associated with increased infant mortality, preterm birth, premature rupture of membranes, placenta previa, and abruptio placenta (Andres, et al. 2000). Smokers have heavier placentas, and their placentas contain more lesions characteristic of placental underperfusion (Naeye. 1978). Effects of maternal smoking during pregnancy are well documented on fetal growth: it results in growth restriction (Andres, et al. 2000,DiFranza, et al. 2004,Peacock, et al. 1998,Wang, et al. 1997), and smaller birth weight (Andres, et al. 2000,Cornelius, et al. 2000,Naeye. 1978), as well as smaller head circumference (Cornelius, et al. 2000,DiFranza, et al. 2004) compared with infants without smoke-exposure. Maternal smoking during pregnancy alters fetal enzyme activity and protein metabolism both at 12-17 weeks of pregnancy (Jauniaux, et al. 1999), and at term (Jauniaux, et al. 2001).

Neonates of smoking mothers have nicotine withdrawal symptoms (Godding, et al. 2004,Law, et al. 2003) and hypertonicity (Huizink, et al. 2006,Law, et al. 2003), increased excitability (Law, et al. 2003), and increased tremors (Huizink, et al. 2006).

Maternal smoking during pregnancy is associated with increased childhood morbidity (Cnattingius. 2004), congenital heart defects (Malik, et al. 2008), and mortality (Andres, et al. 2000,Cnattingius. 2004). There are reports of an increased amount of behavioral disturbances (Williams, et al. 1998), and attention deficit hyperactivity disorder, as well as other externalizing behavioral problems (Cornelius, et al. 2000,Huizink, et al. 2006). The findings on cognitive function are contradictory (Cornelius, et al. 2000,DiFranza, et al. 2004,Huizink, et al. 2006), but no effect on intelligence quotient has been noted when maternal intelligence quotient and education are taken into account (Batty, et al. 2006,Breslau, et al. 2005).

Environmental tobacco smoke

Environmental tobacco smoke is associated with smaller birthweight (Cornelius, et al. 2000), increased susceptibility to respiratory (Cornelius, et al. 2000,Strachan, et al. 1997) and ear infections (DiFranza, et al. 2004), a higher prevalence of and more severe asthma (Cornelius, et al. 2000,Strachan, et al. 1998), and a general adverse effect on pulmonary function (DiFranza, et al. 2004). The risk of SIDS is reported to be increased in infants exposed to environmental tobacco smoke (Cornelius, et al. 2000,DiFranza, et al. 2004).

2.7.5 Maternal smoking during pregnancy and brain development

Kinney et al. (Kinney, et al. 1993) have described how ^{3}H-nicotine binding changes during gestation in the fetal brainstem. They found that ^{3}H-nicotine binding was high in tegmental nuclei

important to cardiopulmonary integration, arousal, attention, REM sleep, and somatic motor control. The binding decreased during the last half of gestation. In major cerebellar-relay nuclei (principal inferior olive and griseum pontis) no decrease in the binding was seen. Similar findings were observed in the study of SIDS and other infants of American Indians who had suddenly died, as ^{3}H-nicotine binding was found to decrease with increasing age postnatally (Duncan, et al. 2008). The same group (Nachmanoff, et al. 1998) examined ^{3}H-nicotine binding in brainstems of SIDS victims. No difference was found between SIDS victims, acute controls and chronic controls with oxygenation disorders. However, in SIDS infants exposed to maternal cigarette smoking during pregnancy, there was no expected upregulation of nicotinic receptor binding in three nuclei that are related to arousal and cardiorespiratory control. The upregulation of brain nicotinic receptors has been shown after nicotine exposure in rodents (Marks, et al. 1983,Schwartz, et al. 1983) and in humans after cigarette smoking (Benwell, et al. 1988). Also prenatal exposure to nicotine causes upregulation of nicotinic cholinergic receptor binding sites (Slotkin. 1998), even in small doses that do not affect growth (Navarro, et al. 1989).

A recent report by the same study group (Duncan, et al. 2008), found that in American Indian infants, the nicotinic receptor binding was reduced in controls exposed to maternal smoking as opposed to the increase in binding in a study by Nachmanoff et al. (Nachmanoff, et al. 1998). The reduced binding was not seen in SIDS infants. In smoke-exposed first-trimester human fetuses, the expression of both nicotinic and muscarinic acetylcholine receptors was altered in the brainstem and cerebellum (Falk, et al. 2005). Maternal smoking was associated with reduced serotonin receptor binding in the arcuate nucleus in SIDS infants (Kinney, et al. 2003).

In addition to changes in specific nicotine binding in the brainstem, there is evidence of changes in many other aspects of brain structure and function in SIDS infants exposed to maternal smoking. The amount of brainstem gliosis in SIDS victims correlates with the number of cigarettes mother smoked during pregnancy (Storm, et al. 1999), and there is a significant correlation between maternal smoking during pregnancy and cerebellar alterations (Lavezzi, et al. 2006). Matturri and co-workers (Matturri, et al. 2006) found several anomalies in SIDS infants, including hypodevelopment of arcuate and hypoglossus nuclei, increased gliosis in the brainstem, alterations in the cerebellar cortex, somatostatin-positive nucleus hypoglossus revealing a delayed maturation of its neurons, and tyrosine hydroxylase negativity in the locus coeruleus, indicating decreased catecholamine synthesis. When several risk factors for SIDS were correlated with the observed brainstem alterations, the findings correlated only to maternal smoking during pregnancy. Smoking during pregnancy was almost always present in SIDS infants with brainstem alterations.

In sudden perinatal and infant death, tyrosine hydroxylase, the enzyme responsible for the biosynthesis of noradrenaline and adrenaline, expression was low, and there was significant correlation between maternal smoking during pregnancy and negativity of tyrosine hydroxylase staining (Lavezzi, et al. 2005). The authors suggested that a fall in the tyrosine hydroxylase is associated with brain hypoxia following smoke exposure.

2.7.6 Effects of maternal smoking during pregnancy on child's cardiovascular state

Table 7 describes how maternal smoking during pregnancy affects the cardiovascular state of the fetuses, newborn, infants and children. Maternal smoking during pregnancy increases fetal HR, decreases fetal HRV, and diminishes the amount of fetal movements (Kelly, et al. 1984,Lindblad, et al. 1988,Pijpers, et al. 1984,Sindberg Eriksen, et al. 1984). Most effects are presumed to be caused by nicotine, as smoking non-nicotine cigarettes caused only small changes in maternal and fetal parameters (Kelly, et al. 1984). Fetal aortic and umbilical vein diameter and blood flow have mostly been observed to increase after the mother has smoked (Lindblad, et al. 1988,Pijpers, et al.

1984,Sindberg Eriksen, et al. 1984). At least some of the variability in the findings may result from differences in the actual nicotine levels (Lindblad, et al. 1988).

After birth, infants exposed to maternal smoking during pregnancy have lower epinephrine concentrations in the umbilical arterial blood compared with infants from non-smoking families (Oncken, et al. 2003), and their umbilical arteries contain lower amounts of prostacyclin and precursors of NO which are known to be mediators of vasodilatation (Ulm, et al. 1995).

The baseline HR and HRV in antenatally smoke-exposed infants are similar to those of non-exposed infants from birth until 2-3 months of age (Browne, et al. 2000,Cohen, et al. 2008,Cohen, et al. 2010,Galland, et al. 2000a), although one study reported lower HF variability of HRV only in REM sleep in antenatally smoke-exposed infants at 2-3 months of age (Franco, et al. 2000). At one year of age, baseline HR is reported to be lower in infants whose mothers smoked during the pregnancy (Cohen, et al. 2010).

Baseline BP levels are found to be either similar or higher up to six years of age in smoke-exposed infants compared with infants whose mothers have not smoked during pregnancy (Beratis, et al. 1996,Blake, et al. 2000,Browne, et al. 2000,Cohen, et al. 2008,Cohen, et al. 2010,Morley, et al. 1995). In one study, higher BP levels in antenatally smoke-exposed children significantly correlated with the number of cigarettes the mother had smoked during the pregnancy (Beratis, et al. 1996).

Similarly to baseline variables, HR and HRV responses to a head-up tilt in antenatally smoke-exposed infants have been found to be mostly similar to those of non-exposed infants, although at 2-3 months and at one year of age, one group has reported a more prominent tachycardic response to the tilt test (Browne, et al. 2000,Cohen, et al. 2008,Cohen, et al. 2010,Galland, et al. 2000a). Findings on BP responses to a tilt in infants exposed to maternal smoking during pregnancy are even more variable (Browne, et al. 2000,Cohen, et al. 2008,Cohen, et al. 2010).

Table 7. Effects of maternal smoking during pregnancy on child's cardiovascular state

Fetus		
HR	↑	(Kelly, et al. 1984,Lindblad, et al. 1988,Pijpers, et al. 1984,Sindberg Eriksen, et al. 1984)
HRV	↓	(Kelly, et al. 1984)
Movements	↓	(Kelly, et al. 1984)
Blood flow		
Fetal aorta	↔	(Pijpers, et al. 1984)
	↑	(Lindblad, et al. 1988,Sindberg Eriksen, et al. 1984)
Umbilical vein	↑	(Lindblad, et al. 1988,Sindberg Eriksen, et al. 1984)
Vessel diameter		
Fetal aorta	↔	(Pijpers, et al. 1984)
	↑	(Sindberg Eriksen, et al. 1984)
Fetal umbilical vein	↑	(Sindberg Eriksen, et al. 1984)
Intervillous blood flow	↓	(Lehtovirta, et al. 1978)
Newborn (0-1 month)		
Umbilical arterial blood concentrations of		
Epinephrine	↓	(Oncken, et al. 2003)
Prostacyclin	↓	(Ulm, et al. 1995)
Precursors of nitric oxide	↓	(Ulm, et al. 1995)
Baseline		
BP	↑	(Beratis, et al. 1996,Browne, et al. 2000)
	↔	(Cohen, et al. 2008,Cohen, et al. 2010)
HR	↔	(Browne, et al. 2000,Cohen, et al. 2008,Cohen, et al. 2010,Galland, et al. 2000a)
HRV	↔	(Galland, et al. 2000a)
Response to a head-up tit		
BP	↑	(Cohen, et al. 2008)
	↔	(Cohen, et al. 2010)
SBP / DBP	↓/↔	(Browne, et al. 2000)

HR	↔	(Browne, et al. 2000,Cohen, et al. 2008,Cohen, et al. 2010,Galland, et al. 2000a)
HRV	↔	(Browne, et al. 2000)
Infant at 2-3 months of age		
Baseline		
SBP	↑	(Browne, et al. 2000)
	↔	(Cohen, et al. 2010)
DBP	↑	(Cohen, et al. 2010)
HR	↔	(Browne, et al. 2000,Cohen, et al. 2010,Franco, et al. 2000,Galland, et al. 2000a)
HRV	↔	(Galland, et al. 2000a)
HF in REM	↓	(Franco, et al. 2000)
Response to a head-up tilt		
BP	↑	(Cohen, et al. 2010)
SBP/DBP	↓/↔	(Browne, et al. 2000)
HR	↔	(Browne, et al. 2000,Galland, et al. 2000a)
	↑	(Cohen, et al. 2010)
HRV	↔	(Browne, et al. 2000)
Infant at 1 year of age		
Baseline		
BP	↔	(Cohen, et al. 2010)
	↑	(Beratis, et al. 1996)
HR	↓	(Cohen, et al. 2010)
Response to a head-up tilt		
BP	↔	(Cohen, et al. 2010)
HR	↑	(Cohen, et al. 2010)
Childhood		
BP at 2 years of age	↔	(Beratis, et al. 1996)
SBP at 6 years of age	↑	(Blake, et al. 2000)
BP at 7.5-8 years of age		
ex-preterm with GA <33 wk	↓	(Morley, et al. 1995)
ex-preterm with GA ≥33 wk	↑	(Morley, et al. 1995)

Definition and abbreviations: ↑ = an increase; ↓ = a decrease; ↔ = no difference. In fetuses, the arrows describe the actual responses. In newborns, infants, and children the arrows describe the response type of the infants exposed to maternal smoking during pregnancy compared with non-exposed infants.

2.7.7 Effects of maternal smoking during pregnancy on sleeping parameters of infants

Maternal smoking during pregnancy has not been found to have a significant effect on sleep structure in term infants. No differences have been found between antenatally smoke-exposed and non-exposed infants in total sleep time, awake time, sleep efficiency, duration, or amount of different sleep stages (Chang, et al. 2003,Franco, et al. 1999,Horne, et al. 2002,Kahn, et al. 1994). Nor have differences been found in SpO_2 levels in REM and NREM sleep (Chang, et al. 2003,Franco, et al. 2000). One study reported higher respiratory rates in smoke-exposed infants during QS at 2-3 months of age (Horne, et al. 2002), but this finding has not been confirmed (Franco, et al. 2000).

Two studies have evaluated sleep parameters in preterm infants exposed to maternal smoking during pregnancy close to term-equivalent age (Sawnani, et al. 2004,Stephan-Blanchard, et al. 2008). The findings are conflicting. In the earlier study by Sawnani et al. (Sawnani, et al. 2004), smoke-exposed infants showed normal sleep structure. However, more recently, Stephan-Blanchard et al. (Stephan-Blanchard, et al. 2008) found more wakefulness after sleep onset and more active sleep in prenatally smoke-exposed preterm infants compared with non-exposed preterm infants.

3 AIMS OF THE STUDY

The aim of this study was to evaluate acute cardiovascular control in infants with SIDS risk factors. The rationale for this study was based on the hypothesis that infants succumbing to SIDS may have impaired vestibulo-mediated cardiovascular control. According to animal studies, this controlling mechanism is vital during life-threatening situations and cardiovascular shock. It was postulated that hypoxia could be responsible for the possible defect.

The baroreflex and vestibulo-mediated cardiovascular control, heart rate response to spontaneous arousals, and heart rate variability during NREM sleep were tested in infants with

- chronic hypoxia (I)
- bronchopulmonary dysplasia, previous intermittent hypoxic episodes and increased risk for SIDS (II)
- intrauterine tobacco smoke exposure with possible intrauterine hypoxia and increased risk for SIDS (III)
- premature infants at the gestational age of 34-39 weeks (IV)

4 SUBJECTS AND METHODS

4.1 Study subjects

For this thesis, we performed cardiovascular tests during polysomnographically confirmed sleep in altogether 70 infants. This group comprised control term infants (n=20), and infants with previous hypoxic episodes or prematurity with the following risk factors for sudden infant death: univentricular heart (UVH, n=9, I), bronchopulmonary dysplasia (BPD, n=10, II), exposure to maternal smoking during pregnancy (n=11, III) or prematurity (n=20, IV) (Table 8). Twenty preterm infants were studied close to term age before discharge from hospital (IV), and the other 50 infants were studied at a (corrected) age of 2 – 4 months (I-III). All the infants were studied in the Children's Hospital, Helsinki University Central Hospital.

Table 8. General demographic data of all the study infants

	Control	UVH	BPD	Smoke	Preterm
n	20	9	10	11	20
GA (weeks)	39.8 ± 1.1	39.6 ± 1.5	26.8 ± 2.4	40.9 ± 1.4	30.9 ± 2.4
Birth weight (g)	3444 ± 324	3298 ± 439	936 ± 241	3508 ± 400	1480 ± 482
Birth height (cm)	50 ± 1.6	49 ± 2.1	35 ± 3.2	50 ± 1.8	39 ± 4.0
Apgar (1/5/10 min)	8.9/9.9/10	NA	4.4/NA/NA	8.6/9.9/10	6.5/8.0/9.2
Umbilical pH	7.25 ± 0.06	NA	NA	7.26 ± 0.06	7.25 ± 0.08
PMA at the time of the study (weeks)	52.1 ± 3.6	51.1 ± 1.4	51.4 ± 4.1	52.8 ± 3.2	35.9 ± 1.5
PNA at the time of the study (weeks)	12.4 ± 3.4	11.9 ± 1.8	24.6 ± 4.7 corr. age 11.4 ± 4.0	12.0 ± 2.1	4.9 ± 3.5 corr age -4.1 ± 1.5
Study weight (g)	5912 ± 940	4969 ± 527	4541 ± 388	5573 ± 987	2101 ± 300
Study height (cm)	60 ± 3.2	58 ± 2.5	56 ± 2.8	59 ± 3.5	44 ± 2.1

Definition and abbreviations: Values are means ± SD. BPD = bronchopulmonary dysplasia; corr. age = corrected age; GA = gestational age; NA = not available; PMA = postmenstrual age; PNA = postnatal age; preterm = preterm infants studied near term; smoke = smoke-exposed infants; UVH = univentricular heart.

4.1.1 Study age 2 – 4 months (I-IV)

Twenty full-term, healthy infants with uneventful medical history were studied at the mean age of 12 ± 3.4 weeks as control infants for all four studies. Apart from over-the-counter medication for constipation, no medication was used, and the infants' growth was within normal limits (Haschke, et al. 2000). These infants were from non-smoking families and they were recruited from the maternity hospitals of Helsinki and Uusimaa in Helsinki by means of a written form. Interested parents contacted the researchers.

Infants with univentricular heart (I)

Nine infants with univentricular heart were born full-term and studied at the mean age of 12 ± 1.8 weeks. All UVH infants were hypoxic with SpO_2 baseline levels between 77 and 91%, and all but one UVH infant had pulmonary circulation that was dependent on a Blalock-Taussig shunt. One UVH infant was small for date (UVH infant no 9), and the other eight UVH infants were appropriate for gestational age. At the time of the study, one UVH infant weighed less than expected from normal data and two had mild muscle hypotonia. The growth and neurological development of the others was within normal limits. Eight infants used aspirin and diuretics. Table 9 presents additional demographic data on these infants. The families of these infants were contacted prior to cathetrization and asked if they would be

interested in participating in the study; the study was planned for the night before cathetrization. One or two researchers met the parents before the study and reviewed the study protocol.

Table 9. Demographic data of infants with univentricular heart.

No	Sex	Diagnosis	Surgery performed	Age at surgery (d)	Mean SpO_2 (%)	BP (mmHg)	Medication at the time of the study
1	F	DIVL, TGA, HAA, CoA	Norwood I	10	85.7	79/33 (50)	ASA, furosemide
2	M	HLHS, LSVC	Norwood I	6	78.0	78/43 (63)	ASA, furosemide, spironolactone, digoxin
3	M	DILV, TGA, HAA, CoA, VSD	Norwood I	14	78.5	95/54 (66)	ASA, furosemide, spironolactone
4	F	TGA, RV hypoplasia, VSD, HAA, CoA, dextrocardia, LSVC	Pulmonary artery banding, CoA correction	2	76.5	106/58 (80)	none
5	F	HLHS	Norwood I	7	77.2	74/48 (61)	ASA, furosemide, enalapril
6	F	AVSD, PA, MA, common atrium, dextrocardia, right isomerism	BT-shunt	2	85.5	76/40 (63)	ASA, furosemide, sotalol
7	M	HLHS	Norwood I	7	82.9	90/41 (64)	ASA, furosemide, spironolactone
8	M	HLHS	Norwood I	14	81.3	89/43 (62)	ASA, furosemide, spironolactone, digoxin
9	F	DORV, LV-hypoplasia, AVSD, PS, TAPVD, PDA, right isomerism, common atrium, asplenia	BT-shunt, correction of TAPVD	21	90.6	104/65 (84)	ASA, furosemide, spironolactone

Definition and abbreviations: Blood pressure values are presented as systolic/diastolic (mean). Medication other than vitamin, iron or electrolyte supplement is presented. ASA = aspirin 15-25 mg x 1; BP = blood pressure at the time of the study; BT-shunt = Blalock-Taussig shunt; CoA = coarctation of the aorta; DILV = double inlet left ventricle; DORV = double outlet right ventricle; HAA = hypoplastic aortic arch; HLHS = hypoplastic left heart syndrome; LV = left ventricle; LSVC = left superior vena cava; MA = mitral atresia; PA = pulmonary atresia; RV = right ventricle. SpO_2 = arterial oxyhemoglobin saturation at the time of the study

Infants with bronchopulmonary dysplasia (II)

Ten preterm infants with the diagnosis of BPD (Jobe, et al. 2001) and frequent desaturations despite intensive critical care and ventilation therapy were identified when the infant was in the children's ward in the Children's Hospital, Helsinki University Central Hospital. When the infant was at 1 to 2 months of corrected age, the mother was contacted and the study was presented in oral and written form. These infants were studied at a mean corrected age of 11 ± 4.0 weeks. Table 10 presents detailed demographic data of these BPD infants.

Table 10. Demographic data of infants with bronchopulmonary dysplasia.

No	Sex	GA (wk)	Birth weight (g)	Corr. age at study (wk)	Study weight (g)	Surf (n)	Vent (d)	CPAP (d)	O_2 PMA	IVH (R/L)	PVL (+/-)	NEC (+/-)	Sepsis (n)	Medication at the time of the study
1	M	29+0	1350	9.0	4970	6	17	43	56	-/-	-	-	0	O_2 0.1l/min
2	F	25+5	820	7.9	4250	2	58	29	41	-/-	+	-	3	HCT, spironolact., lansoprazole
3	M	25+4	900	11.4	4940	2	32	4	35	2/3	+	+	1	-
4	F	24+6	590	19.4	4760	2	83	27	42	2/2	-	-	1	salbutamol
5	F	24+5	810	10.9	5110	2	29	30	35	2/2	-	-	1	-
6	M	29+2	990	10.6	4030	4	10	26	37	-/-	-	-	1	-
7	F	28+6	1120	17.3	4480	3	17	29	38	-/-	-	-	1	-
8	M	27+2	910	6.7	4180	1	25	27	37	1/1	-	-	2	-
9	F	30+0	1220	11.4	4550	2	6	27	38	-/-	-	-	1	-
10	M	23+0	650	9.3	4140	2	84	100	>60	1/1	+	-	2	nCPAP+ O_2, HCT, spironolact., salbutamol, cisapride

Definition and abbreviations: Medication other than vitamin, iron or electrolyte supplement is presented. BPD = bronchopulmonary dysplasia; Corr. age = corrected age; nCPAP = nasal continuous positive airway pressure; d = days; g = grams; GA = gestational age; HCT = hydrochlorothiatzide; IVH = intraventricular hemorrhagia; L = left; NEC = necrotizing enterocolitis; PVL = periventricular leucomalacia; PMA = postmenstrual age; R = right; spironolact. = spironolactone; Surf = surfactant (Curosurf®, Chiesi, Parma, Italy); Vent = ventilatory support; O_2 = oxygen supply.

Infants exposed to maternal smoking during pregnancy

Eleven full-term infants with exposure to maternal cigarette smoking during pregnancy were recruited from the Women's Hospital and Kätilöopisto maternity hospital. To be included in this study, smoking mothers were required to have smoked at least 5 cigarettes/day for >2/3 of pregnancy, but in practice, all of the recruited mothers smoked at least 10 cigarettes/day. The initial criterion of smoking status was retrieved from the maternity charts of the mother, and the smoking status before, during and after the pregnancy was confirmed from the mother at the time of the study. Suitable families were identified in the hospital, and the study protocol was introduced to them in written form. When the infant was 1 to 2 months of age, the researcher contacted the mother and inquired about her willingness to participate in the study. These infants exposed to maternal smoking during pregnancy were studied at a mean age of 12 ± 2.1 weeks. They were healthy and no prescription drugs were used. Demographic data are presented in Table 8 and parental smoking data are shown in Table 11.

Table 11. Parental smoking of smoke-exposed infants

Type of exposure	Smoked cigarettes/d, mean ± (range)
Maternal smoking before pregnancy	20 ± 2 (10-30)
Maternal smoking during pregnancy	13 ± 3 (10-20)
Maternal smoking after pregnancy	14 ± 3 (10-25)
Paternal smoking	10 ± 9 (0-20)

4.1.2 Study age close to term age (IV)

Twenty preterm infants near term age were recruited while in Kätilöopisto maternity hospital neonatal ward due to prematurity. The researcher presented the study to parents in oral and

written form and if they were interested in participating in the study, the study was planned as close to term age as possible while still in hospital, but no earlier than 34 weeks of PMA. Five infants suffered from BPD (Jobe, et al. 2001) and five were exposed to maternal cigarette smoking during pregnancy. The study was carried out at a mean PMA of 36 ± 1.5 weeks. Detailed demographic data are presented in Table 12.

Table 12. Demographics of the preterm infants studied at PMA of 34-39 weeks

No	Sex	GA (wk)	Birth weight (g)	Study PMA (wk)	Study weight (g)	Surf (n)	Vent (d)	CPAP (d)	O_2 PMA	BPD (+/-)	Sepsis (n)	M. sm (+/-)	Theo (+/-)	Medication at the time of the study
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+0	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+0	2395	0	0	3	32+1	-	0	+	+	
9	F	27+3	770	38+3	2310	3	6	38	41+1	+	0	+	+	HCT, spironolactone, O_2 0.2-0.4l/min
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, O_2 0.2l/min
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, O_2 0.1l/min
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+0	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	-	-	

Definition and abbreviations: Medication other than vitamin, iron or electrolyte supplement is presented. One preterm infant had intraventricular hemorrhages which resolved spontaneously on both sides (subject no 9), with a normal MRI at term age. Additional one had on MRI at term age a suspicion of mild periventricular leukomalacia and a small hypodensic area possibly resulting from a small hemorrhagic insult (subject no 14). BPD = bronchopulmonary dysplasia; CPAP = continuous positive airway pressure; F = female; GA = gestational age; HCT = hydrochlorothiatzide; M = male; M. sm = maternal smoking during pregnancy; PMA = postmenstrual age; Surf = surfactant (Curosurf®, Chiesi, Parma, Italy); Theo = has received theophylline; Vent = ventilatory support; O_2 = oxygen supply

4.2 Study protocol

Control infants (I-IV), smoke-exposed infants (III) and preterm infants with BPD (II) at 2-4 months of age were studied during their normal night time sleep in a sleep laboratory at the Children's Hospital, Helsinki University Central Hospital. The infant and his/her parent

arrived between 6 p.m. and 7 p.m. when the recording electrodes were attached. When the infant fell asleep according to his/her daily routine – usually between 8 p.m. and 11 p.m. – the polysomnographic recording was started. The recording was finished when all the tests were performed or in the morning when the infant woke up. One or both parents accompanied the infant during the study.

Infants with univentricular heart (I) were studied in the pediatric cardiac ward when they came for the cardiac catheterization procedure as a preparation for the stage-two operation (bidirectional Glenn, in preparation for Fontan circulation) for univentricular heart. These infants were studied the night before the cardiac catheterization procedure as they spend this night in the hospital. The study protocol was the same as described above but the parent did not always stay with the infant during the study.

Preterm infants near term age (IV) were studied in the Kätilöopisto maternity hospital neonatal ward during a nap, mostly in the evening. After the recording electrodes were attached, the polysomnographic recording was started when the infant fell asleep, which was usually after feeding. The recording was finished when the tests had been performed. These recordings were shorter in duration than other recordings because of the nap study design, as these infants were mainly asleep with little time awake without a strong circadian rhythm. Because of this, together with the short sleep cycles, not all the recordings of these infants had enough data for the heart rate variability analysis, or spontaneous arousals. Some parents stayed with the infant during the study.

The infant was sleeping on a custom-made canvas sheet with rigid frames, which was placed on top of the normal hospital bed for infants.

4.2.1 Linear side motion test

In quiet NREM sleep, before the beginning of the test period, the mat was manually lifted up from the bed in a horizontal position. After a steady period of 1-2 minutes a back-and-forth movement with a radius of 0.5 meters was performed for 3-5 seconds. The side movement was performed in a rocking manner to avoid abrupt changes in direction of the movement, which could arouse the infant. Test onset and finish were marked with an electronic event marker. After the side motion test there was another steady period of at least 1-2 minutes before the infant was lowered back on to the bed. The infant stayed in a horizontal position during the whole test. Infants were closely observed for any signs of arousal such as a sigh or movement of a hand. Those tests with a subcortical arousal (McNamara, et al. 1998) were marked and tests were performed until no arousal was noted. Tests with a cortical arousal were terminated when the arousal occured and excluded from the study. There was at least one minute of quiet sleep between the subsequent tests. After the side motion tests in a supine position were completed, the same tests were performed in a prone position (for 11 controls and all UVH infants). Apart from the sleeping position of the infant, the study protocol was the same between the supine and prone tests.

4.2.2 Head-up tilt test

In quiet NREM sleep, the infant was manually tilted head-up during 2-3 seconds to a 45° angle and held in that position for 45 seconds, after which the infant was lowered back to a horizontal position. Care was taken to keep the blood pressure cuff at heart level during the tilt. An electrical event marker was used to mark the beginning and the end of the tests. Inspection for arousals took place as previously described, and cortical arousals were excluded. Tilt tests in a prone position (for 11 controls and all UVH infants) were performed after the supine tests were accomplished. The protocol for the prone did not differ from the supine tilt tests.

4.3 Methodology

The core of the study protocol was the basic polysomnographic recording, and continuous non-invasive BP monitoring (Figure 4). The study equipment included a PC enabling real-time data observation and preliminary sleep staging for the tests. The used electrodes were noninvasive, and did not seem to disturb the infants – except the nasal airflow measurement in some infants.

During the study, all the infants slept at first in a supine position, which was their accustomed sleeping position. After the tests in a supine position, all UVH infants and 11 control infants were turned into a prone position, and the tests were repeated. None was accustomed to sleeping in a prone position. No invasive monitoring methods were used, and no blood samples were taken. The purpose was to let the infants sleep as normally as possible and not to disturb their sleep despite the tests.

4.3.1 Electrocardiogram

The electrocardiogram (ECG) was evaluated from the lead II position: one on the cardiac apex in the mid-clavicular/-axial line on the left and the other just below the right clavicula on the right. Electrodes were disposable. From ECG, heart rate and possible arrhytmias were assessed, and it served as a basis for calculations of heart rate variability.

4.3.2 Blood pressure measurement

In addition to the polysomnographic recording, blood pressure was measured noninvasively during the tests in the beginning using a Finometer (Finapres Medical Systems, Amsterdam, Netherlands), which was updated to a Finapres (Finapres Medical Systems, Amsterdam, Netherlands) in 2005. Both use the volume-clamp method of Penãz to measure continuous blood pressure, and they enable beat-to-beat evaluation of blood pressure. A modified adult XL-sized finger cuff was wrapped around the wrist of the infant after he/she had fallen asleep, but the measurement was not started until the infant was in quiet NREM sleep and the tests were about to begin. Care was taken to keep the cuff at heart level during the tests. The servo adjustment was turned off for the test periods and the blood pressure measurement was turned off when the tests were finished, the infant woke up, or the sleep stage changed to REM sleep.

4.3.3 Other polysomnographic measurements

The electroencephalogram (EEG) included two channels for the scoring of the sleep stages. Of these, C_3/A_2 depicts central and O_2/A_1 occipital activation. For C_3 and O_2, standard multi-use electrodes with small metallic cups were used. The electrodes were placed according to the international 10-20 system: C_3 on the central vertex, 20% on the left side and O_2 on the occipital vertex, 5% from the occipital protuberance. These cups were filled with conductance paste and attached to cleaned skin with water-soluble paste and gauze. For A_1 and A_2, positioned on the left and right mastoids, respectively, flat disposable electrodes were used that attach firmly to the skin but are easy to remove.

Two electro-oculograms were recorded to evaluate eye movements during sleep. One disposable electrode was placed obliquely up from the lateral canthus of the right eye (right elecro-oculogram, EOG-R) and the other obliquely down from the lateral canthus of the left eye (left electro-oculogram, EOG-L). A_2 was used as a reference electrode for both EOG-R and EOG-L. The electro-oculogram measures potential differences and changes between positive cornea and negative retina (Grigg-Damberger, et al. 2007). When two channels are in use, eye movements are seen as sharp deflections either towards or away from each other.

Chin electromyogram (EMG_{chin}) measures genioglossus muscle tone activity and thus helps in the scoring of different sleep stages. Two disposable electrodes were placed underneath the chin, about 1cm apart.

The diaphragm electromyogram (EMG_{diaphr}) records diaphragmatic muscle tone, thus helping to evaluate respiratory effort. Two disposable electrodes were used, one placed just below the sternum and the other on the right clavicular midline at the same level.

Breathing movements (thoracic respiratory motion) were transmitted via a stretch-sensitive piezo-electric sensor belt wrapped around the infant's lower chest or upper abdomen.

A single-use nasal cannula was selected according to the size of the infant's nostrils, and nasal airflow was recorded using a warming pneumotachometer (RSSHR 3500, Hans Rudolph, Missouri, USA). The other end of the tube from the capnometer (Capnomac Ultima ULT-SVI, Datex, Helsinki, Finland) to measure end-tidal carbon dioxide ($EtCO_2$) was attached to the nasal cannula at the base of the nasal end. The curvature or height of the nasal airflow curve was not changed by this procedure. The size of the cannulae was chosen according to the size of the infant's nostrils and they were initially placed on every study infant, but removed if clinically evident that the infant was disturbed by them. $EtCO_2$ was not measured for the preterm infants near term age.

Arterial oxyhemoglobin saturation (SpO_2) was measured using a non-invasive pulse oximeter (Biox 3800e, Ohmeda, Boulder, CO, USA) attached to either foot. Preterm infants requiring a SpO_2 recording for clinical reasons, had a separate pulse oximeter with alarm function placed on the other foot.

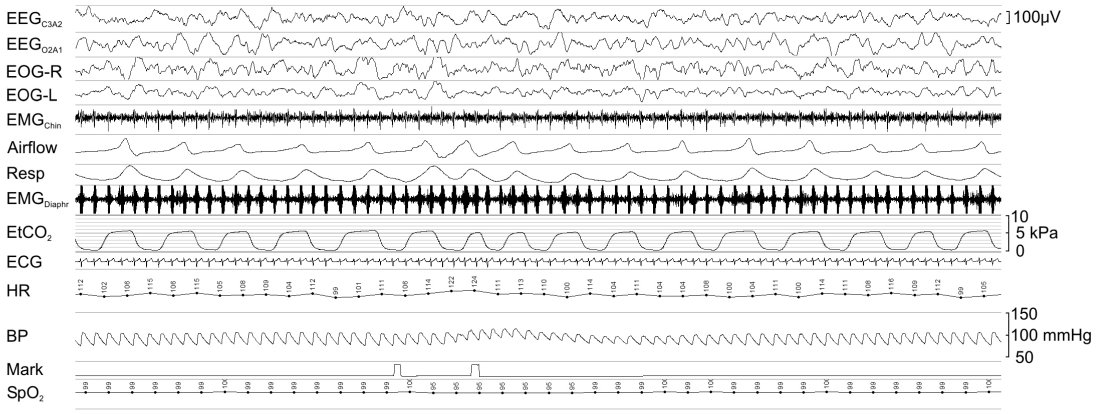

Figure 4. An example of polygraphic recording during the side motion test. The onset and end of the side motion test are indicated by the mark signal. BP = blood pressure (Finapres/Finometer); ECG = electrocardiogram; EEG = electroencephalogram; EMG = electromyogram; EOG-L = left electro-oculogram; EOG-R = right electro-oculogram; $EtCO_2$ = end-tidal carbon dioxide content of the breathing air; HR = heart rate; Resp = respiratory movements; SpO_2 = pulse oximeter arterial oxyhemoglobin saturation. The amplitudes of EEG, electro-oculogram, EtCO2 and BP signals are shown with a scale bar.

4.4 Data analysis

In the beginning (Study I), the sleep study was recorded with the Amlab (Amlab Technology Pty Ltd., Sydney, Australia), which was updated to the Siesta (Compumedics, Abbotsford,

Australia) polygraphic system with 16-bit amplitude resolution in 2005 (Studies II-IV). Sampling frequency was for ECG and EMG 200 Hz in the Amlab and 512 Hz in the Siesta. The SpO_2 signal was collected at 1 Hz and other signals at 100 Hz in the Amlab and at 128 Hz in the Siesta. In addition to real-time data on the computer screen, all the data were stored. The data were converted to the European Data Format and then analyzed with Somnologica sleep polygraph software (Medcare, Reykjavik, Iceland) and special purpose software.

4.4.1 Polysomnographic measures

First, the sleep was manually staged according to the criteria of Guilleminault and Soquet (Guilleminault, et al. 1982) and the Pediatric Task Force of the American Academy of Sleep Medicine (Grigg-Damberger, et al. 2007) in 30-second epochs. If airflow data were recorded, central, mixed and obstructive apneas were scored, otherwise apnea was evaluated from the respiratory belt and EMG_{diaphr} as absence of breathing movements. Apnea was determined as a respiratory pause of two or more respiratory cycles. Central apnea was scored when there was simultaneously absence of airflow and respiratory movements (lack of breathing activity in the respiratory belt and EMG_{diaphr}) when the infant was sleeping. When respiratory movements were seen on the respiratory belt and EMG_{diaphr}, but no airflow was present, apnea was classified as obstructive. Mixed apnea showed both types of apnea components during the same cessation of airflow. Desaturations were marked when they did not coincide with arousal (possible movement artefact).

All the test data were visually inspected to exclude artifacts and to evaluate whether the quality of the original data was sufficient for the analysis. Using the special purpose software, the ECG R-peak, systolic and diastolic blood pressure values during the tests were manually identified from the raw data. All the signals were analyzed at the original sampling rate.

4.4.2 Heart rate change to spontaneous arousal

To assess general cardiac reactivity (Trinder, et al. 2003), heart rate response for spontaneous arousal from NREM sleep was determined by selecting a spontaneous arousal lasting at least 15 seconds and determined by chin EMG activation and body movements. ECG R-peaks were manually identified with the help of special purpose software. The heart rate 20 seconds before the arousal was calculated as the baseline and the slope of change (beats/min/min) in heart rate during the first 10 seconds of arousal was calculated.

4.4.3 Heart rate variability

Frequent alternation of heart rate from breathing and signals from the autonomic nervous system (heart rate variability, HRV) were analyzed in 2-min segments by a Somnologica software HRV analyzer. This software uses an oversampling technique to interpolate the original sampling rate (200 Hz or 512 Hz) up to ten times to increase accuracy. The following frequency bands were selected according to the current literature for infant HRV analysis (Kirjavainen, et al. 2004,Rosenstock, et al. 1999): 0.04-0.15 Hz (low-frequency variability), 0.15-1.0 Hz (high-frequency variability), and 0.003-1.0 Hz (total power). Logarithmic transformation (log10) was used to normalize the distribution.

4.4.4 Baroreflex sensitivity (I)

We tried to assess baroreflex sensitivity in all the UVH infants and 11 control infants noninvasively by selecting a spontaneous increase in SBP together with a decrease in HR or vice versa (Drouin, et al. 1997b). In this analysis, changes in SBP ranging from 10 to 20% are compared with simultaneous, opposite changes in HR, with the analysis period being at least 10 cardiac cycles long. Beat-to-beat values of RR intervals are then plotted against SPB

values of the preceding cardiac cycle, and analyzed with linear regression. This analysis was not performed for other study groups because no events fulfilling these criteria were found for the UVH or 11 control infants during quiet NREM sleep.

4.4.5 Arterial oxyhemoglobin saturation (II)

For BPD infants, an intensive care monitoring system (Agilent Technologies and Clinisoft, Anandic Medical Systems, Diessenhofen, Switzerland) automatically collected SpO_2 during the stay in the neonatal intensive care unit (Figure 5). Data were collected every two minutes.

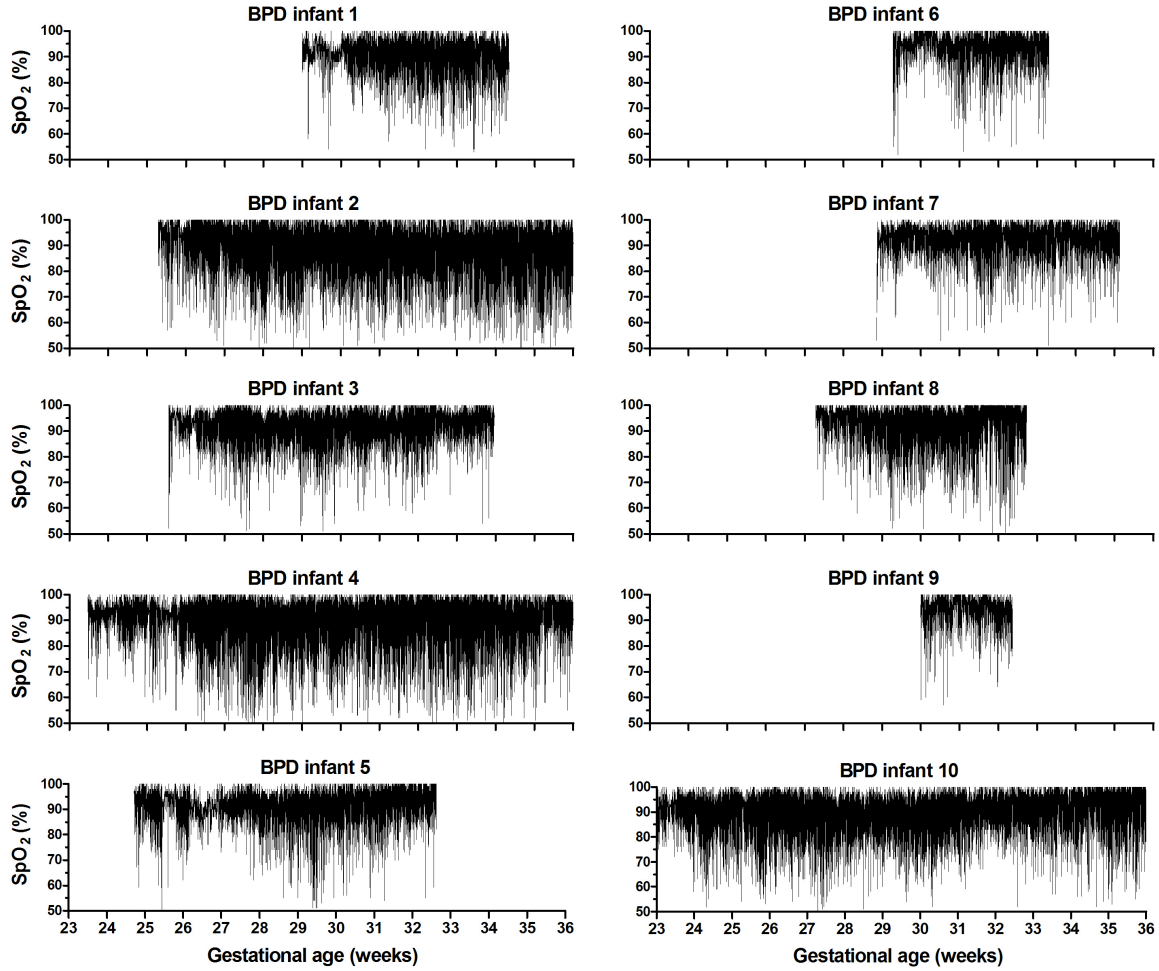

Figure 5. Arterial oxyhemoglobin saturations (SpO_2) of infants with bronchopulmonary dysplasia (BPD). One sample every 2 minutes from the beginning of the treatment in the neonatal intensive care unit.

4.5 Statistical analyses

All the data are given as mean ± standard deviation, SD, (range), unless otherwise specified. For the statistical analysis, BP and HR data were divided into four time intervals: baseline (20-5 s preceding the test), immediate (0-5 s from the test onset), early (10-15 s from the test onset) and late response (25-40 s from either onset of side motion or the end of the tilt test). The two-way repeated measures analysis of variance (ANOVA) general linear model was

used to analyze the differences between study groups. If the assumption of sphericity was not met (Mauchly's test), Huynh-Feldt correction was adopted. When the overall repeated-measures ANOVA showed a significant difference, post hoc tests were conducted to determine the specific time point of difference. Sidak's multiple comparison correction was used for within-subject effects.

Demographic data, HR variability and HR reactivity were compared using Student's T-test. Linear correlation was used in studies II and IV to evaluate the correlation between demographic features and test responses.

Statistical analyses were performed with the Statistical Software Package for Social Sciences, software versions from 11.0 to 15.0 for Windows (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

4.6 Ethical considerations

The parents received oral and written information about the study and written informed consent was obtained from the parents. Participation in the study was on a volunteer basis and possible participation did not affect the medical care of the infant unless the study revealed information that was of medical importance. In that case the attending physician was orally informed about the condition (no research data were available to clinicians). The Ethics Review Committee of the Hospital for Children and Adolescents of the Helsinki University Central Hospital, Helsinki, Finland, had approved the study protocol. The parents were not paid to participate in the study, but the families were covered for the extra travel expenses to the hospital and back home during the night. The purpose was to let the infant sleep as undisturbed as possible. There were no invasive measurements. Cessation of the study took place on the request of the parent or if the well-being of the infant was compromised.

5 RESULTS

5.1 Polysomnographic findings

5.1.1 Recording time, total sleep time and sleep stages

Table 13 presents descriptive sleep data from the recordings. Recording time and total sleep time were longer in control and UVH infants, as for them the tests were performed in both supine and prone positions. Proportions of different sleep stages (N1-2, N3, REM) were, however, similar among all infants studied at 2-4 months of age. Preterm infants have significantly shorter recording time and total sleep time, as well as a higher percentage of quiet sleep, because for them the study was performed as a nap study, and the recording was mostly not started until quiet sleep was seen on the online recording. In addition, in preterm infants, the mean recording time was only marginally longer than one hour, (64 ± 41 minutes, range 19 – 166), thus apparent differences in sleep stage distribution are unreliable.

Table 13. Recording time, sleep time, sleep stage distribution, and SpO_2 data

	RecT (min)	**TST (min)**	**N1-2 (%)**	**N3 (%)**	**REM (%)**	**SpO_2 (%)**
Control	221 ± 108 (88-498)	176 ± 86 (75-383)	30 ± 8.6 (16-46)	46 ± 9.2 (28-64)	25 ± 7.7 (9-39)	98 ± 0.8 (96-99)
UVH	156 ± 100 (35-394)	124 ± 57 (35-232)	24 ± 13 (3-45)	47 ± 12 (25-63)	28 ± 9.6 (5-38)	82 ± 4.8 (77-91)*
BPD	134 ± 32 (57-170)*	109 ± 30 (54-141)*	26 ± 10 (12-44)	49 ± 10 (33-69)	25 ± 11 (6-39)	98 ± 1.0 (96-99)
Smoke	145 ± 54 (56-249)*	114 ± 37 (53-194)*	34 ± 15 (13-61)	40 ± 11 (17-54)	27 ± 9.0 (16-42)	99 ± 0.7 (97-100)
Preterm	64 ± 41 (19-166)*	46 ± 20 (19-86)*	14 ± 9.0 (0-35)*	71 ± 20 (0-35)*	15 ± 17 (0-62)*	97 ± 2.3 (92-99)*

Definition and abbreviations: BPD = infants with bronchopulmonary dysplasia; Control = control infants; Preterm = preterm infants near term age; RecT = recording time; REM = rapid eye movement; N1-2 = non-rapid eye movement sleep stages 1-2; N3 = non-rapid eye movement sleep stage 3; Smoke = infants exposed to maternal smoking during pregnancy; SpO_2 = arterial oxyhemoglobin saturation; TST = total sleep time; UVH = infants with univentricular heart; values are means ± SD (range); *$p < 0.05$ (comparisons made to control infants)

Arterial oxyhemoglobin saturation (SpO_2)

SpO_2 was within normal range in all but UVH infants, although in preterm infants SpO_2 was slightly lower compared with control infants ($p = 0.004$). UVH infants were clearly hypoxemic at the time of the study; their SpO_2 was 82 ± 4.8 (77 – 91) % ($p < 0.0001$).

5.1.2 Test characteristics

The number of both side motion and tilt tests needed to achieve a test without arousal varied greatly. This resulted in high variability in the number of tests performed per studied infant (Table 14). The percentage of tests that resulted in subcortical or cortical arousal varied

considerably among the studied infants, but there were no significant differences between the study groups. In one control infant supine, and in two UVH infants prone, all tilt tests resulted in arousal. Prone tests were successfully performed in eight control infants. When prone, the side motion test was successfully performed in six, and the tilt test in five UVH infants.

Table 14. Cardiovascular tests

Position	Group	tilt tests (n)	side motion tests (n)	arousals from tilt (%)	arousals from side motion (%)
Supine					
	Control	6 ± 4 (2-18)	7 ± 4 (3-19)	60 ± 25 (0-100)	48 ± 28 (0-86)
	UVH	5 ± 2 (3-9)	4 ± 2 (2-7)*	49 ± 21 (25-89)	39 ± 22 (0-83)
	BPD	5 ± 2 (3-7)	9 ± 2 (4-15)	44 ± 27 (0-75)	49 ± 25 (20-93)
	Smoke	3 ± 1 (2-7)	7 ± 2 (4-12)	44 ± 21 (0-75)	45 ± 27 (0-83)
	Preterm	4 ± 2 (1-7)	6 ± 3 (3-14)	55 ± 24 (0-86)	50 ±30 (0-86)
Prone					
	Control	4 ± 2 (1-9)	3 ± 2 (0-6)	60 ± 27 (0-89)	33 ± 24 (0-67)
	UVH	7 ± 2 (5-9)	5 ± 3 (3-10)	86 ± 15 (60-100)	47 ± 26 (0-67)

Definition and abbreviations: BPD = infants with bronchopulmonary dysplasia; Control = control infants; Preterm = preterm infants near term age; Smoke = infants exposed to maternal smoking during pregnancy; UVH = infants with univentricular heart; values are means ± SD (range); *$p < 0.05$ (comparisons made to control infants)

5.2 Linear side motion test – supine position

Figures 6-8 present cardiovascular responses to the linear side motion test in a supine position for all study infants. Figure 6 shows systolic blood pressure (SBP), Figure 7 diastolic blood pressure (DBP), and Figure 8 heart rate (HR) responses.

Control infants showed biphasic BP responses with an initial increase followed by a decrease below baseline levels and normalization. Heart rate showed a similar initial increase as BP, but it returned close to baseline already 10-15 seconds after the test.

UVH infants presented with flat initial BP responses to the side motion test, and their HR response was attenuated compared with the control infants. For this thesis, a new statistical analysis was performed using a total of 20 control infants, but the overall significance of the results did not change considerably (that is, no new significant differences emerged and no old differences lost significance) (Viskari-Lähdeoja et al., unpublished results). The inter-subject variability in the responses of UVH infants did not differ significantly from the control infants (group mean; HR $p = 0.22$, SBP $p = 0.41$, DBP $p = 0.66$) (Viskari-Lähdeoja et al., unpublished results).

BP responses of BPD infants as a group did not differ from those of the control infants to the side motion test. From the individual curves it is evident, however, that half of the BPD infants had mild or absent initial BP response followed by a considerable BP decrease. The amount of BP deviation from the control or group mean at 10-15 seconds from the test onset did not correlate with GA, estimated amount of hypoxic exposure based on desaturations while in the neonatal invasive care unit, number of events with SpO_2 <85%, ventilator time, CPAP support or supplementary oxygen, drugs used, or intraventricular hemorrhage, PVL, necrotizing enterocolitis, or sepsis during the neonatal period. Although the HR response was biphasic in BPD infants similarly to control infants, it was smaller in magnitude in BPD infants. Furthermore, inter-subject variability of BP, but not HR, was significantly higher in BPD infants compared with control infants (group mean; SBP $p < 0.0001$, DBP $p < 0001$, HR $p = 0.13$).

Smoke-exposed infants showed initially flat BP responses to the side motion test. The following dip in both BP values was more pronounced and prolonged for up to 25-40 seconds after the test. Also the initial HR increase was smaller in smoke-exposed infants compared with control infants. The inter-subject variability did not differ significantly from the control infants (group mean; HR $p = 0.73$, SBP $p = 0.38$, DBP $p = 0.23$).

Preterm infants near term presented with initially flat BP levels after the onset of the test, but SBP levels showed a slight decrease 25-40 seconds after the test. An attenuated HR response was also seen in preterm infants near term compared with control infants. Infants with a diagnosis of BPD, exposure to maternal smoking during pregnancy, or current theophylline treatment had responses to the side motion test similar to those of other preterm infants. Neither HR nor BP responses showed a correlation with GA at birth. PMA at the time of the study showed only a weak association with post-SBP levels (adjusted R square 0.22, $p=0.02$). The inter-subject variability did not differ between the groups (group mean; HR $p = 0.98$, SBP $p = 0.37$, DBP $p = 0.28$).

LINEAR SIDE MOTION TEST SUPINE – SYSTOLIC BLOOD PRESSURE

	baseline 20-5s before test onset	initial 0-5s from test onset	early 10-15s from test onset	late 25-40s from test onset
Control	0	2.2 ± 1.5	-2.4 ± 2.4	-0.5 ± 1.7
UVH	0	-1.0 ± 2.1*	-1.5 ± 1.8	-0.8 ± 1.9
BPD	0	0.0 ± 2.0	-5.8 ± 6.6	-2.1 ± 2.5
Smoke	0	0.6 ± 1.6*	-5.6 ± 3.4*	-3.8 ± 2.3*
Preterm	0	0.0 ± 2.7*	0.2 ± 2.8*	-2.3 ± 2.6*

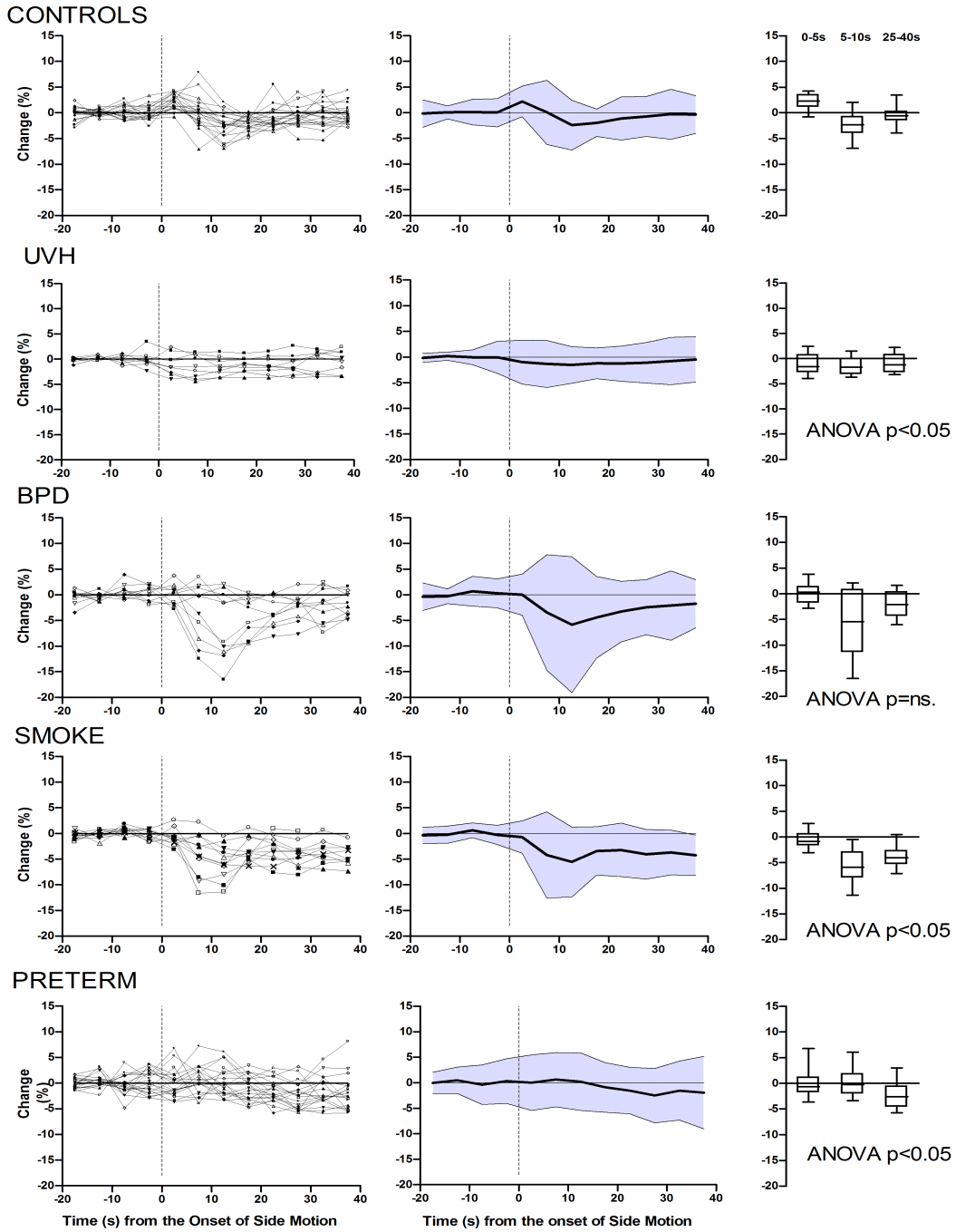

Figure 6. Systolic blood pressure responses (% from baseline) to the supine side motion test. At the top, table with average group responses. * p<0.05 for pairwise comparisons to control infants when ANOVA showed significant group differences. For each study group, individual curves are in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA compared to control infants. ns.= non-significant

LINEAR SIDE MOTION TEST SUPINE – DIASTOLIC BLOOD PRESSURE

	baseline 20-5s before test onset	initial 0-5s from test onset	early 10-15s from test onset	late 25-40s from test onset
Control	0	5.3 ± 2.7	-1.9 ± 2.5	0.6 ± 2.3
UVH	0	-0.8 ± 2.6*	-2.0 ± 2.4	-1.1 ± 2.9
BPD	0	2.1 ± 2.4	-4.0 ± 6.0	-1.1 ± 2.4
Smoke	0	1.3 ± 1.4*	-4.0 ± 2.2*	-2.7 ± 1.3*
Preterm	0	0.7 ± 3.9*	-0.1 ± 3.7	-1.3 ± 4.1

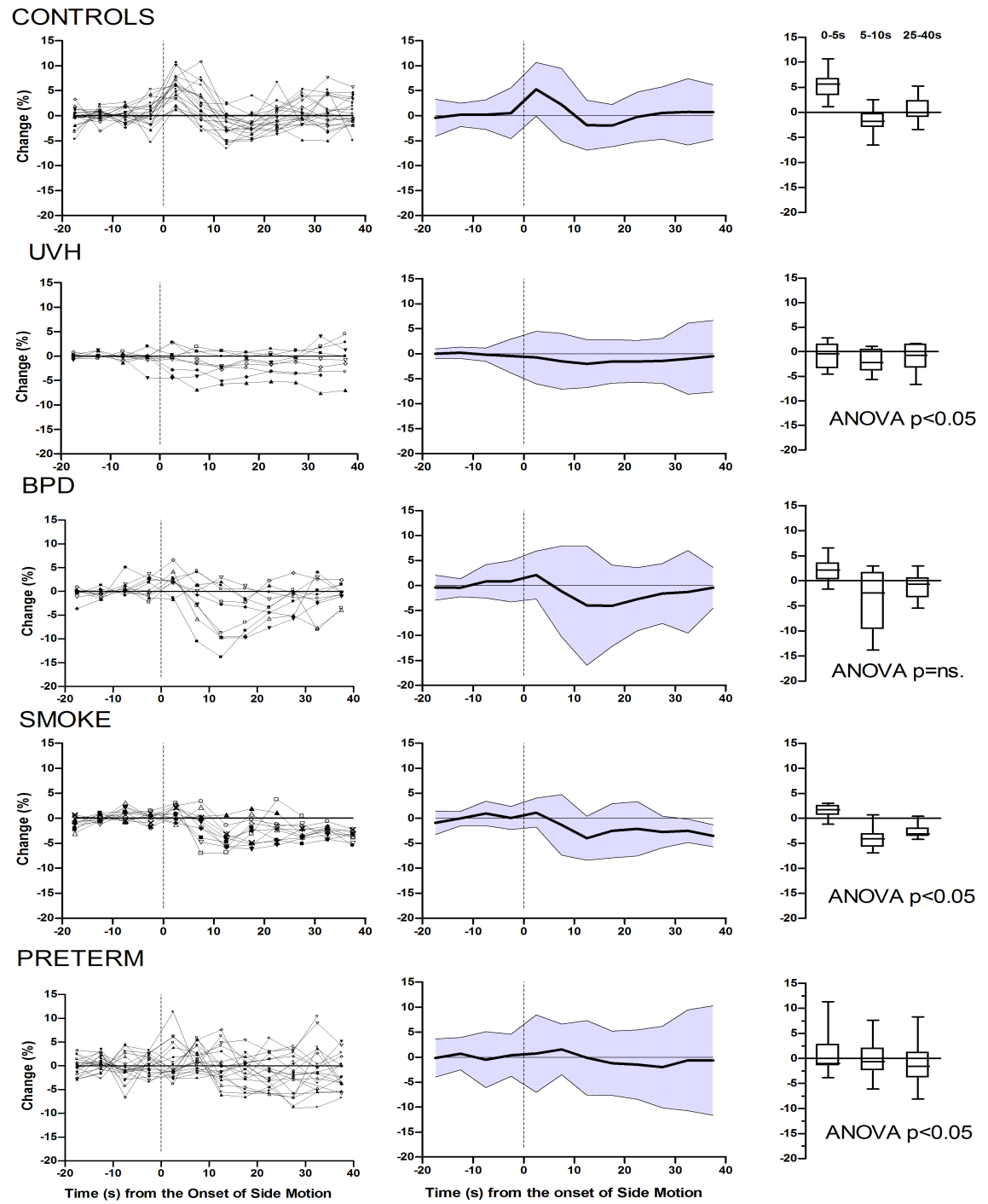

Figure 7. Diastolic blood pressure responses (% from baseline) to the supine side motion test. At the top, table with average group responses. * $p<0.05$ for pairwise comparisons to control infants when ANOVA showed significant group differences. For each study group, individual curves are in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA compared to control infants. ns.= non-significant

LINEAR SIDE MOTION TEST SUPINE – HEART RATE

	baseline 20-5s before test onset	initial 0-5s from test onset	early 10-15s from test onset	late 25-40s from test onset
Control	0	5.2 ± 3.0	-1.7 ± 2.8	0.6 ± 2.3
UVH	0	-0.7 ± 2.2*	-0.8 ± 1.4	-0.4 ± 1.5
BPD	0	2.1 ± 4.6*	-1.4 ± 3.4	1.3 ± 2.1
Smoke	0	2.0 ± 2.9*	-1.6 ± 2.5	-0.9 ± 2.1
Preterm	0	2.7 ± 3.0*	-0.1 ± 2.8	0.6 ± 2.5

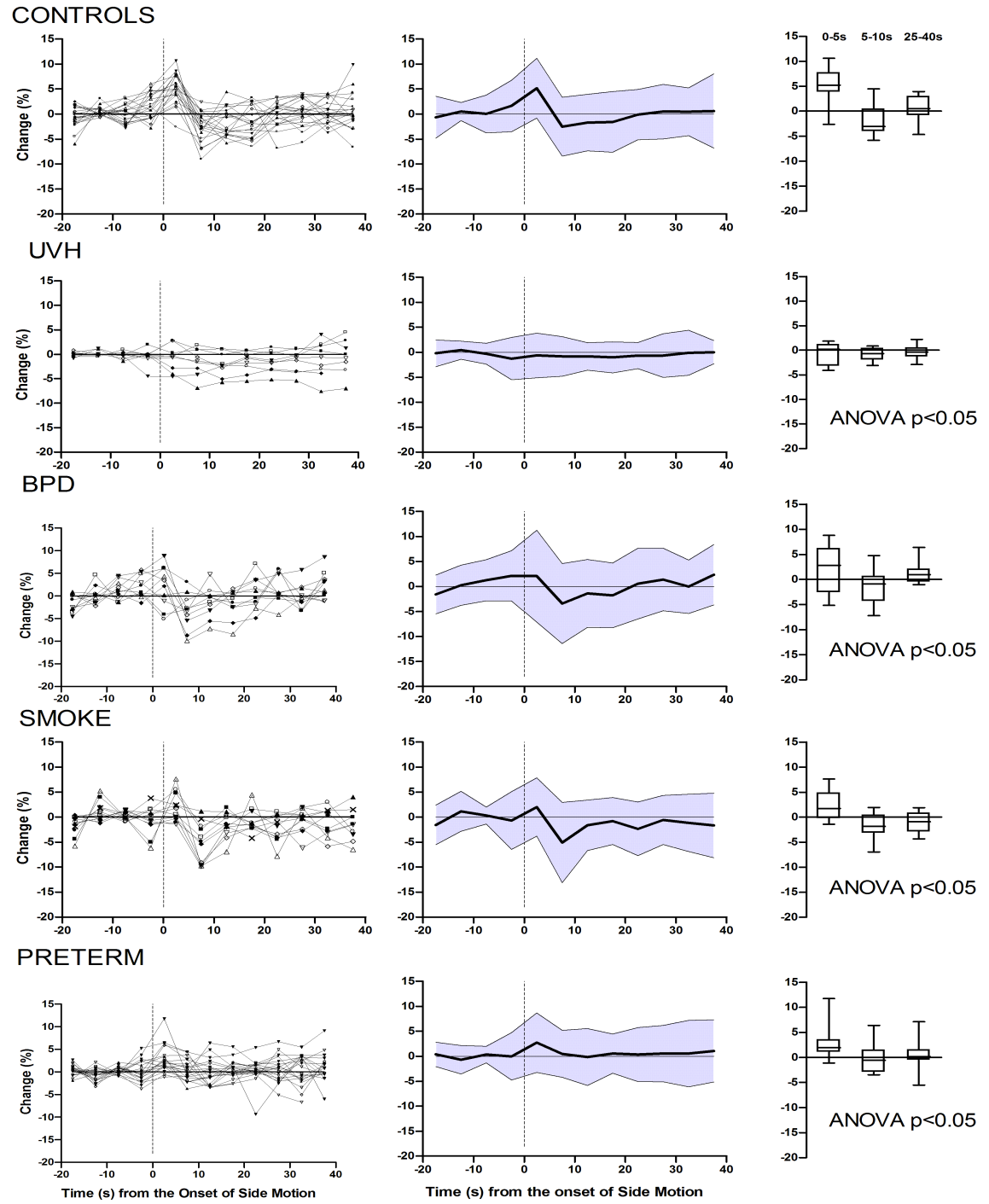

Figure 8. Heart rate responses (% from baseline) to the supine side motion test. At the top, table with average group responses. * p<0.05 for pairwise comparisons to control infants when ANOVA showed significant group differences. For each study group, individual curves are in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA compared to control infants. ns.= non-significant

5.3 Head-up tilt test – supine position

Figures 9-11 present the cardiovascular responses for all study infants during a supine head-up tilt test. Figure 9 shows SBP, Figure 10 DBP, and Figure 11 HR responses.

Control infants showed significant inter-subject variability in their BP responses to the tilt test. On average, there was no initial change in SBP, followed by a decrease that continued even after the end of the test period. DBP showed a biphasic curve with initial increase, followed by a decrease which continued after the end of the test. HR response was biphasic, with an initial increase followed by a decrease and return to baseline.

UVH infants presented similar BP responses to those of control infants, but their HR response was clearly abnormal, with HR remaining above baseline even at 10-15 seconds after initiation of the test. For this thesis, statistical analysis was performed using all 20 control infants as a comparison group to enable better comparison with other groups. No change from the initial analysis emerged at significant and non-significant time points with the increased number of control infants (Viskari-Lähdeoja et al., unpublished results). The inter-subject variability in the responses of UVH infants did not differ significantly from those of the control infants (group mean; HR $p = 0.50$, SBP $p = 0.77$, DBP $p = 0.66$) (Viskari-Lähdeoja et al., unpublished results).

The BP and HR responses of the BPD infants as a group did not differ from those of the control infants in the head-up tilt test. BPD infants, however showed greater inter-subject variability in their BP responses (group mean; SBP $p < 0.0001$, DBP $p < 0.01$). Four BPD infants showed sustained BP increases to the tilt test. The amount of deviation from the control or group mean at 10-15 seconds from the test onset did not correlate with GA, estimated amount of hypoxic exposure based on destaturations while in the neonatal invasive care unit, number of events with SpO_2 <85%, ventilator time, CPAP support or supplementary oxygen, drugs used, or intraventricular hemorrhage, PVL, necrotizing enterocolitis, or sepsis during the neonatal period.

On average, smoke-exposed infants did not show different HR or BP responses compared with control infants. Their inter-subject variability did not differ significantly from the control infants (group mean; HR $p = 0.92$, SBP $p = 0.21$; DBP $p = 0.13$).

Preterm infants near term showed, on average, flat BP and HR responses with no significant changes from baseline, but in this study group, the inter-subject variability in BP responses was even greater than in the control infants (group mean; HR $p = 0.07$, SBP $p = 0.009$, DBP $p = 0.005$). Those currently on theophylline treatment or with intrauterine smoke exposure showed similar responses to those of other infants. Infants with BPD seemed to more often show a decrease in BP in response to tilt, but their HR responses were similar to other preterm infants'. No association was found between GA at birth or PMA, and HR or BP responses.

HEAD-UP TILT TEST SUPINE – SYSTOLIC BLOOD PRESSURE

	baseline 20-5s before test onset	initial 0-5s from test onset	early 10-15s from test onset	late 25-40s from end of tilt test
Control	0	0.6 ± 3.5	-6.7 ± 4.9	-4.0 ± 3.1
UVH	0	0.9 ± 3.1	-5.5 ± 3.3	-1.8 ± 2.3
BPD	0	1.1 ± 3.8	-3.1 ± 10.8	-3.5 ± 3.3
Smoke	0	1.2 ± 4.5	-4.6 ± 7.7	-5.6 ± 3.3
Preterm	0	-2.7 ± 5.0*	-3.9 ± 9.4	-2.7 ± 5.7

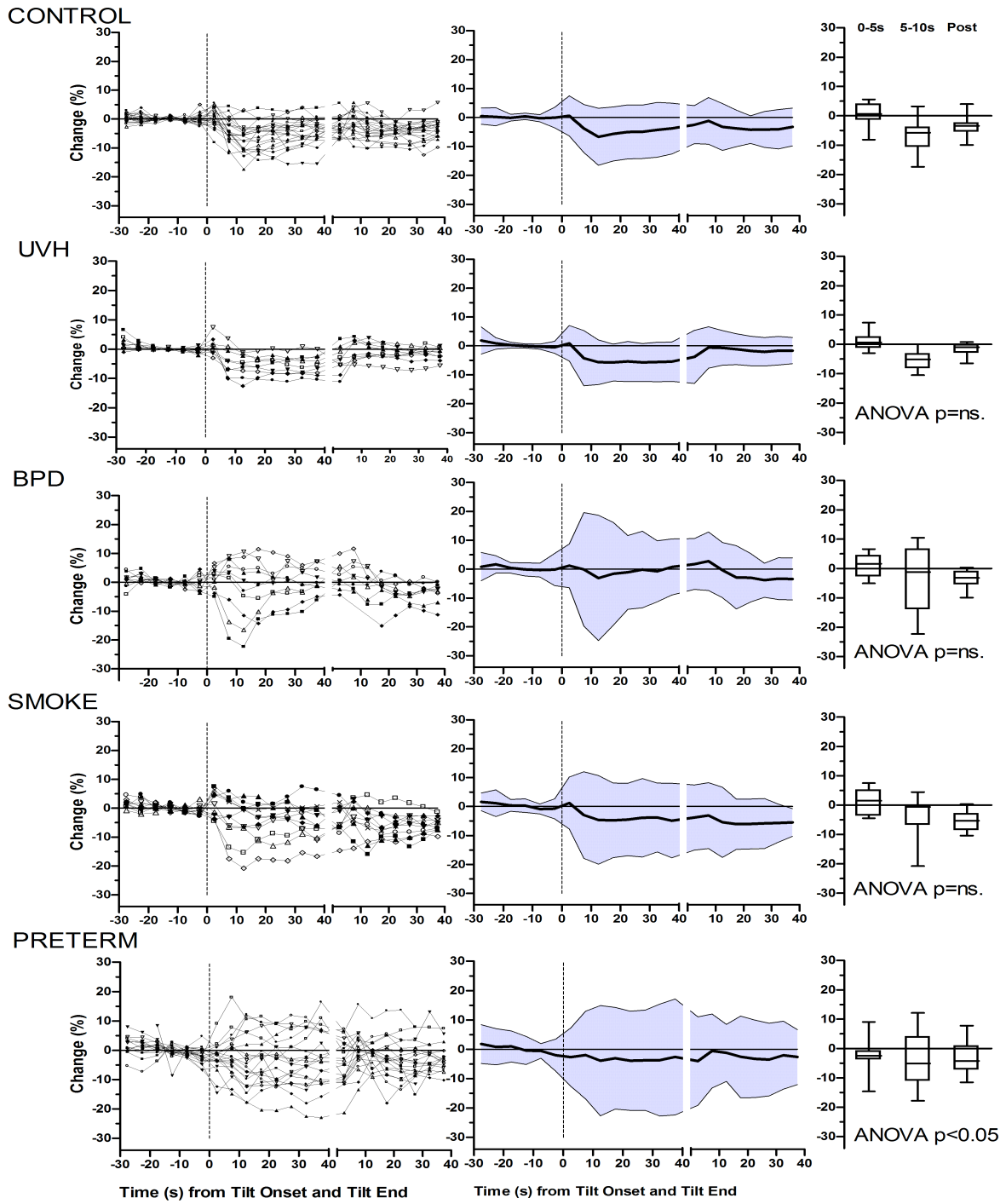

Figure 9. Systolic blood pressure responses (% from baseline) to the supine head-up tilt test. At the top, table with average group responses. * $p<0.05$ for pairwise comparisons to control infants when ANOVA showed significant group differences. For each study group, individual curves are in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA compared to control infants. ns.= non-significant

HEAD-UP TILT TEST SUPINE – DIASTOLIC BLOOD PRESSURE

	baseline 20-5s before test onset	initial 0-5s from test onset	early 10-15s from test onset	late 25-40s from end of tilt test
Control	0	4.6 ± 4.5	-3.6 ± 5.5	-2.1 ± 2.8
UVH	0	2.4 ± 3.4	-4.5 ± 4.0	-1.6 ± 2.2
BPD	0	4.9 ± 4.3	0.5 ± 10.4	-2.1 ± 3.7
Smoke	0	2.8 ± 4.3	-1.6 ± 9.6	-4.7 ± 2.5
Preterm	0	-2.5 ± 6.1*	-3.0 ± 12.6	-1.8 ± 6.5

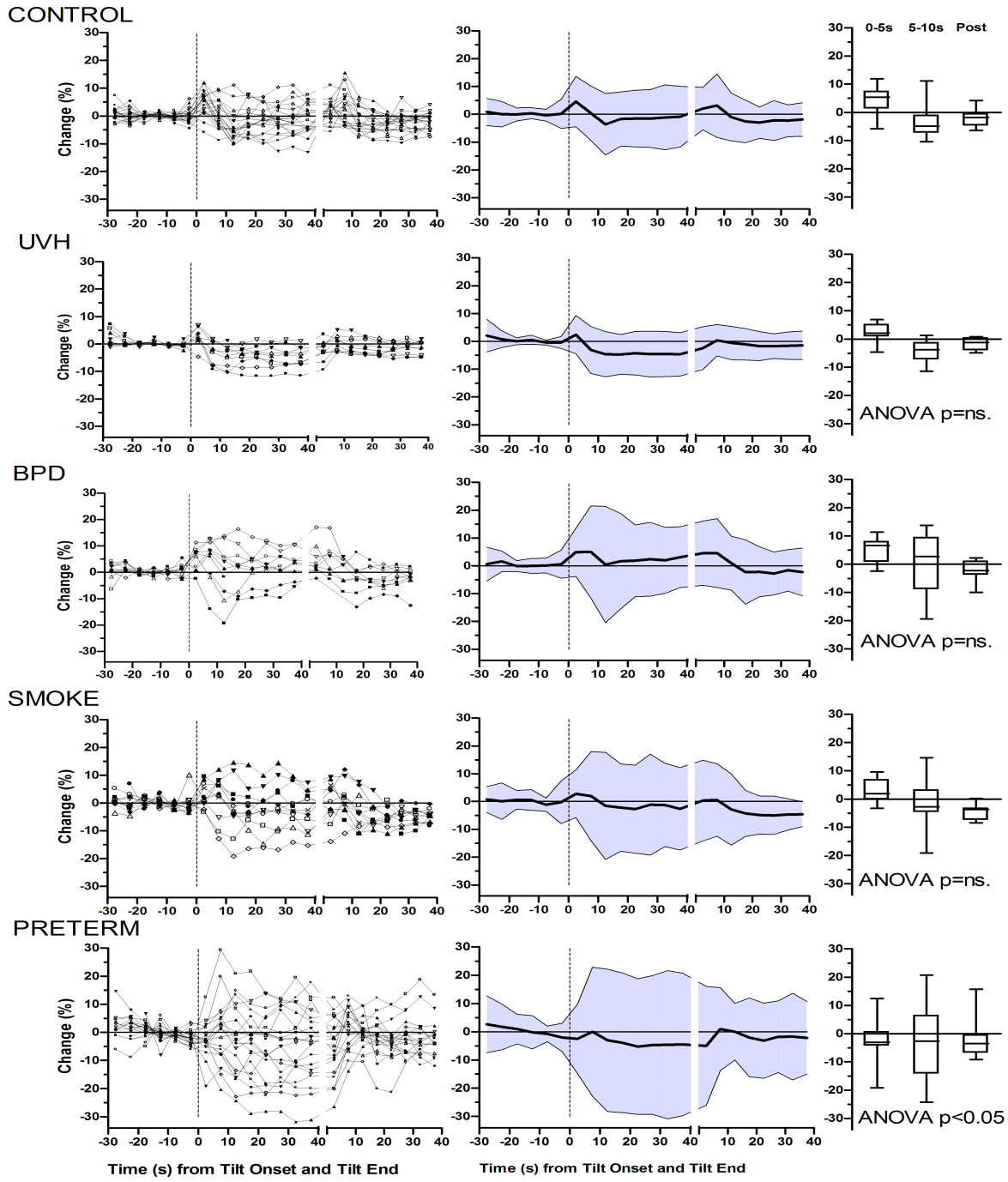

Figure 10. Diastolic blood pressure responses (% from baseline) to the supine head-up tilt test. At the top, table with average group responses. * p<0.05 for pairwise comparisons to control infants when ANOVA showed significant group differences. For each study group, individual curves are in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA compared to control infants. ns.= non-significant

HEAD-UP TILT TEST SUPINE – HEART RATE

	baseline 20-5s before test onset	initial 0-5s from test onset	early 10-15s from test onset	late 25-40s from end of tilt test
Control	0	4.6 ± 3.8	-4.0 ± 3.7	-1.4 ± 2.5
UVH	0	4.1 ± 5.5	2.6 ± 3.4*	-1.2 ± 1.0
BPD	0	6.2 ± 5.6	-1.0 ± 5.3	0.2 ± 2.7
Smoke	0	5.9 ± 4.7	-1.2 ± 4.1	-2.6 ± 2.6
Preterm	0	2.8 ± 3.8	1.1 ± 5.5*	-0.2 ± 4.7

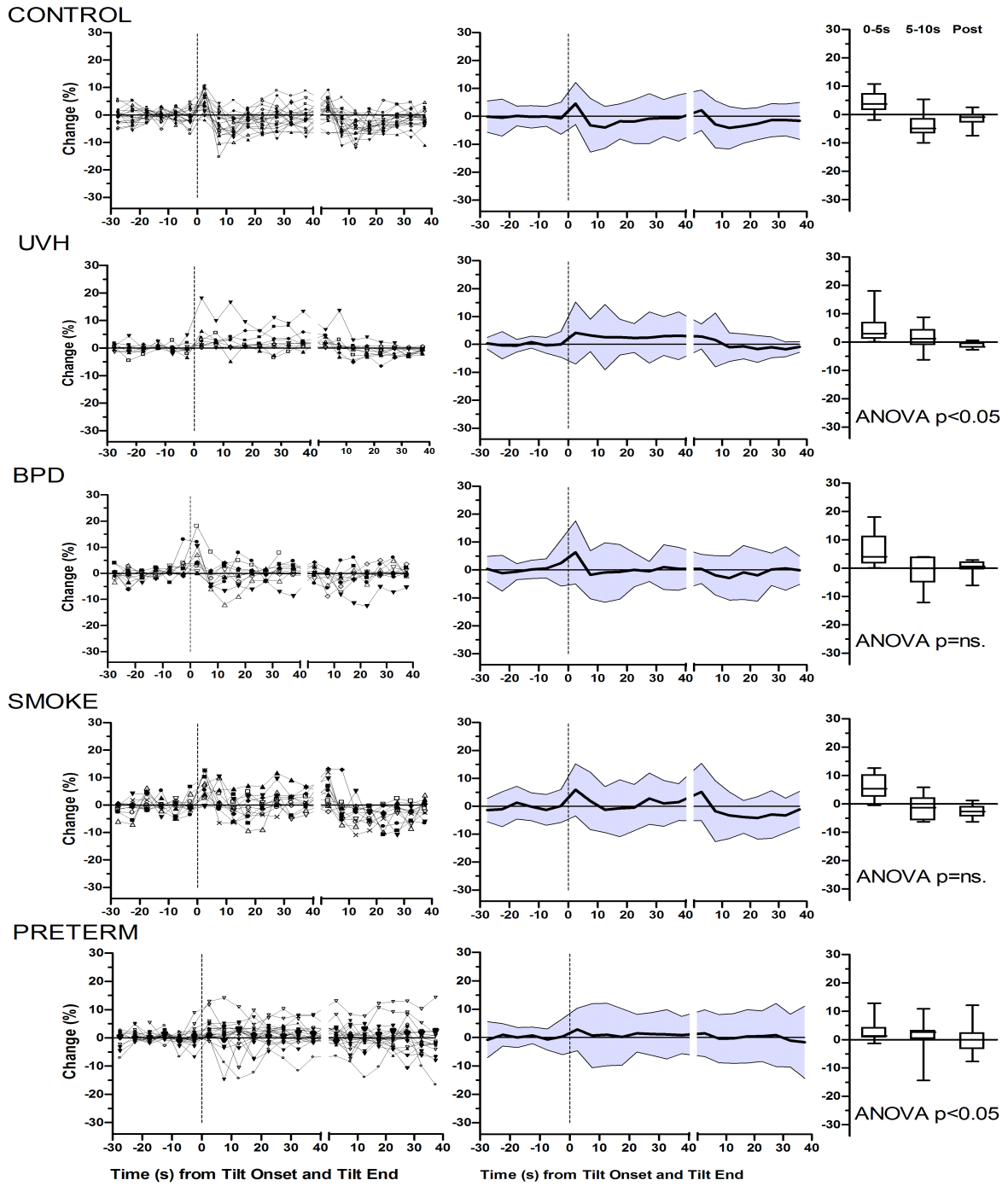

Figure 11. Heart rate responses (% from baseline) to the supine head-up tilt test. At the top, table with average group responses. * $p<0.05$ for pairwise comparisons to control infants when ANOVA showed significant group differences. For each study group, individual curves are in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA compared to control infants. ns.= non-significant

5.4 Linear side motion test – prone position

Figures 12-14 present the cardiovascular responses of those control and UVH infants who were successfully studied both supine and prone (8 controls and 6 UVH infants). As is evident from the graphs, neither BP (Figure 12 for SBP, and Figure 13 for DBP) nor HR (Figure 14) responses to side motion differed between sleeping positions in controls or in UVH infants.

LINEAR SIDE MOTION TEST PRONE – SYSTOLIC BLOOD PRESSURE

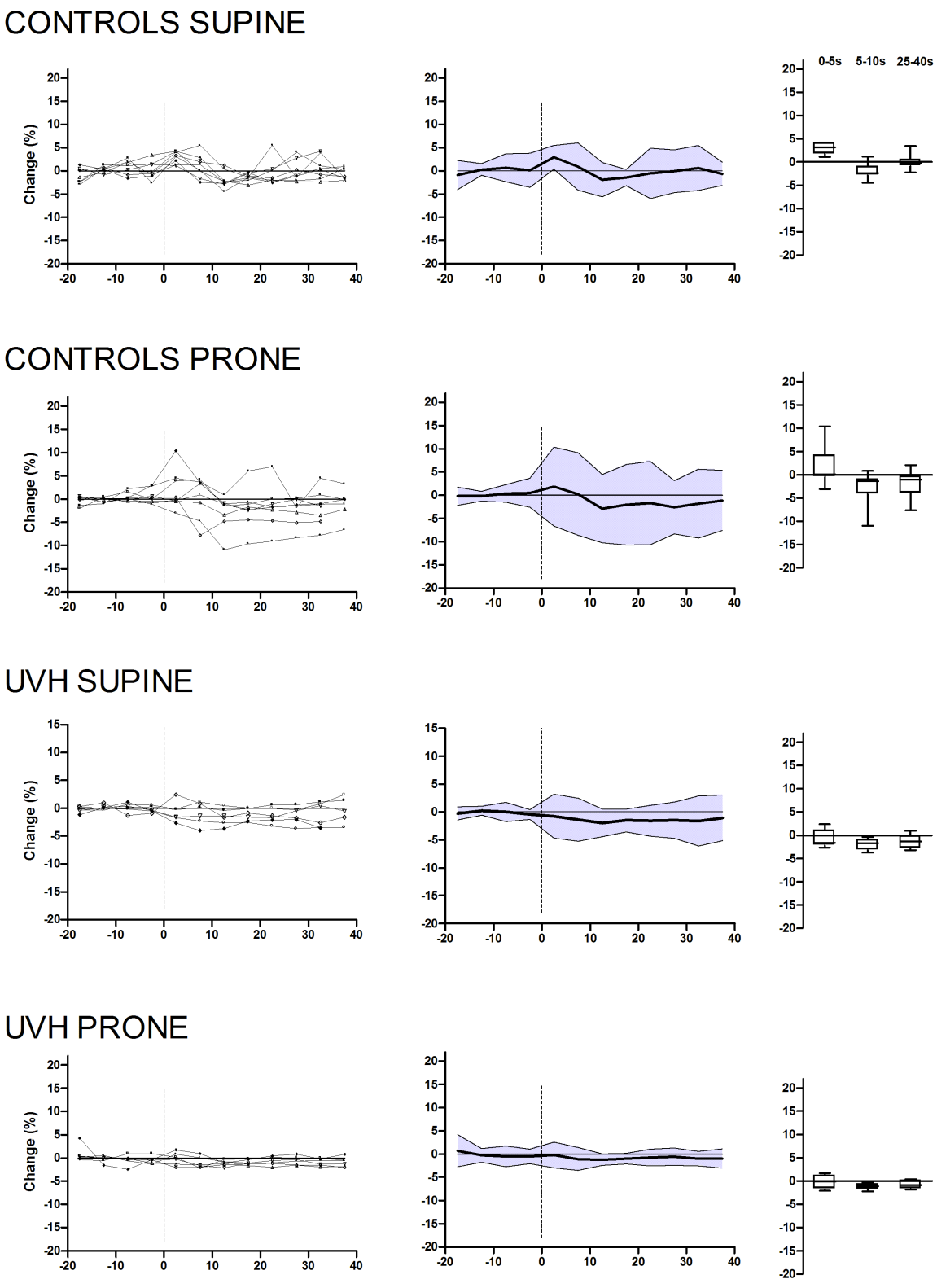

Figure 12. Systolic blood pressure responses (% from baseline) to prone side motion test (8 controls and 6 UVH infants). For each group individual curves are drawn in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA showed non-significant differences between the groups.

LINEAR SIDE MOTION TEST PRONE – DIASTOLIC BLOOD PRESSURE

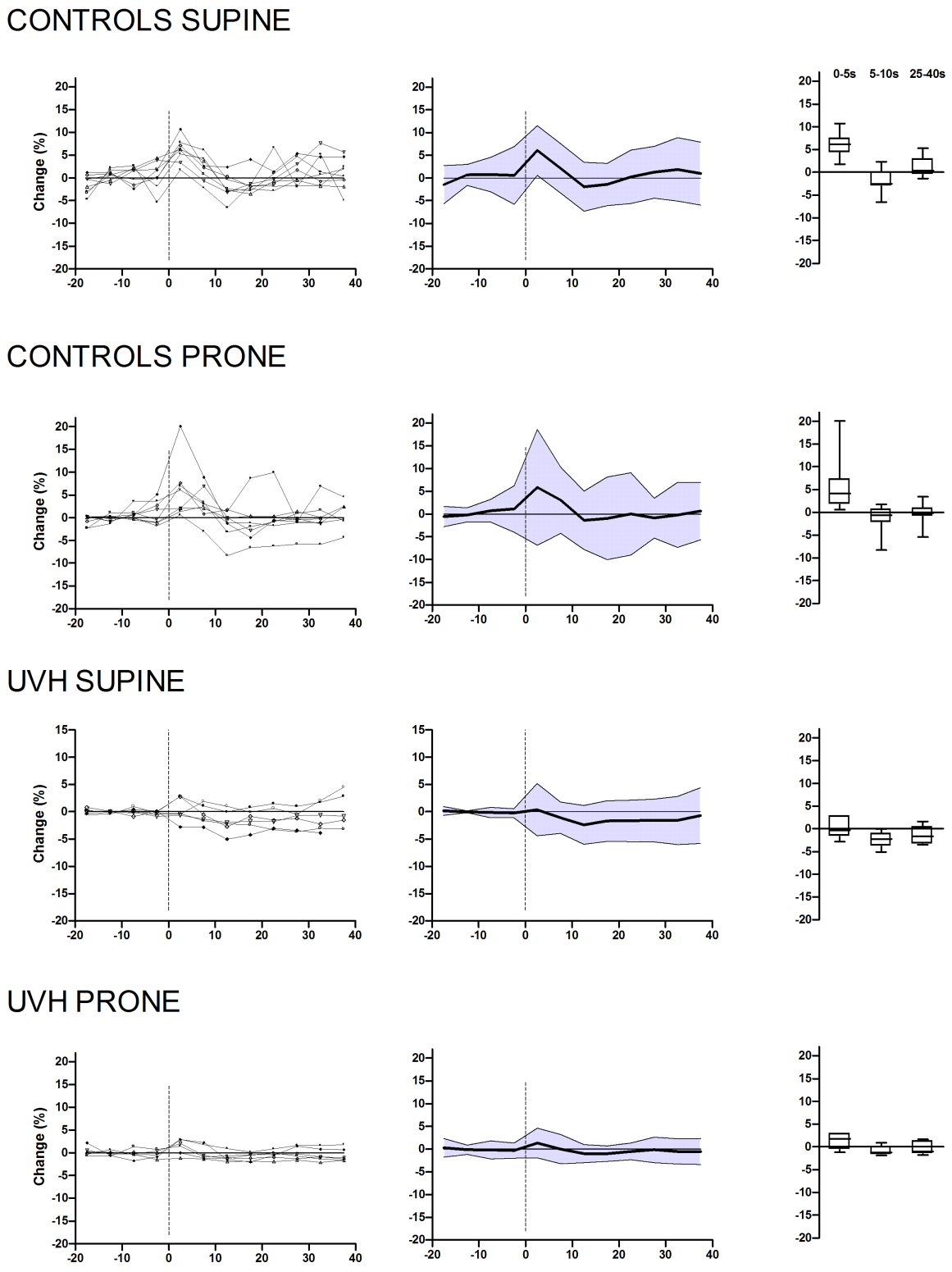

Figure 13. Diastolic blood pressure responses (% from baseline) to prone side motion test (8 controls and 6 UVH infants). For each group individual curves are drawn in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA showed non-significant differences between the groups.

LINEAR SIDE MOTION TEST PRONE – HEART RATE

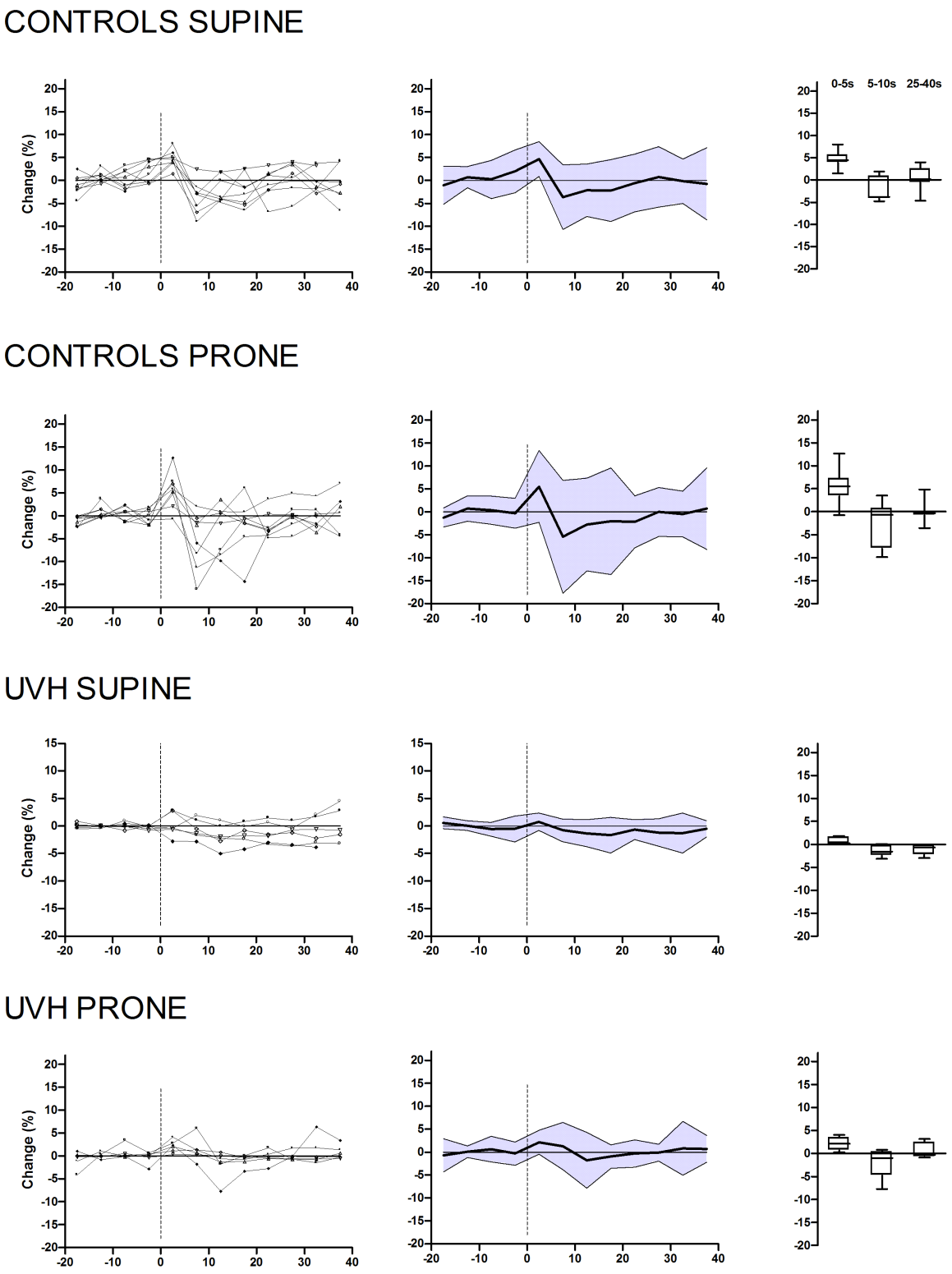

Figure 14. Heart rate responses (% from baseline) to prone side motion test (8 controls and 6 UVH infants). For each group individual curves are drawn in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA showed non-significant differences between the groups.

5.5 Head-up tilt test – prone position

Figures 15-17 show the cardiovascular responses to the head-up tilt test of those control and UVH infants who were successfully studied both supine and prone (8 controls and 5 UVH infants). Sleeping position did not have an effect on BP (Figure 15 for SBP, and Figure 16 for DBP) or HR (Figure 17) responses to the tilt test in either control or UVH infants.

HEAD-UP TILT TEST PRONE – SYSTOLIC BLOOD PRESSURE

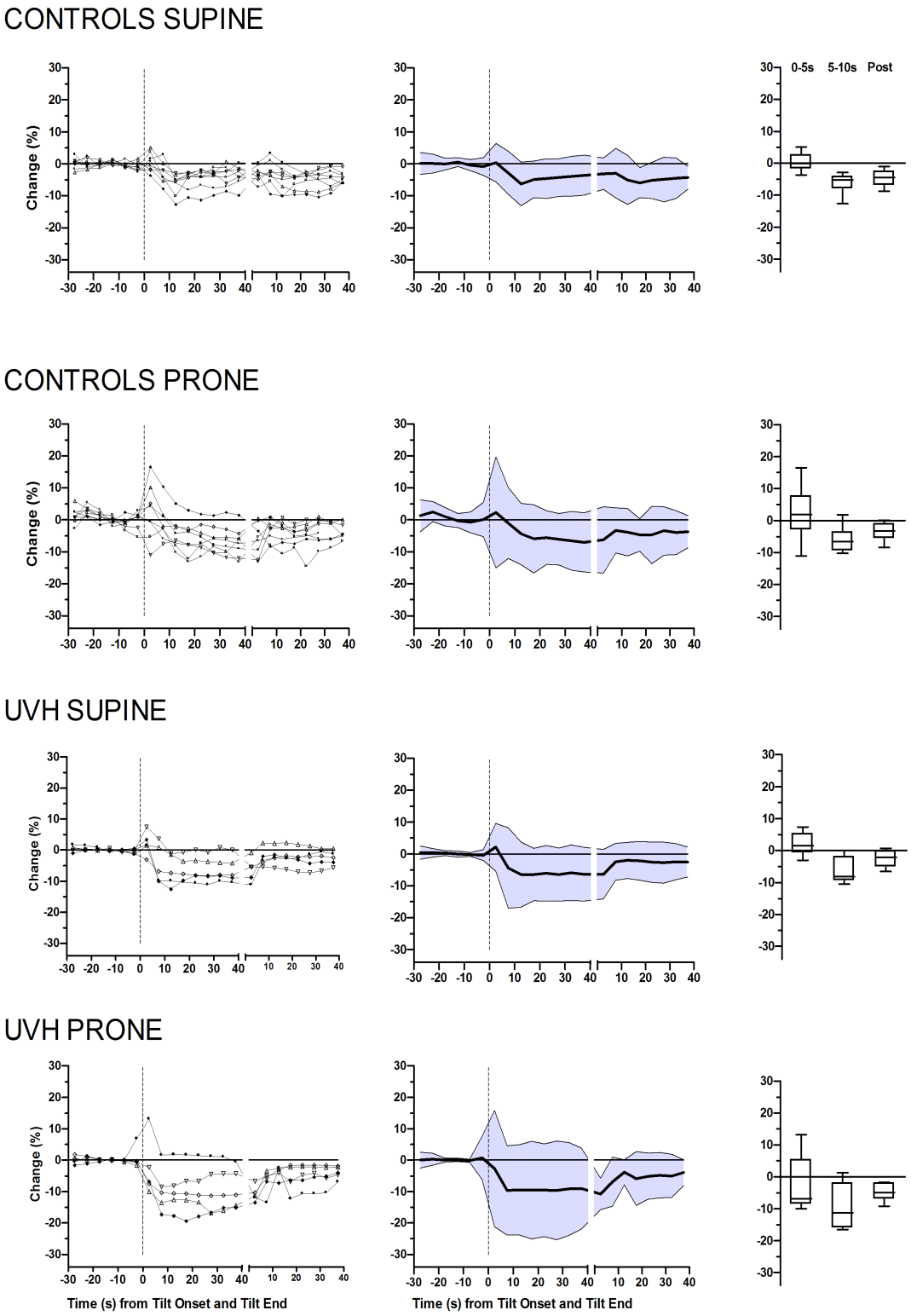

Figure 15. Systolic blood pressure responses (% from baseline) to the prone head-up tilt test (8 controls and 5 UVH infants). For each group individual curves are drawn in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA showed non-significant differences between the groups.

HEAD-UP TILT TEST PRONE – DIASTOLIC BLOOD PRESSURE

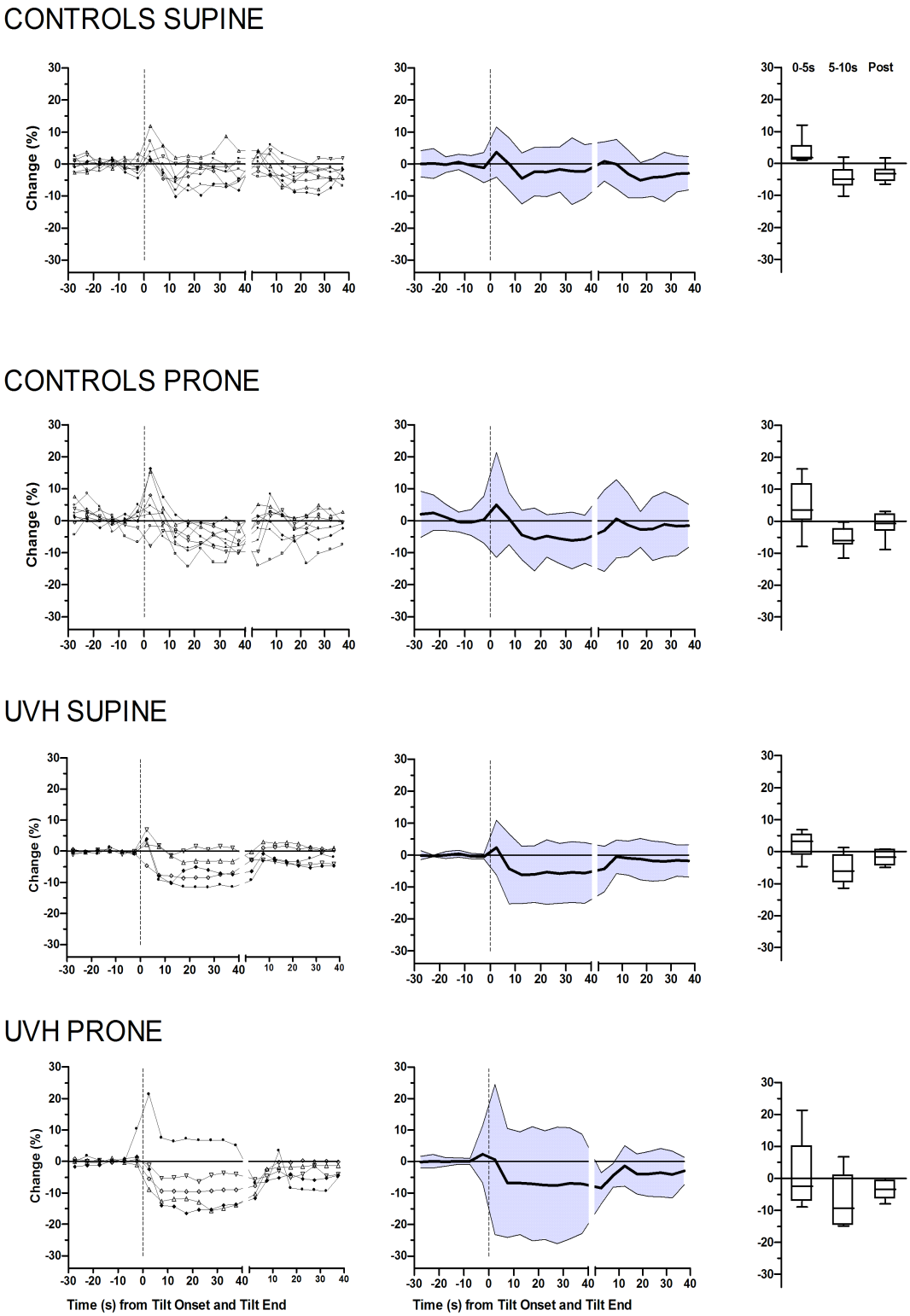

Figure 16. Diastolic blood pressure responses (% from baseline) to the prone head-up tilt test (8 controls and 5 UVH infants). For each group individual curves are drawn in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA showed non-significant differences between the groups.

HEAD-UP TILT TEST PRONE – HEART RATE

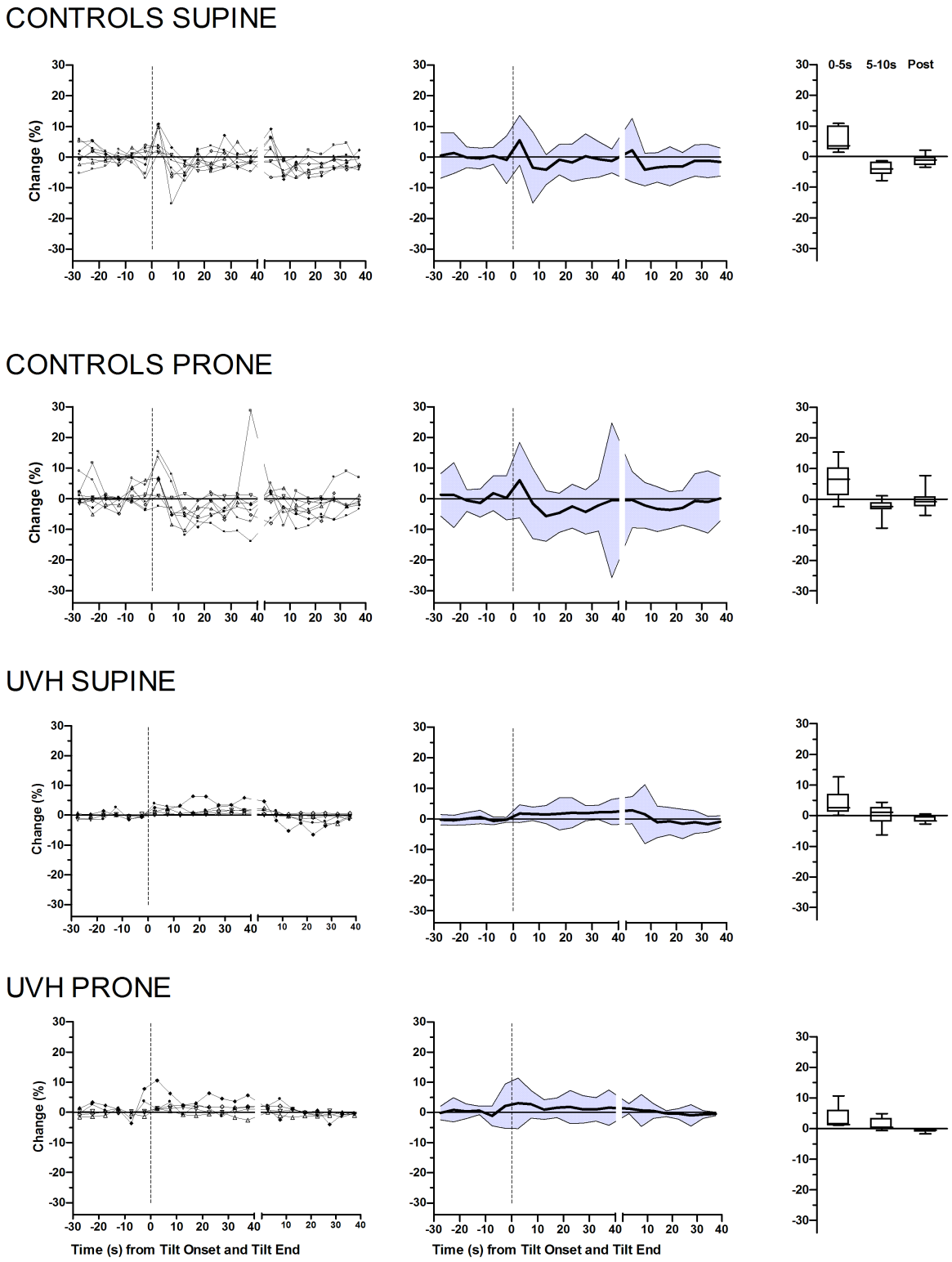

Figure 17. Heart rate responses (% from baseline) to the prone head-up tilt test (8 controls and 5 UVH infants). For each group individual curves are drawn in the left panel. The middle panel shows a mean curve and a shaded area of ± 2 SD. In the right panel, time intervals according to which statistical analysis was performed. ANOVA showed non-significant differences between the groups.

5.6 Heart rate responses to spontaneous arousals

HR responses to spontaneous arousals in a supine position were successfully carried out in all control, BPD and smoke-exposed infants, for 8/9 (89%) of UVH infants (missing data for no 1), and 17/20 (85%) of preterm infants (missing data for subjects no 2, 3, and 7). HR responses to spontaneous arousals were similar to control infants' in BPD, smoke-exposed, and preterm infants (Table 15). BPD infants with suppression in the side motion test showed similar increases in HR to spontaneous arousals as the other BPD infants. UVH infants showed significantly attenuated HR increases to spontaneous arousals compared with the twenty control infants ($p = 0.0006$) (Viskari-Lähdeoja et al., unpublished results). Baseline HR levels were similar in infants at 2-4 months of age. In preterm infants studied at term, however, the baseline HR was higher compared with control infants ($P < 0.0001$).

In a prone position, HR responses to spontaneous arousals were analyzed for 9 of 11 (82%) controls and 4 of 9 (44%) UVH infants. There were no differences between the groups in the HR response to spontaneous arousals or baseline HR levels (Table 14). The values for baseline HR or HR responses to spontaneous arousals did not differ between the sleeping positions in control or UVH infants.

Table 15. Heart rate responses to spontaneous arousals in slow-wave sleep

Position	Group	*n*	HR acceleration (beats/min/min)	HR (/min)
Supine				
	Control	20	147 ± 45 (48–205)	118 ± 9 (96–132)
	UVH	8	73 ± 44 (14–158)*	118 ± 13 (97–136)
	BPD	10	186 ± 58 (92 – 266)	122 ± 15 (91–143)
	Smoke	11	122 ± 26 (79–172)	121 ± 6 (108–134)
	Preterm	17	137 ± 50 (65 – 235)	146 ± 14 (123–175)*
Prone				
	Control	9	127 ± 39 (77–197)	122 ± 9 (103–134)
	UVH	4	100 ± 48 (55–159)	122 ± 4 (118–126)

Definition and abbreviations: BPD = infants with bronchopulmonary dysplasia; Control = control infants; HR = heart rate; Preterm = preterm infants studied at gestational age of 34-39 weeks = Smoke = infants exposed to maternal smoking during pregnancy; UVH = infants with univentricular heart; *$p < 0.05$ (comparisons made to control infants)

5.7 Heart rate variability

Table 16 presents heart rate variability (HRV) in supine and prone positions during slow-wave sleep. When supine, HRV was analyzed in 18 of 20 (90%) control infants (no HRV analysis for infants no 7 and 9), all UVH, smoke and BPD infants, and 11 of 20 (55%) preterm infants. The low ratio of successful analyses of HRV for preterm infants stems from the different study set-up as described above. The preterm infants without HRV analysis were subjects no 2, 3, 9, 10, 12, and 16-19. When prone, HR variability was computed for 6 of 9 (67%) UVH infants and 8 of 11 (73%) control infants.

Baseline HR was similar at 2-4 months of age, but significantly higher in preterm infants studied near term. Breathing frequency during the analyzed 2-min periods was similar in all infants studied at (corrected) 2-4 months of age. Preterm infants studied at term age, however, showed a significantly higher breathing frequency compared with control infants ($p < 0.0001$). Average HR or breathing frequency did not differ between sleeping positions in either control or UVH infants.

In Study I, supine HRV was not significantly different between the study groups, but only nine control infants were studied. When compared with a total of 18 control infants, UVH infants showed lower values of LF variability, HF variability, and TP. The LF/HF ratio in UVH infants was similar to that of control infants, showing equal decreases in both LF and HF variability (Viskari-Lähdeoja et al., unpublished results).

When prone, UVH infants showed significantly lower LF variability ($p = 0.004$) and TP ($p = 0.02$) compared with control infants (Table 15). However, in HF variability, the difference was insignificant. Those control ($n = 6$) and UVH ($n = 8$) infants with both supine and prone measurements, showed no differences in any HRV indices (LF, HF, TP, LF/HF) between sleeping positions. The small number of infants with prone HRV measurements reduces the value of these findings.

HRV was calculated only in a supine position for BPD infants, infants with intrauterine smoke exposure, and preterm infants near term age. For BPD infants, LF variability, HF variability and LF/HF ratio were similar to those observed in control infants, but TP was slightly higher ($p = 0.02$). The HRV of those infants with suppression in the side motion test supine (infants no 1, 3, 4, 6, 7) did not differ from the other BPD infants. In smoke-exposed infants, HRV was similar in all frequency domains to that in the control infants. Preterm infants near term age showed lower HF variability ($p = 0.006$) and a higher LF/HF ratio ($p < 0.0001$) compared with control infants, but these infants also showed higher HR and breathing rate (Viskari-Lähdeoja et al., unpublished results).

Table 16. Heart rate variability in slow-wave sleep

Position	Group	*n*	LFV	HFV	TP	LF/HF ratio	HR (min)	RR (/min)
Supine								
	Control	18	2.9 ± 0.3	2.8 ± 0.3	3.3 ± 0.2	1.0 ± 0.1	120 ± 9	33 ± 8
	UVH	9	2.6 ± 0.5*	2.4 ± 0.6*	3.1 ± 0.4*	1.1 ± 0.2	123 ± 11	40 ± 10
	BPD	10	3.0 ± 0.4	3.0 ± 0.4	3.5 ± 0.2*	1.0 ± 0.2	120 ± 7	33 ± 7
	Smoke	11	3.0 ± 0.3	2.9 ± 0.2	3.4 ± 0.2	1.0 ± 0.1	121 ± 13	32 ± 6
	Preterm	11	3.0 ± 0.4	2.4 ± 0.3*	3.4 ± 0.3	1.3 ± 0.1*	146 ± 12*	59 ± 15*
Prone								
	Control	8	3.0 ± 0.2	2.7 ± 0.2	3.4 ± 0.3	1.1 ± 0.1	122 ± 6	34 ± 8
	UVH	6	2.3 ± 0.5*	2.5 ± 0.6	2.9 ± 0.4*	1.0 ± 0.1	127 ± 9	39 ± 8

Definition and abbreviations: BPD = infants with bronchopulmonary dysplasia; Control = control infants; HFV = high-frequency heart rate variability; LFV = low-frequency heart rate variability; Preterm = preterm infants near term age; RR = respiratory rate; Smoke = infants exposed to maternal smoking during pregnancy; TP = total power of heart rate variability; UVH = infants with univentricular heart; for heart rate variability, values are $\log_{10}$ value, arbitrary units; *$p < 0.05$ (comparisons made to control infants)

5.8 Arterial oxyhemoglobin saturation (II)

We could find no correlation between the degree of response deviation from the control or BPD group mean at 10-15 seconds from the test onset and the estimated amount of total hypoxic exposure (area under SpO_2 of 100% or 85%) or number of SpO_2 desaturations under 85% during the early neonatal period (Figure 5).

6 DISCUSSION

In this thesis, the main hypothesis was that infants at risk of SIDS would show impaired vestibulo-mediated cardiovascular control. The hypothesis arose from previous animal studies showing the importance of vestibular and cerebellar nuclei function in the recovery from cardiovascular shock, and from the autopsy studies of human SIDS victims showing disruption in some of the nuclei participating in blood pressure (BP) control, including vestibular nuclei (Filiano, et al. 1992,Kinney, et al. 1995,Kinney, et al. 2001,Lavezzi, et al. 2005,Matturri, et al. 2006,Waters, et al. 1999). Our SIDS hypothesis was that the SIDS victims would have impaired cardiovascular responses during life-threatening events that would contribute to their death. Possible causative factors for the impaired blood pressure control and vestibular nuclei dysfunction could be previous hypoxic episodes either during pregnancy or postnatally as parts of vestibulo-fastigial pathways, such as cerebellar Purkinje cells are known to be sensitive to hypoxia (Hutton, et al. 2007,Pae, et al. 2005,Sarna, et al. 2003).The impaired vestibular function should be seen as altered heart rate and blood pressure responses to the tilt and side motion test at the highest SIDS risk age of 2-4 months.

The main finding of the study was that UVH, antenatally smoke-exposed, preterm infants close to term age, and some BPD infants had altered BP responses to side motion. In the tilt test, UVH, BPD, and smoke-exposed infants showed as a group normal average BP responses. Heart rate (HR) response to the tilt test was normal in BPD and smoke-exposed infants, but UVH infants presented with tachycardia. Preterm infants at term, therefore, showed flat BP and HR responses. BPD and premature infants also showed highly variable tilt test BP reponses where some showed increased and some decreased BP levels when compared to healthy controls. The explanation for this observed high inter-subject but not intra-subject variability in BP reponses to tilting is not evident.

6.1 Blood pressure control and sudden infant death syndrome

The observed defective vestibulo-mediated cardiovascular control is not expected to be manifested in infants' normal life since infants have a limited need for postural blood pressure compensation, and there are several other compensatory mechanisms involved in BP control. Cardiovascular control is a complex process with several inputs improving the accuracy of the regulatory system (Persson. 1996,Yates, et al. 2005). Overall BP control does not seem to be altered by a long-term absence of one type of signal, but acute control of BP is found to become more inaccurate (Kerman, et al. 1998,Persson. 1996,Timmers, et al. 2003,Yates, et al. 2000). The inappropriate, acute BP control could become important when the cardiovascular system is challenged more severely in extreme, life-threatening situations, and predispose these infants to SIDS. Failure of vestibulo-mediated cardiovascular control in critical situations has been implicated as one possible mechanism is SIDS (Harper. 2000). However, it is likely that this impaired control mechanism would not be a sufficient precursor for SIDS alone, but other factors would also have to be present (Filiano, et al. 1994), such as appropriate age, prone position, and respiratory infection.

Infants who have succumbed to SIDS show evidence of suffering hypoxia before death (Jones, et al. 2003,Opdal, et al. 1998,Rognum, et al. 1988). Also many risk factors for SIDS are associated with hypoxic exposure, including obstructive sleep apnea (Kahn, et al. 1992,Kato, et al. 2001,McNamara, et al. 2000), maternal smoking during pregnancy (Kelly, et al. 1984,Longo. 1976,Longo. 1977), placental dysfunction (Smith, et al. 2004), and prematurity (Darnall, et al. 2006).

Study I included infants with univentricular heart, who suffered from chronic postnatal hypoxia with pulse oximetry values of around 75-85% after the first stage of palliative surgery performed during the neonatal period. Although not a traditional SIDS risk group, these infants have similar sudden, unexplained deaths during infancy (Fenton, et al. 2003). In Study II we evaluated preterm infants who had developed BPD and demonstrably had suffered from repetitive hypoxia during early life. The infants in Study III were all exposed to moderate maternal smoking during pregnancy which presumably causes intrauterine hypoxia (Kelly, et al. 1984,Longo. 1976,Longo. 1977). Both prematurity and maternal smoking during pregnancy are risk factors for SIDS (Alm, et al. 1998,Blair, et al. 1996,Blair, et al. 2006,Blair, et al. 2009,Cnattingius. 2004,Halloran, et al. 2006,Thompson, et al. 2006). In Study IV, we aimed to characterize the development of cardiovascular control in preterm infants to see if altered cardiovascular responses are already present close to term age.

6.2 Blood pressure measurement

One of the strengths of this study is the novel study method of the linear side motion test that enables the evaluation of vestibulo-mediated cardiovascular responses. To our knowledge, there are no other previous reports on a similar approach. In addition, acute cardiovascular responses to the head-up tilt test especially in UVH, BPD and smoke-exposed infants had not previously been characterized. We also used considerable effort to exclude arousals because arousal is known to cause a prominent cardiovascular response (Horner. 1996,Trinder, et al. 2003). The considerable effect of arousal on the study variables was also evident from Study I. All the tests were performed during polysomnograhically confirmed NREM sleep reducing possible variability in responses due to different sleep stages, as it was evident from Study I that tests performed during REM sleep showed more arousal responses.

The continuous, noninvasive measurement of blood pressure using an adult finger cuff around the infant's wrist has recently been validated for term and preterm infants offering a novel noninvasive method of continuous BP measurement (Drouin, et al. 1997a,Harrington, et al. 2001,Yiallourou, et al. 2006). This method enables characterization of acute cardiovascular responses without the risks and ethical problems of invasive catheters.

In this thesis, heart rate and blood pressure responses were studied in sleep, when the cardiovascular state is stabile and arousal does not influence the responses. Infants with different types of exposure to hypoxia and concurrent risk of SIDS were selected for the study. Originally, blood pressure measurements and tests were planned to be performed in both NREM and REM sleep. However, during the first study with UVH and control infants, it became evident that the propensity to arouse to blood pressure measurement and tests in REM sleep was very high. For most infants studied in both NREM and REM sleep, no successful tests without arousal were acquired in REM sleep. This lower arousal threshold in REM sleep has also been noted in other studies (Galland, et al. 1998,Harrington, et al. 2001,Yiallourou, et al. 2008). Therefore, the intention to study responses in REM sleep was abandoned, as repeated arousals to tests in REM sleep result in sleep fragmentation and the test results would mainly display the arousal response.

6.3 Linear side motion test

The linear side motion test was used to study vestibular and fastigial pathways in cardiovascular control. Other methods to evaluate vestibulo-mediated cardiovascular control are head rotation (Carter, et al. 2008,Radtke, et al. 2003) and linear forward-backwards acceleration (Yates, et al. 1999). The head down rotation test would easily induce arousal from sleep, and thus requires the awake state for stabile testing condition. To our knowledge, linear side motion has not been used as a vestibular test in other studies, so direct comparison to other studies is not possible.

Healthy control infants at 2-4 months of age show biphasic HR and BP responses to the linear side motion test. UVH, BPD, smoke-exposed and preterm infants had clearly attenuated initial HR responses compared to control infants, and furthermore, in UVH infants this initial response was virtually absent. BP responses showed somewhat more variation among the groups. UVH, smoke, and preterm infants at term all showed initially attenuated BP responses to the side motion test, suggesting defective vestibulo-mediated cardiovascular control. This type of response was also evident in some of the BPD infants.

Smoke-exposed and preterm infants at term showed delayed BP recovery from the side motion test, and 50% of the BPD infants showed flat or decreased BP responses. We could not find a correlation between demographic data and hypotensive side motion test responses in BPD infants. However, it is possible that the small group size prevented us from finding significant differences. This increased and delayed hypotensive response is most likely caused by inadequate peripheral vasoconstriction (Wieling, et al. 1998). This inadequate vasoconstriction is not likely to be caused by immaturity alone, as already term and preterm newborns as a group have been observed to possess the ability to respond to postural challenge adequately, i.e. by increasing peripheral vascular resistance (Lagercrantz, et al. 1990,Picton-Warlow, et al. 1970,Waldman, et al. 1979). Nevertheless, there, was considerable variability in the vascular resistance responses induced by the tilt test in these reported studies.

The effect of sleeping position was evaluated in the first study of control and UVH infants. Because the cardiovascular responses to side motion and head-up tilt tests were similar in both sleeping positions, this was not studied in BPD, smoke-exposed and preterm infants.

These findings show that initial cardiovascular responses especially to the vestibular test are altered in some SIDS risk groups. The exact causes of these alterations in vestibulo-mediated cardiovascular control remain unclear, but hypoxia may be one of them. However, especially in the case of BPD and UVH infants, the diseases themselves may affect these pathways by other means than through hypoxia. In UVH infants, however, we could find no correlation between cardiovascular responses and the extent of surgery or possible perfusion during surgery, and as the cardiac anomalies were variable, the most evident common factor in these infants was chronic postnatal hypoxia. Similarly, in BPD infants, we tried to correlate HR and BP responses to several background characteristics, but no such correlations were found. Smoke-exposed infants, therefore, were healthy and did not have other possibly confounding morbidities. Results in preterm infants suggest that at least in preterm infants vestibulo-mediated cardiovascular control is attenuated near term age, and this raises the question of how these pathways develop in full-term infants from birth up to four months.

The specific location of defective vestibulo-mediated BP control remains speculative. The deficit may reside anywhere in the signaling pathway, from afferent vestibular neurons to the central commanding regions. In animal studies, both direct damage to the vestibular nerve and bilateral lesions in the cerebellar fastigial nuclei were found to produce similar, unstable BP control (Doba, et al. 1974,Jian, et al. 1999). Furthermore, after transection of vestibular nerves, fastigial nuclei lesions do not produce any further deficit in the BP control, indicating a

common reflex arc for these pathways (Doba, et al. 1974,Yates. 1992). On the other hand, cerebellar fastigial regions are considered especially important for compensatory actions during hypotension (Lutherer, et al. 1983) These BP compensatory actions of the cerebellum are suggested to function through vestibular pathways to restore spontaneous drops in BP during sleep (Harper, et al. 2000b); this may be important considering the assumption that at least some SIDS deaths result from a cardiovascular collapse (Harper, et al. 2000b,Harper. 2000).

6.4 Head-up tilt test

The head-up tilt test measures orthostatic response mainly from the baroreflex, although peripheral venous reflexes and vestibular sympathoreflexes are known to participate in cardiovascular control during postural challenge (Persson. 1996,Thompson, et al. 1983,Yates, et al. 1987). The baroreflex shows a fast vagal inhibition and a slower sympathetic activation, and the latency for vasoconstriction during orthostatic challenge has been estimated to be several seconds (Gulli, et al. 2005,Scher, et al. 1963,Warner. 1958). This rather long latency would suggest a longer, initial hypotensive period during the head-up tilt test before compensation of BP, but instead the cardiovascular response is almost immediate (Carter, et al. 2008,Doba, et al. 1974,Sprangers, et al. 1991). Vestibulo-mediated cardiovascular control during postural challenge is physiologically plausible as vestibular end-organs sense changes in orientation and movement. Animal studies have shown that vestibulo- and fastigial-mediated rapid compensation is responsible for this initial cardiovascular response before the baroreflex-mediated response is activated (Doba, et al. 1974,Jian, et al. 1999,Yates, et al. 2005). Combined baroreflex denervation and fastigial nuclei lesions also produce an additive hypotensive effect, which supports their compensatory effects on cardiovascular control. This vestibulo-mediated cardiovascular control appears to be especially important during movement and dangerous situations such as during hypovolemia and endotoxin shock (Doba, et al. 1974,Lutherer, et al. 1983). During orthostatic testing, bilateral vestibular lesions induce increased BP variability (Jian, et al. 1999), and abolishing vestibular or fastigial information during hypotensive situations causes an accentuated hypotensive response (Doba, et al. 1974,Lutherer, et al. 1983).

Tilt angle in animal studies has varied between 20° and 60° with graded responses where the most prominent cardiovascular changes are seen at a head-up tilt of 60° (Doba, et al. 1974,Jian, et al. 1999). In adults, the acute cardiovascular responses are essentially the same when the tilt angle varies from 70° to 90° and the tilt rise time varies from 1.5 to 3s (Sprangers, et al. 1991). In children and adolescents, a 30 min tilt test for syncope shows similar results between 60° and 70° (Lewis, et al. 1997), but it seems that cardiovascular effects of lower tilt angles and acute responses are not well characterized. In earlier infant tilt studies (Tables 2-5) the tilt angle has varied between 15° and 90°, but most authors have given no rationale for the chosen tilt angle. For this thesis study, the angle of the tilt was selected as 45° because a more vertical end-tilt angle would have made it more difficult to perform the tests without inducing arousals in the sleeping infants. This angle of tilt produces 70% of the changes the 90° tilt would induce (Andrasyova, et al. 1996); however, a greater angle of tilt could have resulted in more prominent cardiovascular responses.

As reported earlier in adults (Sprangers, et al. 1991), even healthy infants showed variability in their BP responses to the head-up tilt test. This inter-subject variability was exaggerated in BPD and preterm infants, possibly indicating impaired vestibulo-mediated cardiovascular control. As these study groups share prematurity as a common factor, another possibility is that immaturity itself may contribute to a more labile BP control during postural challenge. However, the tilt responses of the preterm infants and some of the BPD infants also resemble

those of anesthetized, paralyzed cats after bilateral fastigial lesions (Doba, et al. 1974). In these animals, fastigial or vestibular lesions produced augmentation of the initial fall in BP, a delay in the initial compensated phase, and a failure of BP to return to baseline levels.

The performed current studies did not clarify or explain for the exact cause of BP variability in either healthy controls or in other study infants. Moreover, we do not know whether the BP variability remains after the acquisition of upright posture with standing and walking. The increased BP variability may also be associated with a certain developmental phase, so BPD and preterm infants may present an earlier ("more immature") developmental stage of cardiovascular control. It may be that acquisition of upright posture increases the vestibular stimulus, but it appears that there is a paucity of data concerning this. A literary search revealed only two studies performed both before and after the infant learns to stand or walk, i.e. around 12-18 months of age. In the earlier study by Magrini et al. (Magrini, et al. 1989), the authors used a discrete method for BP measurement, and thus there are no data concerning acute BP responses. Cohen et al. (Cohen, et al. 2010) performed head-up tilt tests in infants from birth up to one year of age with the Finometer. They reported that both peak HR and BP responses, as well as postural BP compensation, improve with age. The authors did not find significant variability in the cardiovascular responses between the study infants, which suggests that the capability to adjust BP improves with increasing age. However, sleep staging was based on behavioral criteria and subcortical arousals were not excluded; thus, there is a possibility that the tilt test responses in this study are in fact cardiovascular responses to subcortical arousals induced by the tilt test. However, this is the only study currently providing data on acute cardiovascular responses to postural challenge at the time of acquisition of upright posture.

Initial tachycardic HR response did not differ between control infants and other study groups. Interestingly, however, UVH and preterm infants did not show the following bradycardic response, but instead the HR of these infants remained above baseline levels. This tachycardic response to tilt may be associated with an impaired ability to increase systemic vascular resistance in these infants. However, similar HR responses are also reported during the head-up tilt test in infants with a life-threatening event (Edner, et al. 1997).

If the final sequelae in SIDS involves hypotension and inadequate restoration of BP (Harper. 2000,Ledwidge, et al. 1998), those infants presenting with hypotension in the tilt test could be assumed to be at a greater risk of SIDS. Furthermore, some BPD and preterm infants presented with a hypertensive response, which could even be protective if faced with this type of shock-like situation. It is not clear, however, why and which infants respond differently to postural challenge.

6.5 Cardiac reactivity and baroreflex sensitivity

HR responses to spontaneous arousals were evaluated to assess general cardiovascular reactivity. HR changes during the initial 10 s of spontaneous arousals were similar among control infants and BPD, smoke-exposed, and preterm infants. This makes the interpretation of the other test results more straightforward. As the general cardiovascular reactivity was normal, the altered BP responses to the side motion test implies abnormal vestibulo-mediated cardiovascular control instead of abnormal control through final common control pathways. In UVH infants, however, HR reactivity was significantly slowed down compared with control infants, although there was a significant overlap. Baseline HR was similar between control and UVH infants. This lower HR reactivity could suggest damaged innervation of the

heart in UVH infants. Nevertheless, in that case, baseline HR levels should also be higher; this was not observed (Alexopoulos, et al. 1988).

HRV was assessed in the studied infants to gain more information about the balance between sympathetic and parasympathetic cardiovascular control. HRV analysis was not the major target of the studies, and not all the studied infants had long enough periods with stabile breathing in quiet NREM sleep to gain data for reliable HRV analysis. The HRV analysis period was selected not to coincide with the tests, and it was made from quiet NREM sleep to exclude external causes of variation and possible (spontaneous) arousals, which could influence the HRV parameters. The values of HRV analysis are directly comparable among infants studied at 2-4 months of age, since the baseline HR and breathing frequencies were similar in these infants. Thus, relatively similar HRV parameters between control, BPD, and smoke infants can be considered as an additive indication of normal baseline cardiovascular function.

Preterm infants studied close to term age showed markedly higher baseline HR and breathing frequencies compared to controls. Baseline HR level and breathing frequency affect HRV considerably (Rosenstock, et al. 1999). Thus, HRV in this study group cannot be directly compared to that of the others. A further limitation of the HRV analysis in these preterm infants is that due to the short recordings and the shorter quiet NREM periods than observed in control infants, HRV analysis could be carried out in only about half of the infants (11 out of 20). Although the role and interpretation of HRV in infants is not as well characterized as in adults (Rosenstock, et al. 1999), the developmental pattern is well described with a lower vagal component of HRV in preterm infants compared with term infants. Thus, the lower HF variability of HRV, and the higher HR and breathing rates in preterm infants are similar to the findings that have previously been described in the literature.

In accordance with other studies (Buchhorn, et al. 2002,Ohuchi, et al. 2001), UVH infants showed significantly lower HR variability as seen in all HRV indices compared with control infants. The reason for this HR dysregulation is not known, but it may relate to their abnormal cardiac anatomy or previous surgery.

We were not able to find events fulfilling the criteria used by Drouin et al (Drouin, et al. 1997b) for assessment of spontaneous baroreflex sensitivity. This may relate at least partly to the study design, as blood pressure measurement was used only for the test periods, and thus the time without tests but with BP measurement available for evaluation of baroreflex sensitivity was rather short for each infant. Moreover, we measured BP only during quiet NREM sleep, whereas in the earlier studies the state of the infant has not been mentioned (Drouin, et al. 1997b) or controlled (Gournay, et al. 2002), which leaves the possibility that in these studies baroreflex sensitivity measurements were taken during wakefulness or REM sleep.

6.6 Study limitations

One significant limitation is the small group size in all the studies, as a result of the difficulties of recruiting suitable infants, and the nature of the study with time- and work-consuming methodology. Nevertheless, the rather small sample size makes it more difficult to expand and draw conclusions from our results to overall infant physiology, and it may have prevented us from finding other significant differences in these infant groups. However, many similar studies by other groups have reported a similar group size.

The control infants were recruited from the delivery hospital by giving a general information letter about the study to the parents, and if interested, the parents contacted the researchers. This method of recruitment is prone to selection bias because those parents

interested in participating in the study may not represent a general parent population. The parents could either be more aware of the factors influencing the child's health, or they could suspect something in their child. In a study like this, however, good parent co-operation is crucial because participation in the study involved one night in the hospital setting and the placement of the measuring devices, although no invasive methods were used.

We were unable to correlate cardiovascular response types to postnatal hypoxic exposure such as SpO_2 during the intensive care period in Study II. In addition, all study groups showed somewhat different cardiovascular reaction patterns although they were mostly clearly different from that of the control group. A direct link to hypoxic exposure during pregnancy or after birth remains speculative, although it cannot be discarded either.

One limitation of Study III is that we did not have objective data on smoking. The classification of mother's smoking status was based on maternity charts and personal information. Although classification of smoking status may be intentionally or unintentionally falsified, it is unlikely that mothers would repeatedly have classified themselves as smokers if they did not smoke. Regarding control infants, researchers verbally confirmed the non-smoking status from the mother before the infant was included in the study. Objective data on maternal smoking during pregnancy can be assessed by nicotine or cotinine evaluations (blood, urine, saliva) during pregnancy (Russell, et al. 2004). Thus, the study families should have been gathered long before birth. Not all families contacted were willing to participate in the study, and the reasons given were mostly infant characteristics, external factors such as siblings or moving to another city, or having to spend one night in a hospital. Thus, the number of families recruited initially should have been markedly higher than the number of infants we intended to study. Also nicotine/cotinine evaluations should have been carried out at least in every trimester of pregnancy to reliably quantify smoke exposure. Evaluation of infant urine or serum cotinine levels at the time of the study is somewhat easier to organize as the cotinine levels are evaluated in only those infants that are actually participating in the study, but this method reliably assesses only recent postnatal exposure to tobacco smoke and can also be acquired from other environmental sources (father, daycare provider, relatives) (DiFranza, et al. 2004).

Preterm infants in Study IV had variable background characteristics such as exposure to maternal smoking during pregnancy, BPD, theophylline or antibiotic therapy, and amount of ventilatory support. Although the results were fairly similar in the linear side motion test, some of the variability especially in the tilt test may result from these background differences. On the other hand, as differences in background characteristics did not have a clear influence on cardiovascular responses to linear side motion tests, these background variabilities did not appear to have a general influence on our study aspects of cardiovascular control.

Although the EEG features of sleep in preterm infants are more immature compared with the infants at the age of 2-4 months (Grigg-Damberger, et al. 2007), we tried to ensure that the tests were made during quiet (NREM) sleep by observing the other polysomnographic features, such as breathing, EMG tonus, and eye movements.

A significant limitation of Study IV is the lack of age-matched control infants. The comparison with full-term infants studied at a considerably older age makes it impossible to evaluate which of the differences are caused by prematurity and which are related to normal maturation of the infant physiology. This could better be addressed by obtaining longitudinal data on infant cardiovascular responses to the head-up tilt test and the side motion test. Some reports (Cohen, et al. 2010,Witcombe, et al. 2010,Yiallourou, et al. 2008) have already gathered some longitudinal data, but direct comparison is difficult because of different methodology as described above in the literature review. Future studies could evaluate this maturational aspect by studying infants at a range of ages from birth until six or maybe even 12 months of age.

7 SUMMARY AND CONCLUSIONS

In conclusion this study shows that

1) Healthy infants at 2-4 months of age have clear vestibulo-mediated cardiovascular responses, seen as well-defined, uniform, and biphasic HR and BP responses to linear side motion.
2) HR responses to 45˚ head-up tilting are uniform in normal infants at 2-4 monts of age. This HR reponse is biphasic, with a sudden increase followed by a decrease and a return to the baseline HR level. Also BP responses are biphasic; however, the initial response may vary from an increase to a decrease followed by a slow return to the baseline level, and there is a considerable inter-subject variation in BP responses, especially in SBP reponses.
3) The side-motion test results indicate that vestibulo-mediated cardiovascular control is attenuated in infants with UVH, smoke-exponsed infants, preterm infants near term age, and in some, but not all prematurely born infants with BPD.
4) Acute blood pressure responses to postural challenge are similar to those of control infants in UVH, BPD and smoke-exposed infants studied at 2-4 months of age, and attenuated in preterm infants close to term age. However, there is increased inter-subject variability in the BP responses in BPD and preterm infants when compared to controls. This indicates more labile BP control in these study groups compared with control infants. We suggest that this lability arises from the observed attenuated vestibulo-mediated cardiovascular control.
5) BPD infants, smoke-exposed infants, and premature infants have normal HR reactivity to spontaneous arousals. UVH infants show attenuated HR reactivity. HRV is normal in BPD and smoke-exposed infants, whereas HF variability is lower in preterm infants, and all HRV components are decreased in UVH infants.

This study presents data on the regulation of HR and BP during sleep both in healthy term born infants and in infants with certain SIDS risk factors or hypoxemia. As the research has shown, infants succumbing to SIDS do appear normal and healthy until they die, and most of the infants at risk of SIDS do not die. Thus, major physiological or anatomical defects are not likely to be found in these risk groups; it must be subtle changes and factors or responses that are not readily measured that lead to SIDS. As some reports raise the possible role of defective cardiovascular control in SIDS (Harper. 2000,Meny, et al. 1994,Poets, et al. 1999), evaluating HR and BP patterns to different stimuli during sleep, may help us understand how the infant physiology works and in what ways it may be altered in those at risk of SIDS.

This study clearly indicates that infants who present with previous hypoxia, prematurity or smoke exposure have impaired vestibulo-mediated cardiovascular control. According to animal studies, this control is likely to be necessary or vital in life-threatening situations. Therefore, the observed cardiovascular dysfunction may render these infants susceptible to SIDS. Data in this thesis also clarify and confirm the earlier findings of variable responses to the head-up tilt test in infants, and extends the knowledge to some SIDS risk groups. Especially notewothy is the significant inter-subject variability in the tilt test responses that is evident in some of the study groups. The observed dysfunction of vestibulo-mediated cardiovascular control may explain the variability in BP regulation after postural challenge.

These findings raise many new questions especially about the developmental aspects of normal infant cardiovascular control, and whether the differences found in this study persist further into infancy and childhood. The results must be confirmed in larger studies with possibly more emphasis on diminishing the background differences. Further, pathological

evaluation of vestibular and fastigial pathways in SIDS infants would show if there are anatomical correlations to this hypothesis on altered vestibular and fastigial pathways in SIDS.

It is unlikely that the subtle alterations in cardiovascular control during sleep found in this thesis study are of significance in the daily life of these infants, because cardiovascular control relies on a multitude of inputs (Persson. 1996,Yates, et al. 2005). When facing a critical situation, however, together with other endogenous or exogenous risks for SIDS, these alterations in vestibulo-mediated cardiovascular control may contribute to the sequelae resulting in sudden death.

ACKNOWLEDGEMENTS

This study was carried out in 2003-2012 at the Children's Hospital, University of Helsinki, and Helsinki University Central Hospital. I am grateful to Docent Jari Petäjä (Director of the Department of Gynecology and Pediatrics, Helsinki University Central Hospital), Professor Mikael Knip (former Chair of the Children's Hospital, University of Helsinki), Docent Eero Jokinen (Head of the Department of Pediatrics, Helsinki University Central Hospital), Professor Emeritus Christer Holmberg and Profesor Emeritus Erkki Savilahti for providing excellent research facilities. I also want to sincerely thank Professor Markku Heikinheimo (Head of the Institute of Clinical Medicine and former Director of the Pediatric Graduate School), and Docent Jussi Merenmies (the present Director of the Pediatric Graduate School) for their interest in educating young researchers and for creating a supportive research environment.

This study was financially supported by the Biomedicum Helsinki Foundation, the Emil Aaltonen Foundation, the Finnish Medical Foundation, The Finnish Sleep Research Society, The Foundation for Pediatric Research, the Päivikki and Sakari Sohlberg Foundation, and the Research Funds of Helsinki University Central Hospital.

I warmly thank all the study participants and their parents who kindly took part in the studies and thus made this thesis possible.

I am most grateful to my supervisor, Docent Turkka Kirjavainen, for introducing me to the magnificent world of infant physiology and sleep. This has been a long journey, but a rewarding one. We started from the basics, you taught me how to set up a polysomnographic recording and how to use all the programmes. And here we are now, after numerous study nights at the Children's Hospital and days at the computer, with all the data, able to discuss our findings and generate new ideas. Thank you for all your support and guidance during these years. Your enthusiasm and depth of knowledge are admirable.

I also wish to thank my thesis commitee, Professor Sture Andersson and Docent Olli Pitkänen. Sture for your ever positive and constructive support. Despite your numerous duties and research projects, you always found a moment for discussion and gave us practical ideas on how to overcome large and small obstacles. Discussions with you gave me confidence in this project. Olli for your encouraging comments and ability to see the forest for the trees. I admire your enthusiastic attitude towards everything, including this study.

I wish to express my sincere gratitude to the official reviewers of this thesis, Professor Pekka Kääpä and Docent Jyri Toikka for their valuable advice and constructive comments on this thesis. Jacqueline Välimäki is gratefully acknowledged for editing the English language.

I warmly thank my coauthor Dr. Timo Hytinantti, who had the ability to always ask the right questions. I also thank my coauthor Docent Eero Jokinen for your kind support.

I wish to express my gratitude to the nurses at LV37 in Kätilöopisto Maternity Hospital, and K4 and K7 in the Children's Hospital for their open and helpful attitude towards our study. I also want to thank Marita Suni for assisting with the background paperwork. Docent Kimmo Sainio and Dr. Satu Kivitie-Kallio are also thanked for letting us carry out sleep studies in

their departments during the night, and Docent Anna-Liisa Järvenpää for her positive attitude towards our project in the Kätilöopisto Maternity Hospital.

Docent Erna Kentala and Professor Tero Kivelä at the Department of Ophthalmology are thanked for their support and letting me have time off to finish my thesis.

I thank all my research colleagues in Biomedicum 2 for their pleasant company and support. I especially want to thank Sonja Strang-Karlsson, Anne Sarajuuri, Helena Olkinuora, and Satu Pirilä for sharing the room and thoughts during these years.

My warmest thanks to all my friends outside this research work. Especially I wish to thank the ”Olari girls” Liisukka, Laku, Kata, Katri, Tuuli, and Suvi for all the great times together, listening to my worries on research and whatever, joining in my happiness, and for being there.

I express my gratitude to my parents-in-law, Leena and Matti, for including me in their family, and Otso, my brother-in-law, for wonderful music and great conversations whenever we meet.

My loving thanks to my dear parents Kaija and Pauli for all their support and love. Also, your concrete help in baby-sitting and dinner preparations made it possible to finish this project. My dear sister Jenni is thanked for the great and small conversations on anything in the world, including the field of medicine and pediatric research. Your family is more dear to me every day.

Last, but not least, my heartfelt thanks go to my family. Hilla, my precious little girl – you amaze me every day and your smile melts my heart. Your arrival put things into perspective, and it is a privilege to see you grow and learn. My dear husband Tuomas I want to thank for everything; for sharing your everyday life with me, for our lovely Hilla, for those experiences on the mountains and underwater, and for putting up with me amongst many other things. You help me to see the big picture, but no detail is too small for you when I have asked your opinion. You gave me encouragement when I did not believe in myself. I love you.

Espoo, January 2013

Suvi Viskari-Lähdeoja

REFERENCES

Abdel-Rahman A, Dechkovskaia AM, Sutton JM, Chen WC, Guan X, Khan WA, Abou-Donia MB. Maternal exposure of rats to nicotine via infusion during gestation produces neurobehavioral deficits and elevated expression of glial fibrillary acidic protein in the cerebellum and CA1 subfield in the offspring at puberty. Toxicology 2005 May 5;209(3):245-261.

Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. Am J Physiol 1985 Oct;249(4 Pt 2):H867-75.

Alexopoulos D, Yusuf S, Johnston JA, Bostock J, Sleight P, Yacoub MH. The 24-hour heart rate behavior in long-term survivors of cardiac transplantation. Am J Cardiol 1988 Apr 15;61(11):880-884.

Alm B, Milerad J, Wennergren G, Skjaerven R, Oyen N, Norvenius G, Daltveit AK, Helweg-Larsen K, Markestad T, Irgens LM. A case-control study of smoking and sudden infant death syndrome in the Scandinavian countries, 1992 to 1995. The Nordic Epidemiological SIDS Study. Arch Dis Child 1998 Apr;78(4):329-334.

American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome. The changing concept of sudden infant death syndrome: diagnostic coding shifts, controversies regarding the sleeping environment, and new variables to consider in reducing risk. Pediatrics 2005 Nov;116(5):1245-1255.

American Academy of Pediatrics. Task Force on Infant Sleep Position and Sudden Infant Death Syndrome. Changing concepts of sudden infant death syndrome: implications for infant sleeping environment and sleep position. Pediatrics 2000 Mar;105(3 Pt 1):650-656.

Andrasyova D, Kellerova E. Blood pressure and heart rate response to head-up position in full-term newborns. Early Hum Dev 1996 Mar 22;44(3):169-178.

Andres RL, Day MC. Perinatal complications associated with maternal tobacco use. Semin Neonatol 2000 Aug;5(3):231-241.

Andriessen P, Oetomo SB, Peters C, Vermeulen B, Wijn PF, Blanco CE. Baroreceptor reflex sensitivity in human neonates: the effect of postmenstrual age. J Physiol 2005 Oct 1;568(Pt 1):333-341.

Andriessen P, Schoffelen RL, Berendsen RC, de Beer NA, Oei SG, Wijn PF, Blanco CE. Noninvasive assessment of blood pressure variability in preterm infants. Pediatr Res 2004 Feb;55(2):220-223.

Arpino C, D'Argenzio L, Ticconi C, Di Paolo A, Stellin V, Lopez L, Curatolo P. Brain damage in preterm infants: etiological pathways. Ann Ist Super Sanita 2005;41(2):229-237.

Barmack NH. Central vestibular system: vestibular nuclei and posterior cerebellum. Brain Res Bull 2003 Jun 15;60(5-6):511-541.

Barron DJ, Kilby MD, Davies B, Wright JG, Jones TJ, Brawn WJ. Hypoplastic left heart syndrome. Lancet 2009 Aug 15;374(9689):551-564.

Bass JL, Corwin M, Gozal D, Moore C, Nishida H, Parker S, Schonwald A, Wilker RE, Stehle S, Kinane TB. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. Pediatrics 2004 Sep;114(3):805-816.

Batty GD, Der G, Deary IJ. Effect of maternal smoking during pregnancy on offspring's cognitive ability: empirical evidence for complete confounding in the US national longitudinal survey of youth. Pediatrics 2006 Sep;118(3):943-950.

Benditt DG, Ferguson DW, Grubb BP, Kapoor WN, Kugler J, Lerman BB, Maloney JD, Raviele A, Ross B, Sutton R, Wolk MJ, Wood DL. Tilt table testing for assessing syncope. American College of Cardiology. J Am Coll Cardiol 1996 Jul;28(1):263-275.

Benwell ME, Balfour DJ, Anderson JM. Evidence that tobacco smoking increases the density of (-)-[3H]nicotine binding sites in human brain. J Neurochem 1988 Apr;50(4):1243-1247.

Beratis NG, Panagoulias D, Varvarigou A. Increased blood pressure in neonates and infants whose mothers smoked during pregnancy. J Pediatr 1996 Jun;128(6):806-812.

Bhandari A, Panitch HB. Pulmonary outcomes in bronchopulmonary dysplasia. Semin Perinatol 2006 Aug;30(4):219-226.

Blair PS, Sidebotham P, Evason-Coombe C, Edmonds M, Heckstall-Smith EM, Fleming P. Hazardous cosleeping environments and risk factors amenable to change: case-control study of SIDS in south west England. BMJ 2009 Oct 13;339:b3666.

Blair PS, Mitchell EA, Heckstall-Smith EM, Fleming PJ. Head covering - a major modifiable risk factor for sudden infant death syndrome: a systematic review. Arch Dis Child 2008 Sep;93(9):778-783.

Blair PS, Platt MW, Smith IJ, Fleming PJ, CESDI SUDI Research Group. Sudden infant death syndrome and sleeping position in pre-term and low birth weight infants: an opportunity for targeted intervention. Arch Dis Child 2006 Feb;91(2):101-106.

Blair PS, Fleming PJ, Bensley D, Smith I, Bacon C, Taylor E, Berry J, Golding J, Tripp J. Smoking and the sudden infant death syndrome: results from 1993-5 case-control study for confidential inquiry into stillbirths and deaths in infancy. Confidential Enquiry into Stillbirths and Deaths Regional Coordinators and Researchers. BMJ 1996 Jul 27;313(7051):195-198.

Blake KV, Gurrin LC, Evans SF, Beilin LJ, Landau LI, Stanley FJ, Newnham JP. Maternal cigarette smoking during pregnancy, low birth weight and subsequent blood pressure in early childhood. Early Hum Dev 2000 Feb;57(2):137-147.

Boyd NR, Windsor RA, Perkins LL, Lowe JB. Quality of measurement of smoking status by self-report and saliva cotinine among pregnant women. Matern Child Health J 1998 Jun;2(2):77-83.

Brandenberger G, Buchheit M, Ehrhart J, Simon C, Piquard F. Is slow wave sleep an appropriate recording condition for heart rate variability analysis? Auton Neurosci 2005 Aug 31;121(1-2):81-86.
Breslau N, Paneth N, Lucia VC, Paneth-Pollak R. Maternal smoking during pregnancy and offspring IQ. Int J Epidemiol 2005 Oct;34(5):1047-1053.
Browne CA, Colditz PB, Dunster KR. Infant autonomic function is altered by maternal smoking during pregnancy. Early Hum Dev 2000 Sep;59(3):209-218.
Buchhorn R, Hulpke-Wette M, Nothroff J, Paul T. Heart rate variability in infants with heart failure due to congenital heart disease: reversal of depressed heart rate variability by propranolol. Med Sci Monit 2002 Oct;8(10):CR661-6.
Carter JR, Ray CA. Sympathetic responses to vestibular activation in humans. Am J Physiol Regul Integr Comp Physiol 2008 Mar;294(3):R681-8.
Chang AB, Wilson SJ, Masters IB, Yuill M, Williams J, Williams G, Hubbard M. Altered arousal response in infants exposed to cigarette smoke. Arch Dis Child 2003 Jan;88(1):30-33.
Chen CM, Tsai TC, Lan MC. Effect of body tilting on physiological functions in healthy term neonates. Acta Paediatr 1995 May;84(5):474-477.
Chen WJ, King KA, Lee RE, Sedtal CS, Smith AM. Effects of nicotine exposure during prenatal or perinatal period on cell numbers in adult rat hippocampus and cerebellum: a stereology study. Life Sci 2006 Nov 2;79(23):2221-2227.
Chess PR, D'Angio CT, Pryhuber GS, Maniscalco WM. Pathogenesis of bronchopulmonary dysplasia. Semin Perinatol 2006 Aug;30(4):171-178.
Chong A, Murphy N, Matthews T. Effect of prone sleeping on circulatory control in infants. Arch Dis Child 2000 Mar;82(3):253-256.
Christensen AE, Tobiassen M, Jensen TK, Wielandt H, Bakketeig L, Host A. Repeated validation of parental self-reported smoking during pregnancy and infancy: a prospective cohort study of infants at high risk for allergy development. Paediatr Perinat Epidemiol 2004 Jan;18(1):73-79.
Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine Tob Res 2004 Apr;6 Suppl 2:S125-40.
Cohen G, Jeffery H, Lagercrantz H, Katz-Salamon M. Long-term reprogramming of cardiovascular function in infants of active smokers. Hypertension 2010 Mar;55(3):722-728.
Cohen G, Vella S, Jeffery H, Lagercrantz H, Katz-Salamon M. Cardiovascular stress hyperreactivity in babies of smokers and in babies born preterm. Circulation 2008 Oct 28;118(18):1848-1853.
Cohen G, Lagercrantz H, Katz-Salamon M. Abnormal circulatory stress responses of preterm graduates. Pediatr Res 2007 Mar;61(3):329-334.
Connor JA, Thiagarajan R. Hypoplastic left heart syndrome. Orphanet J Rare Dis 2007 May 11;2:23.
Cornelius MD, Day NL. The effects of tobacco use during and after pregnancy on exposed children. Alcohol Res Health 2000;24(4):242-249.
Cruz-Sanchez FF, Lucena J, Ascaso C, Tolosa E, Quinto L, Rossi ML. Cerebellar cortex delayed maturation in sudden infant death syndrome. J Neuropathol Exp Neurol 1997 Apr;56(4):340-346.
Curzi-Dascalova L, Figueroa JM, Eiselt M, Christova E, Virassamy A, d'Allest AM, Guimaraes H, Gaultier C, Dehan M. Sleep state organization in premature infants of less than 35 weeks' gestational age. Pediatr Res 1993 Nov;34(5):624-628.
Dampney RA. Functional organization of central pathways regulating the cardiovascular system. Physiol Rev 1994 Apr;74(2):323-364.
Darnall RA, Ariagno RL, Kinney HC. The late preterm infant and the control of breathing, sleep, and brainstem development: a review. Clin Perinatol 2006 Dec;33(4):883-914; abstract x.
Daugherty RM,Jr, Scott JB, Dabney JM, Haddy FJ. Local effects of O2 and CO2 on limb, renal, and coronary vascular resistances. Am J Physiol 1967 Nov;213(5):1102-1110.
Davos CH, Francis DP, Leenarts MF, Yap SC, Li W, Davlouros PA, Wensel R, Coats AJ, Piepoli M, Sreeram N, Gatzoulis MA. Global impairment of cardiac autonomic nervous activity late after the Fontan operation. Circulation 2003 Sep 9;108 Suppl 1:II180-5.
de Burgh Daly M. Peripheral Arterial Chemoreceptors and Respiratory-Cardiovascular Integration. Oxford: Clarendon Press; 1997a. p. 225-287225-287.
de Burgh Daly M. Role of brainstem defence areas. Peripheral Arterial Chemoreceptors and Respiratory-Cardiovascular Integration. Oxford: Clarendon Press; 1997b. p. 432-451432-451.
de Burgh Daly M, Hazzledine JL. The Effects of Artificially Induced Hyperventilation on the Primary Cardiac Reflex Response to Stimulation of the Carotid Bodies in the Dog. J Physiol 1963 Oct;168:872-889.
de Burgh Daly M, Scott MJ. An analysis of the primary cardiovascular reflex effects of stimulation of the carotid body chemoreceptors in the dog. J Physiol 1962 Aug;162:555-573.
de Burgh Daly M, SCOTT MJ. The effects of stimulation of the carotid body chemoreceptors on heart rate in the dog. J Physiol 1958 Nov 10;144(1):148-166.
Dellagrammaticas HD, Kapetanakis J, Papadimitriou M, Kourakis G. Effect of body tilting on physiological functions in stable very low birthweight neonates. Arch Dis Child 1991 Apr;66(4 Spec No):429-432.
Dempsey JA. Crossing the apnoeic threshold: causes and consequences. Exp Physiol 2005 Jan;90(1):13-24.
Diagne M, Delfini C, Angaut P, Buisseret P, Buisseret-Delmas C. Fastigiovestibular projections in the rat: retrograde tracing coupled with gammaamino-butyric acid and glutamate immunohistochemistry. Neurosci Lett 2001 Jul 27;308(1):49-53.
DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. Pediatrics 2004 Apr;113(4 Suppl):1007-1015.

Doba N, Reis DJ. Role of the cerebellum and the vestibular apparatus in regulation of orthostatic reflexes in the cat. Circ Res 1974 Jan;40(4):9-18.
Doyle LW, Anderson PJ. Adult outcome of extremely preterm infants. Pediatrics 2010 Aug;126(2):342-351.
Drouin E, Gournay V, Calamel J, Mouzard A, Roze JC. Feasibility of using finger arterial pressure in neonates. Arch Dis Child Fetal Neonatal Ed 1997a Sep;77(2):F139-40.
Drouin E, Gournay V, Calamel J, Mouzard A, Roze JC. Assessment of spontaneous baroreflex sensitivity in neonates. Arch Dis Child Fetal Neonatal Ed 1997b Mar;76(2):F108-12.
Duncan JR, Randall LL, Belliveau RA, Trachtenberg FL, Randall B, Habbe D, Mandell F, Welty TK, Iyasu S, Kinney HC. The effect of maternal smoking and drinking during pregnancy upon (3)H-nicotine receptor brainstem binding in infants dying of the sudden infant death syndrome: initial observations in a high risk population. Brain Pathol 2008 Jan;18(1):21-31.
Dyckman DJ, Monahan KD, Ray CA. Effect of baroreflex loading on the responsiveness of the vestibulosympathetic reflex in humans. J Appl Physiol 2007 Sep;103(3):1001-1006.
Edner A, Katz-Salamon M, Lagercrantz H, Milerad J. Heart rate response profiles during head upright tilt test in infants with apparent life threatening events. Arch Dis Child 1997 Jan;76(1):27-30.
Elisevich K, Redekop G. The fastigial pressor response. Case report. J Neurosurg 1991 Jan;74(1):147-151.
Evans RG, Ventura S, Dampney RA, Ludbrook J. Neural mechanisms in the cardiovascular responses to acute central hypovolaemia. Clin Exp Pharmacol Physiol 2001 May-Jun;28(5-6):479-487.
Falk L, Nordberg A, Seiger A, Kjaeldgaard A, Hellstrom-Lindahl E. Smoking during early pregnancy affects the expression pattern of both nicotinic and muscarinic acetylcholine receptors in human first trimester brainstem and cerebellum. Neuroscience 2005;132(2):389-397.
Fenton KN, Siewers RD, Rebovich B, Pigula FA. Interim mortality in infants with systemic-to-pulmonary artery shunts. Ann Thorac Surg 2003 Jul;76(1):152-6; discussion 156-7.
Ferber R, Kryger M editors. Principles and Practice of Sleep Medicine in the Child. Philadelphia, Pennsylvania: W.B. Saunders Company; 19957-187-18.
Fewell JE. Protective responses of the newborn to hypoxia. Respir Physiol Neurobiol 2005 Nov 15;149(1-3):243-255.
Fifer WP, Greene M, Hurtado A, Myers MM. Cardiorespiratory responses to bidirectional tilts in infants. Early Hum Dev 1999 Jul;55(3):265-279.
Filiano JJ, Kinney HC. A perspective on neuropathologic findings in victims of the sudden infant death syndrome: the triple-risk model. Biol Neonate 1994;65(3-4):194-197.
Filiano JJ, Kinney HC. Arcuate nucleus hypoplasia in the sudden infant death syndrome. J Neuropathol Exp Neurol 1992 Jul;51(4):394-403.
Finley JP, Hamilton R, MacKenzie MG. Heart rate response to tilting in newborns in quiet and active sleep. Biol Neonate 1984;45(1):1-10.
Foster GE, Brugniaux JV, Pialoux V, Duggan CT, Hanly PJ, Ahmed SB, Poulin MJ. Cardiovascular and cerebrovascular responses to acute hypoxia following exposure to intermittent hypoxia in healthy humans. J Physiol 2009 Jul 1;587(Pt 13):3287-3299.
Foster GE, Poulin MJ, Hanly PJ. Intermittent hypoxia and vascular function: implications for obstructive sleep apnoea. Exp Physiol 2007 Jan;92(1):51-65.
Fox GP, Matthews TG. Autonomic dysfunction at different ambient temperatures in infants at risk of sudden infant death syndrome. Lancet 1989 Nov 4;2(8671):1065-1067.
Franco P, Kato I, Richardson HL, Yang JS, Montemitro E, Horne RS. Arousal from sleep mechanisms in infants. Sleep Med 2010 Aug;11(7):603-614.
Franco P, Verheulpen D, Valente F, Kelmanson I, de Broca A, Scaillet S, Groswasser J, Kahn A. Autonomic responses to sighs in healthy infants and in victims of sudden infant death. Sleep Med 2003 Nov;4(6):569-577.
Franco P, Chabanski S, Szliwowski H, Dramaix M, Kahn A. Influence of maternal smoking on autonomic nervous system in healthy infants. Pediatr Res 2000 Feb;47(2):215-220.
Franco P, Groswasser J, Hassid S, Lanquart JP, Scaillet S, Kahn A. Prenatal exposure to cigarette smoking is associated with a decrease in arousal in infants. J Pediatr 1999 Jul;135(1):34-38.
Franco P, Szliwowski H, Dramaix M, Kahn A. Polysomnographic study of the autonomic nervous system in potential victims of sudden infant death syndrome. Clin Auton Res 1998 Oct;8(5):243-249.
Freeman R. Assessment of cardiovascular autonomic function. Clin Neurophysiol 2006 Apr;117(4):716-730.
Friedman DB, Jensen FB, Matzen S, Secher NH. Non-invasive blood pressure monitoring during head-up tilt using the Penaz principle. Acta Anaesthesiol Scand 1990 Oct;34(7):519-522.
Gabbett TJ, Weston SB, Barrett RS, Gass GC. Cardiovascular regulation during head-up tilt in healthy 20-30-year-old and 70-75-year-old men. Clin Sci (Lond) 2001 Feb;100(2):199-206.
Galland BC, Taylor BJ, Bolton DP, Sayers RM. Heart rate variability and cardiac reflexes in small for gestational age infants. J Appl Physiol 2006 Mar;100(3):933-939.
Galland BC, Hayman RM, Taylor BJ, Bolton DP, Sayers RM, Williams SM. Factors affecting heart rate variability and heart rate responses to tilting in infants aged 1 and 3 months. Pediatr Res 2000a Sep;48(3):360-368.
Galland BC, Taylor BJ, Bolton DP, Sayers RM. Vasoconstriction following spontaneous sighs and head-up tilts in infants sleeping prone and supine. Early Hum Dev 2000b May;58(2):119-132.
Galland BC, Reeves G, Taylor BJ, Bolton DP. Sleep position, autonomic function, and arousal. Arch Dis Child Fetal Neonatal Ed 1998 May;78(3):F189-94.
Ganong WF. Review of Medical Physiology. . 19th ed. Stamford, Connecticut: Appleton & Lange; 1999. p. 568-581, 601-616568-581, 601-616.

George L, Granath F, Johansson AL, Cnattingius S. Self-reported nicotine exposure and plasma levels of cotinine in early and late pregnancy. Acta Obstet Gynecol Scand 2006;85(11):1331-1337.
Georgieff MK, Mills MM, Gomez-Marin O, Sinaiko AR. Rate of change of blood pressure in premature and full term infants from birth to 4 months. Pediatr Nephrol 1996 Apr;10(2):152-155.
Gien J, Kinsella JP. Pathogenesis and treatment of bronchopulmonary dysplasia. Curr Opin Pediatr 2011 Jun;23(3):305-313.
Gilbert R, Salanti G, Harden M, See S. Infant sleeping position and the sudden infant death syndrome: systematic review of observational studies and historical review of recommendations from 1940 to 2002. Int J Epidemiol 2005 Aug;34(4):874-887.
Gilmartin GS, Lynch M, Tamisier R, Weiss JW. Chronic intermittent hypoxia in humans during 28 nights results in blood pressure elevation and increased muscle sympathetic nerve activity. Am J Physiol Heart Circ Physiol 2010 Sep;299(3):H925-31.
Gilmartin GS, Tamisier R, Curley M, Weiss JW. Ventilatory, hemodynamic, sympathetic nervous system, and vascular reactivity changes after recurrent nocturnal sustained hypoxia in humans. Am J Physiol Heart Circ Physiol 2008 Aug;295(2):H778-85.
Giuditta M, Ruggiero DA, Del Bo A. Anatomical basis for the fastigial pressor response. Blood Press 2003;12(3):175-180.
Godding V, Bonnier C, Fiasse L, Michel M, Longueville E, Lebecque P, Robert A, Galanti L. Does in utero exposure to heavy maternal smoking induce nicotine withdrawal symptoms in neonates? Pediatr Res 2004 Apr;55(4):645-651.
Gournay V, Drouin E, Roze JC. Development of baroreflex control of heart rate in preterm and full term infants. Arch Dis Child Fetal Neonatal Ed 2002 May;86(3):F151-4.
Gray PH, Rogers Y. Are infants with bronchopulmonary dysplasia at risk for sudden infant death syndrome? Pediatrics 1994 May;93(5):774-777.
Greenfield AD, Whitney RJ, Mowbray JF. Methods for the investigation of peripheral blood flow. Br Med Bull 1963 May;19:101-109.
Grieve PG, Myers MM, Stark RI, Housman S, Fifer WP. Topographic localization of electrocortical activation in newborn and two- to four-month-old infants in response to head-up tilting. Acta Paediatr 2005 Dec;94(12):1756-1763.
Grigg-Damberger M, Gozal D, Marcus CL, Quan SF, Rosen CL, Chervin RD, Wise M, Picchietti DL, Sheldon SH, Iber C. The visual scoring of sleep and arousal in infants and children. J Clin Sleep Med 2007 Mar 15;3(2):201-240.
Gronlund J, Jalonen J, Valimaki I. Transcephalic electrical impedance provides a means for quantifying pulsatile cerebral blood volume changes following head-up tilt. Early Hum Dev 1997 Jan 3;47(1):11-18.
Guilleminault C, Souquet M. Appendix II: Scoring criteria. In Guilleminault C (Ed) Sleep and Waking Disorders: Indications and techniques. Menlo Park: Addison Wesley Publishing Co.; 1982. p. 415-426415-426.
Gulli G, Cooper VL, Claydon VE, Hainsworth R. Prolonged latency in the baroreflex mediated vascular resistance response in subjects with postural related syncope. Clin Auton Res 2005 Jun;15(3):207-212.
Guntheroth WG, Spiers PS. Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med 1998 Oct 15;339(16):1161; author reply 1162-3.
Gupta JM, Scopes JW. Observations on blood pressure in newborn infants. Arch Dis Child 1965 Dec;40(214):637-644.
Guyton AC. The relationship of cardiac output and arterial pressure control. Circulation 1981 Dec;64(6):1079-1088.
Hack M. Adult outcomes of preterm children. J Dev Behav Pediatr 2009 Oct;30(5):460-470.
Haenninen A, Peltonen T, Hirvonen L. Response of Blood Pressure to Sucking and Tilting in the Newborn Premature Infant. Ann Paediatr Fenn 1964;10:92-98.
Hafstrom O, Milerad J, Sandberg KL, Sundell HW. Cardiorespiratory effects of nicotine exposure during development. Respir Physiol Neurobiol 2005 Nov 15;149(1-3):325-341.
Hainsworth R, Karim F. Left ventricular inotropic and peripheral vasomotor responses from independent changes in pressure in the carotid sinuses and cerebral arteries in anaesthetized dogs. J Physiol 1973 Jan;228(1):139-155.
Hakulinen A, Hirvonen L, Peltonen T. Response of blood pressure to sucking and tilting in the newborn infant. Ann Paediatr Fenn 1962;8:56-61.
Halloran DR, Alexander GR. Preterm delivery and age of SIDS death. Ann Epidemiol 2006 Aug;16(8):600-606.
Harper RM. Sudden infant death syndrome: a failure of compensatory cerebellar mechanisms? Pediatr Res 2000 Aug;48(2):140-142.
Harper RM, Kinney HC, Fleming PJ, Thach BT. Sleep influences on homeostatic functions: implications for sudden infant death syndrome. Respir Physiol 2000a Feb;119(2-3):123-132.
Harper RM, Woo MA, Alger JR. Visualization of sleep influences on cerebellar and brainstem cardiac and respiratory control mechanisms. Brain Res Bull 2000b Sep 1;53(1):125-131.
Harper RM, Richard CA, Rector DM. Physiological and ventral medullary surface activity during hypovolemia. Neuroscience 1999;94(2):579-586.
Harper RM, Bandler R. Finding the failure mechanism in Sudden Infant Death Syndrome. Nat Med 1998 Feb;4(2):157-158.
Harrington C, Kirjavainen T, Teng A, Sullivan CE. nCPAP improves abnormal autonomic function in at-risk-for-SIDS infants with OSA. J Appl Physiol 2003 Oct;95(4):1591-1597.
Harrington C, Kirjavainen T, Teng A, Sullivan CE. Altered autonomic function and reduced arousability in apparent life-threatening event infants with obstructive sleep apnea. Am J Respir Crit Care Med 2002 Apr 15;165(8):1048-1054.
Harrington C, Kirjavainen T, Teng A, Sullivan CE. Cardiovascular responses to three simple, provocative tests of autonomic activity in sleeping infants. J Appl Physiol 2001 Aug;91(2):561-568.
Hasan SU, Simakajornboon N, MacKinnon Y, Gozal D. Prenatal cigarette smoke exposure selectively alters protein kinase C and nitric oxide synthase expression within the neonatal rat brainstem. Neurosci Lett 2001 Mar 30;301(2):135-138.

Haschke F, van't Hof MA. Euro-Growth references for length, weight, and body circumferences. Euro-Growth Study Group. J Pediatr Gastroenterol Nutr 2000;31 Suppl 1:S14-38.
Hauck FR, Thompson JM, Tanabe KO, Moon RY, Vennemann MM. Breastfeeding and Reduced Risk of Sudden Infant Death Syndrome: A Meta-analysis. Pediatrics 2011 Jun 13.
Hauck FR, Tanabe KO. International trends in sudden infant death syndrome: stabilization of rates requires further action. Pediatrics 2008 Sep;122(3):660-666.
Hauck FR, Omojokun OO, Siadaty MS. Do pacifiers reduce the risk of sudden infant death syndrome? A meta-analysis. Pediatrics 2005 Nov;116(5):e716-23.
Heistad D, Abboud FM, Mark AL, Schmid PG. Effect of baroreceptor activity on ventilatory response to chemoreceptor stimulation. J Appl Physiol 1975a Sep;39(3):411-416.
Heistad DD, Abboud FM, Mark AL, Schmid PG. Effect of hypoxemia on responses to norepinephrine and angiotensin in coronary and muscular vessels. J Pharmacol Exp Ther 1975b Jun;193(3):941-950.
Henderson-Smart DJ, De Paoli AG. Prophylactic methylxanthine for prevention of apnoea in preterm infants. Cochrane Database Syst Rev 2010a Dec 8;(12)(12):CD000432.
Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. Cochrane Database Syst Rev 2010b Dec 8;(12)(12):CD000140.
Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database Syst Rev 2010c Jan 20;(1)(1):CD000273.
Hodgman JE, Siassi B. Prolonged QTc as a risk factor for SIDS. Pediatrics 1999 Apr;103(4 Pt 1):814-815.
Hoffman JI, Lister G. The implications of a relationship between prolonged QT interval and the sudden infant death syndrome. Pediatrics 1999 Apr;103(4 Pt 1):815-817.
Holmes MJ, Cotter LA, Arendt HE, Cass SP, Yates BJ. Effects of lesions of the caudal cerebellar vermis on cardiovascular regulation in awake cats. Brain Res 2002 May 31;938(1-2):62-72.
Horne RS, Witcombe NB, Yiallourou SR, Scaillet S, Thiriez G, Franco P. Cardiovascular control during sleep in infants: Implications for Sudden Infant Death Syndrome. Sleep Med 2010 Aug;11(7):615-621.
Horne RS, Ferens D, Watts AM, Vitkovic J, Lacey B, Andrew S, Cranage SM, Chau B, Greaves R, Adamson TM. Effects of maternal tobacco smoking, sleeping position, and sleep state on arousal in healthy term infants. Arch Dis Child Fetal Neonatal Ed 2002 Sep;87(2):F100-5.
Horner RL. Autonomic consequences of arousal from sleep: mechanisms and implications. Sleep 1996 Dec;19(10 Suppl):S193-5.
Horsley T, Clifford T, Barrowman N, Bennett S, Yazdi F, Sampson M, Moher D, Dingwall O, Schachter H, Cote A. Benefits and harms associated with the practice of bed sharing: a systematic review. Arch Pediatr Adolesc Med 2007 Mar;161(3):237-245.
Hovi P, Andersson S, Raikkonen K, Strang-Karlsson S, Jarvenpaa AL, Eriksson JG, Pesonen AK, Heinonen K, Pyhala R, Kajantie E. Ambulatory blood pressure in young adults with very low birth weight. J Pediatr 2010 Jan;156(1):54-59.e1.
Hovi P, Andersson S, Eriksson JG, Jarvenpaa AL, Strang-Karlsson S, Makitie O, Kajantie E. Glucose regulation in young adults with very low birth weight. N Engl J Med 2007 May 17;356(20):2053-2063.
Huizink AC, Mulder EJ. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. Neurosci Biobehav Rev 2006;30(1):24-41.
Hunt CE. Ontogeny of autonomic regulation in late preterm infants born at 34-37 weeks postmenstrual age. Semin Perinatol 2006 Apr;30(2):73-76.
Hunt CE, Hauck FR. Sudden infant death syndrome. CMAJ 2006 Jun 20;174(13):1861-1869.
Hutton LC, Yan E, Yawno T, Castillo-Melendez M, Hirst JJ, Walker DW. Injury of the developing cerebellum: A brief review of the effects of endotoxin and asphyxial challenges in the late gestation sheep fetus. Cerebellum 2007 May 3:1-10.
Imholz BP, Wieling W, van Montfrans GA, Wesseling KH. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. Cardiovasc Res 1998 Jun;38(3):605-616.
Inder TE, Warfield SK, Wang H, Huppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. Pediatrics 2005 Feb;115(2):286-294.
International Paediatric Work Group on Arousals. The scoring of arousals in healthy term infants (between the ages of 1 and 6 months). J Sleep Res 2005 Mar;14(1):37-41.
Jauniaux E, Biernaux V, Gerlo E, Gulbis B. Chronic maternal smoking and cord blood amino acid and enzyme levels at term. Obstet Gynecol 2001 Jan;97(1):57-61.
Jauniaux E, Gulbis B, Acharya G, Gerlo E. Fetal amino acid and enzyme levels with maternal smoking. Obstet Gynecol 1999 May;93(5 Pt 1):680-683.
Jellema WT, Imholz BP, van Goudoever J, Wesseling KH, van Lieshout JJ. Finger arterial versus intrabrachial pressure and continuous cardiac output during head-up tilt testing in healthy subjects. Clin Sci (Lond) 1996 Aug;91(2):193-200.
Jian BJ, Cotter LA, Emanuel BA, Cass SP, Yates BJ. Effects of bilateral vestibular lesions on orthostatic tolerance in awake cats. J Appl Physiol 1999 May;86(5):1552-1560.
Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001 Jun;163(7):1723-1729.
Jones KL, Krous HF, Nadeau J, Blackbourne B, Zielke HR, Gozal D. Vascular endothelial growth factor in the cerebrospinal fluid of infants who died of sudden infant death syndrome: evidence for antecedent hypoxia. Pediatrics 2003 Feb;111(2):358-363.
Kahn A, Groswasser J, Sottiaux M, Kelmanson I, Rebuffat E, Franco P, Dramaix M, Wayenberg JL. Prenatal exposure to cigarettes in infants with obstructive sleep apneas. Pediatrics 1994 May;93(5):778-783.

Kahn A, Groswasser J, Rebuffat E, Sottiaux M, Blum D, Foerster M, Franco P, Bochner A, Alexander M, Bachy A. Sleep and cardiorespiratory characteristics of infant victims of sudden death: a prospective case-control study. Sleep 1992 Aug;15(4):287-292.

Kato I, Franco P, Groswasser J, Scaillet S, Kelmanson I, Togari H, Kahn A. Incomplete arousal processes in infants who were victims of sudden death. Am J Respir Crit Care Med 2003 Dec 1;168(11):1298-1303.

Kato I, Groswasser J, Franco P, Scaillet S, Kelmanson I, Togari H, Kahn A. Developmental characteristics of apnea in infants who succumb to sudden infant death syndrome. Am J Respir Crit Care Med 2001 Oct 15;164(8 Pt 1):1464-1469.

Kaufmann H, Biaggioni I, Voustianiouk A, Diedrich A, Costa F, Clarke R, Gizzi M, Raphan T, Cohen B. Vestibular control of sympathetic activity. An otolith-sympathetic reflex in humans. Exp Brain Res 2002 Apr;143(4):463-469.

Keens TG, Davidson Ward SL. Respiratory Mechanisms and hypoxia. In: Byard RW, Krous HF, editors. Sudden Infant Death Syndrome - Problems, Progress and Possibilities London: Arnold; 2001. p. 66-8266-82.

Kelly J, Mathews KA, O'Conor M. Smoking in pregnancy: effects on mother and fetus. Br J Obstet Gynaecol 1984 Feb;91(2):111-117.

Kerman IA, Yates BJ. Regional and functional differences in the distribution of vestibulosympathetic reflexes. Am J Physiol 1998 Sep;275(3 Pt 2):R824-35.

Kesmodel U, Olsen SF. Smoking habits among pregnant Danish women: reliability of information recorded after delivery. J Epidemiol Community Health 1999 Apr;53(4):239-242.

Khairy P, Poirier N, Mercier LA. Univentricular heart. Circulation 2007 Feb 13;115(6):800-812.

Kinney HC, Randall LL, Sleeper LA, Willinger M, Belliveau RA, Zec N, Rava LA, Dominici L, Iyasu S, Randall B, Habbe D, Wilson H, Mandell F, McClain M, Welty TK. Serotonergic brainstem abnormalities in Northern Plains Indians with the sudden infant death syndrome. J Neuropathol Exp Neurol 2003 Nov;62(11):1178-1191.

Kinney HC, Filiano JJ, White WF. Medullary serotonergic network deficiency in the sudden infant death syndrome: review of a 15-year study of a single dataset. J Neuropathol Exp Neurol 2001 Mar;60(3):228-247.

Kinney HC, Filiano JJ, Sleeper LA, Mandell F, Valdes-Dapena M, White WF. Decreased muscarinic receptor binding in the arcuate nucleus in sudden infant death syndrome. Science 1995 Sep 8;269(5229):1446-1450.

Kinney HC, O'Donnell TJ, Kriger P, White WF. Early developmental changes in [3H]nicotine binding in the human brainstem. Neuroscience 1993 Aug;55(4):1127-1138.

Kinney HC, Brody BA, Finkelstein DM, Vawter GF, Mandell F, Gilles FH. Delayed central nervous system myelination in the sudden infant death syndrome. J Neuropathol Exp Neurol 1991 Jan;50(1):29-48.

Kinney HC, Burger PC, Harrell FE,Jr, Hudson RP,Jr. 'Reactive gliosis' in the medulla oblongata of victims of the sudden infant death syndrome. Pediatrics 1983 Aug;72(2):181-187.

Kirjavainen J, Ojala T, Huhtala V, Kirjavainen T, Kero P. Heart rate variability in response to the sleep-related movements in infants with and without colic. Early Hum Dev 2004 Aug;79(1):17-30.

Klebanoff MA, Levine RJ, Clemens JD, DerSimonian R, Wilkins DG. Serum cotinine concentration and self-reported smoking during pregnancy. Am J Epidemiol 1998 Aug 1;148(3):259-262.

Korvenranta E, Lehtonen L, Peltola M, Hakkinen U, Andersson S, Gissler M, Hallman M, Leipala J, Rautava L, Tammela O, Linna M. Morbidities and hospital resource use during the first 3 years of life among very preterm infants. Pediatrics 2009 Jul;124(1):128-134.

Krous HF, Beckwith JB, Byard RW, Rognum TO, Bajanowski T, Corey T, Cutz E, Hanzlick R, Keens TG, Mitchell EA. Sudden infant death syndrome and unclassified sudden infant deaths: a definitional and diagnostic approach. Pediatrics 2004 Jul;114(1):234-238.

La Rovere MT, Pinna GD, Raczak G. Baroreflex sensitivity: measurement and clinical implications. Ann Noninvasive Electrocardiol 2008 Apr;13(2):191-207.

Lagercrantz H, Edwards D, Henderson-Smart D, Hertzberg T, Jeffery H. Autonomic reflexes in preterm infants. Acta Paediatr Scand 1990 Aug-Sep;79(8-9):721-728.

Lambers DS, Clark KE. The maternal and fetal physiologic effects of nicotine. Semin Perinatol 1996 Apr;20(2):115-126.

Lavezzi AM, Ottaviani G, Mauri M, Matturri L. Alterations of biological features of the cerebellum in sudden perinatal and infant death. Curr Mol Med 2006 Jun;6(4):429-435.

Lavezzi AM, Ottaviani G, Mingrone R, Matturri L. Analysis of the human locus coeruleus in perinatal and infant sudden unexplained deaths. Possible role of the cigarette smoking in the development of this nucleus. Brain Res Dev Brain Res 2005 Jan 1;154(1):71-80.

Law KL, Stroud LR, LaGasse LL, Niaura R, Liu J, Lester BM. Smoking during pregnancy and newborn neurobehavior. Pediatrics 2003 Jun;111(6 Pt 1):1318-1323.

Ledwidge M, Fox G, Matthews T. Neurocardiogenic syncope: a model for SIDS. Arch Dis Child 1998 May;78(5):481-483.

Lehtonen L, Martin RJ. Ontogeny of sleep and awake states in relation to breathing in preterm infants. Semin Neonatol 2004 Jun;9(3):229-238.

Lehtovirta P, Forss M. The acute effect of smoking on intervillous blood flow of the placenta. Br J Obstet Gynaecol 1978 Oct;85(10):729-731.

Leistner HL, Haddad GG, Epstein RA, Lai TL, Epstein MA, Mellins RB. Heart rate and heart rate variability during sleep in aborted sudden infant death syndrome. J Pediatr 1980 Jul;97(1):51-55.

Leon-Velarde F, Villafuerte FC, Richalet JP. Chronic mountain sickness and the heart. Prog Cardiovasc Dis 2010 May-Jun;52(6):540-549.

Lewis DA, Zlotocha J, Henke L, Dhala A. Specificity of head-up tilt testing in adolescents: effect of various degrees of tilt challenge in normal control subjects. J Am Coll Cardiol 1997 Oct;30(4):1057-1060.

Limperopoulos C, Soul JS, Gauvreau K, Huppi PS, Warfield SK, Bassan H, Robertson RL, Volpe JJ, du Plessis AJ. Late gestation cerebellar growth is rapid and impeded by premature birth. Pediatrics 2005 Mar;115(3):688-695.

Lindblad A, Marsal K, Andersson KE. Effect of nicotine on human fetal blood flow. Obstet Gynecol 1988 Sep;72(3 Pt 1):371-382.
Lindqvist R, Lendahls L, Tollbom O, Aberg H, Hakansson A. Smoking during pregnancy: comparison of self-reports and cotinine levels in 496 women. Acta Obstet Gynecol Scand 2002 Mar;81(3):240-244.
Longo LD. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. Am J Obstet Gynecol 1977 Sep 1;129(1):69-103.
Longo LD. Carbon monoxide: effects on oxygenation of the fetus in utero. Science 1976 Oct 29;194(4264):523-525.
Lucey JF. Comments on a sudden infant death article in another journal. Pediatrics 1999 Apr;103(4 Pt 1):812.
Lugliani R, Whipp BJ, Wasserman K. A role for the carotid body in cardiovascular control in man. Chest 1973 May;63(5):744-750.
Lugliani R, Whipp BJ, Seard C, Wasserman K. Effect of bilateral carotid-body resection on ventilatory control at rest and during exercise in man. N Engl J Med 1971 Nov;285(20):1105-1111.
Lutherer LO, Lutherer BC, Dormer KJ, Janssen HF, Barnes CD. Bilateral lesions of the fastigial nucleus prevent the recovery of blood pressure following hypotension induced by hemorrhage or administration of endotoxin. Brain Res 1983 Jun 20;269(2):251-257.
Magrini F, Roberts N, Branzi G, Mondadori C, Reggiani P, Meazza R, Ciulla M. Cardiac responses to head up tilt during early extrauterine life: relevance of active acquisition of erect posture. Cardiovasc Res 1989 May;23(5):460-464.
Mahle WT, Tavani F, Zimmerman RA, Nicolson SC, Galli KK, Gaynor JW, Clancy RR, Montenegro LM, Spray TL, Chiavacci RM, Wernovsky G, Kurth CD. An MRI study of neurological injury before and after congenital heart surgery. Circulation 2002 Sep 24;106(12 Suppl 1):I109-14.
Malik S, Cleves MA, Honein MA, Romitti PA, Botto LD, Yang S, Hobbs CA, National Birth Defects Prevention Study. Maternal smoking and congenital heart defects. Pediatrics 2008 Apr;121(4):e810-6.
Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991 Aug;84(2):482-492.
Malloy MH. Sudden infant death syndrome among extremely preterm infants: United States 1997-1999. J Perinatol 2004 Mar;24(3):181-187.
Malloy MH, Freeman DH,Jr. Birth weight- and gestational age-specific sudden infant death syndrome mortality: United States, 1991 versus 1995. Pediatrics 2000 Jun;105(6):1227-1231.
Malloy MH, Hoffman HJ. Prematurity, sudden infant death syndrome, and age of death. Pediatrics 1995 Sep;96(3 Pt 1):464-471.
Marks MJ, Burch JB, Collins AC. Effects of chronic nicotine infusion on tolerance development and nicotinic receptors. J Pharmacol Exp Ther 1983 Sep;226(3):817-825.
Marshall JM. Peripheral chemoreceptors and cardiovascular regulation. Physiol Rev 1994 Jul;74(3):543-594.
Martin RJ, Miller MJ, Redline S. Screening for SIDS: A neonatal perspective. Pediatrics 1999 Apr;103(4 Pt 1):812-813.
Massin MM, Maeyns K, Lombet J, Rigo J, Gerard P. Heart rate response profiles to tilting in healthy and unhealthy neonates. Med Sci Monit 2002 May;8(5):CR321-5.
Matthews TG. The autonomic nervous system--a role in sudden infant death syndrome. Arch Dis Child 1992 May;67(5):654-656.
Matturri L, Ottaviani G, Lavezzi AM. Maternal smoking and sudden infant death syndrome: epidemiological study related to pathology. Virchows Arch 2006 Dec;449(6):697-706.
Mazursky JE, Birkett CL, Bedell KA, Ben-Haim SA, Segar JL. Development of baroreflex influences on heart rate variability in preterm infants. Early Hum Dev 1998 Nov;53(1):37-52.
McNamara F, Sullivan CE. Obstructive sleep apnea in infants: relation to family history of sudden infant death syndrome, apparent life-threatening events, and obstructive sleep apnea. J Pediatr 2000 Mar;136(3):318-323.
McNamara F, Wulbrand H, Thach BT. Characteristics of the infant arousal response. J Appl Physiol 1998 Dec;85(6):2314-2321.
Meny RG, Carroll JL, Carbone MT, Kelly DH. Cardiorespiratory recordings from infants dying suddenly and unexpectedly at home. Pediatrics 1994 Jan;93(1):44-49.
Mewes AU, Huppi PS, Als H, Rybicki FJ, Inder TE, McAnulty GB, Mulkern RV, Robertson RL, Rivkin MJ, Warfield SK. Regional brain development in serial magnetic resonance imaging of low-risk preterm infants. Pediatrics 2006 Jul;118(1):23-33.
Moon RY, Horne RS, Hauck FR. Sudden infant death syndrome. Lancet 2007 Nov 3;370(9598):1578-1587.
Moons P, Sluysmans T, De Wolf D, Massin M, Suys B, Benatar A, Gewillig M. Congenital heart disease in 111 225 births in Belgium: birth prevalence, treatment and survival in the 21st century. Acta Paediatr 2009 Mar;98(3):472-477.
Morley R, Leeson Payne C, Lister G, Lucas A. Maternal smoking and blood pressure in 7.5 to 8 year old offspring. Arch Dis Child 1995 Feb;72(2):120-124.
Moss AJ, Emmanouilides GC, Monset-Couchard M, Marcano B. Vascular responses to postural changes in normal, newborn infants. Pediatrics 1968 Aug;42(2):250-254.
Moss AJ, Duffie ER,Jr, Emmanouilides G. Blood Pressure and Vasomotor Reflexes in the Newborn Infant. Pediatrics 1963 Aug;32:175-179.
Mountcastle VB editor. Medical Physiology. 13th ed. Saint Louis: The C.V. Mosby Company; 1974958-980958-980.
Myers MM, Gomez-Gribben E, Smith KS, Tseng A, Fifer WP. Developmental changes in infant heart rate responses to head-up tilting. Acta Paediatr 2006 Jan;95(1):77-81.
Nachmanoff DB, Panigrahy A, Filiano JJ, Mandell F, Sleeper LA, Valdes-Dapena M, Krous HF, White WF, Kinney HC. Brainstem 3H-nicotine receptor binding in the sudden infant death syndrome. J Neuropathol Exp Neurol 1998 Nov;57(11):1018-1025.

Naeye RL. Effects of maternal cigarette smoking on the fetus and placenta. Br J Obstet Gynaecol 1978 Oct;85(10):732-737.
Naeye RL. Brain-stem and adrenal abnormalities in the sudden-infant-death syndrome. Am J Clin Pathol 1976 Sep;66(3):526-530.
Naeye RL. Hypoxemia and the sudden infant death syndrome. Science 1974 Nov 29;186(4166):837-838.
Navarro HA, Seidler FJ, Schwartz RD, Baker FE, Dobbins SS, Slotkin TA. Prenatal exposure to nicotine impairs nervous system development at a dose which does not affect viability or growth. Brain Res Bull 1989 Sep;23(3):187-192.
Neubauer JA. Invited review: Physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol 2001 Apr;90(4):1593-1599.
Noda H, Sugita S, Ikeda Y. Afferent and efferent connections of the oculomotor region of the fastigial nucleus in the macaque monkey. J Comp Neurol 1990 Dec 8;302(2):330-348.
Northern Neonatal Nursing Initiative. Systolic blood pressure in babies of less than 32 weeks gestation in the first year of life. Arch Dis Child Fetal Neonatal Ed 1999 Jan;80(1):F38-42.
Official Statistics of Finland. Causes of death [e-publication]. Available at: http://www.stat.fi/til/ksyyt/tau_en.html. Accessed 8/4, 2012.
Official Statistics of Finland. Statistical Report 42/2011. Newborns 2010. Available at: http://www.stakes.fi/EN/tilastot/statisticsbytopic/reproduction/newborns.htm. Accessed 8/4, 2012.
Oh W, Arcilla RA, Oh MA, Lind J. Renal and cardiovascular effects of body tilting in the newborn infant. A comparative study of infants born with early and late cord clamping. Biol Neonat 1966;10(1):76-92.
Ohuchi H, Hasegawa S, Yasuda K, Yamada O, Ono Y, Echigo S. Severely impaired cardiac autonomic nervous activity after the Fontan operation. Circulation 2001 Sep 25;104(13):1513-1518.
O'Kusky JR, Norman MG. Sudden infant death syndrome: increased synaptic density in the central reticular nucleus of the medulla. J Neuropathol Exp Neurol 1994 May;53(3):263-271.
Olson DM, Shewmon DA. Electroencephalographic abnormalities in infants with hypoplastic left heart syndrome. Pediatr Neurol 1989 Mar-Apr;5(2):93-98.
Oncken CA, Henry KM, Campbell WA, Kuhn CM, Slotkin TA, Kranzler HR. Effect of maternal smoking on fetal catecholamine concentrations at birth. Pediatr Res 2003 Jan;53(1):119-124.
Opdal SH, Rognum TO. Gene variants predisposing to SIDS: current knowledge. Forensic Sci Med Pathol 2011 Mar;7(1):26-36.
Opdal SH, Rognum TO, Vege A, Saugstad OD. Hypoxanthine levels in vitreous humor: a study of influencing factors in sudden infant death syndrome. Pediatr Res 1998 Aug;44(2):192-196.
Orem J, Barnes CD editors. Physiology in Sleep. New York: Academic Press Inc.; 19802-552-55.
Owen L, McNeill A. Saliva cotinine as indicator of cigarette smoking in pregnant women. Addiction 2001 Jul;96(7):1001-1006.
Pae EK, Chien P, Harper RM. Intermittent hypoxia damages cerebellar cortex and deep nuclei. Neurosci Lett 2005 Feb 28;375(2):123-128.
Peacock JL, Cook DG, Carey IM, Jarvis MJ, Bryant AE, Anderson HR, Bland JM. Maternal cotinine level during pregnancy and birthweight for gestational age. Int J Epidemiol 1998 Aug;27(4):647-656.
Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. Circulation 2007 Mar 6;115(9):1132-1146.
Penaz J. Criteria for set point estimation in the volume clamp method of blood pressure measurement. Physiol Res 1992;41(1):5-10.
Persson PB. Modulation of cardiovascular control mechanisms and their interaction. Physiol Rev 1996 Jan;76(1):193-244.
Phillipson EA. Control of breathing during sleep. Am Rev Respir Dis 1978 Nov;118(5):909-939.
Picton-Warlow CG, Mayer FE. Cardiovascular responses to postural changes in the neonate. Arch Dis Child 1970 Jun;45(241):354-359.
Pijpers L, Wladimiroff JW, McGhie JS, Bom N. Acute effect of maternal smoking on the maternal and fetal cardiovascular system. Early Hum Dev 1984 Sep;10(1-2):95-105.
Poets CF, Meny RG, Chobanian MR, Bonofiglo RE. Gasping and other cardiorespiratory patterns during sudden infant deaths. Pediatr Res 1999 Mar;45(3):350-354.
Poets CF, Samuels MP, Southall DP. Epidemiology and pathophysiology of apnoea of prematurity. Biol Neonate 1994;65(3-4):211-219.
Quattrochi JJ, McBride PT, Yates AJ. Brainstem immaturity in sudden infant death syndrome: a quantitative rapid Golgi study of dendritic spines in 95 infants. Brain Res 1985 Jan 28;325(1-2):39-48.
Radtke A, Popov K, Bronstein AM, Gresty MA. Vestibulo-autonomic control in man: Short- and long-latency vestibular effects on cardiovascular function. J Vestib Res 2003;13(1):25-37.
Rankova S. Blood pressure in newborn term and preterm infants. Tokai J Exp Clin Med 1989 Jun;14(3):181-190.
Ravits JM. AAEM minimonograph #48: autonomic nervous system testing. Muscle Nerve 1997 Aug;20(8):919-937.
Rees S, Inder T. Fetal and neonatal origins of altered brain development. Early Hum Dev 2005 Sep;81(9):753-761.
Rognum TO, Saugstad OD. Biochemical and immunological studies in SIDS victims. Clues to understanding the death mechanism. Acta Paediatr Suppl 1993 Jun;82 Suppl 389:82-85.
Rognum TO, Saugstad OD, Oyasaeter S, Olaisen B. Elevated levels of hypoxanthine in vitreous humor indicate prolonged cerebral hypoxia in victims of sudden infant death syndrome. Pediatrics 1988 Oct;82(4):615-618.
Rosenstock EG, Cassuto Y, Zmora E. Heart rate variability in the neonate and infant: analytical methods, physiological and clinical observations. Acta Paediatr 1999 May;88(5):477-482.
Russell T, Crawford M, Woodby L. Measurements for active cigarette smoke exposure in prevalence and cessation studies: why simply asking pregnant women isn't enough. Nicotine Tob Res 2004 Apr;6 Suppl 2:S141-51.

Sarajuuri A, Jokinen E, Puosi R, Mildh L, Mattila I, Lano A, Lonnqvist T. Neurodevelopment in children with hypoplastic left heart syndrome. J Pediatr 2010 Sep;157(3):414-20, 420.e1-4.
Sarajuuri A, Lonnqvist T, Mildh L, Rajantie I, Eronen M, Mattila I, Jokinen E. Prospective follow-up study of children with univentricular heart: neurodevelopmental outcome at age 12 months. J Thorac Cardiovasc Surg 2009 Jan;137(1):139-45, 145.e1-2.
Sarajuuri A, Jokinen E, Puosi R, Eronen M, Mildh L, Mattila I, Valanne L, Lonnqvist T. Neurodevelopmental and neuroradiologic outcomes in patients with univentricular heart aged 5 to 7 years: related risk factor analysis. J Thorac Cardiovasc Surg 2007 Jun;133(6):1524-1532.
Sarna JR, Hawkes R. Patterned Purkinje cell death in the cerebellum. Prog Neurobiol 2003 Aug;70(6):473-507.
Sawnani H, Jackson T, Murphy T, Beckerman R, Simakajornboon N. The effect of maternal smoking on respiratory and arousal patterns in preterm infants during sleep. Am J Respir Crit Care Med 2004 Mar 15;169(6):733-738.
Schechtman VL, Harper RM, Wilson AJ, Southall DP. Sleep state organization in normal infants and victims of the sudden infant death syndrome. Pediatrics 1992a May;89(5 Pt 1):865-870.
Schechtman VL, Raetz SL, Harper RK, Garfinkel A, Wilson AJ, Southall DP, Harper RM. Dynamic analysis of cardiac R-R intervals in normal infants and in infants who subsequently succumbed to the sudden infant death syndrome. Pediatr Res 1992b Jun;31(6):606-612.
Schechtman VL, Harper RM, Kluge KA, Wilson AJ, Hoffman HJ, Southall DP. Heart rate variation in normal infants and victims of the sudden infant death syndrome. Early Hum Dev 1989 Jun;19(3):167-181.
Schechtman VL, Harper RM, Kluge KA, Wilson AJ, Hoffman HJ, Southall DP. Cardiac and respiratory patterns in normal infants and victims of the sudden infant death syndrome. Sleep 1988 Oct;11(5):413-424.
Scher AM, Young AC. Servoanalysis of carotid sinus reflex effects on peripheral resistance. Circ Res 1963 Feb;12:152-162.
Scher MS, Steppe DA, Dahl RE, Asthana S, Guthrie RD. Comparison of EEG sleep measures in healthy full-term and preterm infants at matched conceptional ages. Sleep 1992 Oct;15(5):442-448.
Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W, Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007 Nov 8;357(19):1893-1902.
Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W, Caffeine for Apnea of Prematurity Trial Group. Caffeine therapy for apnea of prematurity. N Engl J Med 2006 May 18;354(20):2112-2121.
Schrod L, Walter J. Effect of head-up body tilt position on autonomic function and cerebral oxygenation in preterm infants. Biol Neonate 2002;81(4):255-259.
Schulzke SM, Pillow JJ. The management of evolving bronchopulmonary dysplasia. Paediatr Respir Rev 2010 Sep;11(3):143-148.
Schwartz PJ, Stramba-Badiale M, Segantini A, Austoni P, Bosi G, Giorgetti R, Grancini F, Marni ED, Perticone F, Rosti D, Salice P. Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med 1998 Jun 11;338(24):1709-1714.
Schwartz RD, Kellar KJ. Nicotinic cholinergic receptor binding sites in the brain: regulation in vivo. Science 1983 Apr 8;220(4593):214-216.
Shah DK, Anderson PJ, Carlin JB, Pavlovic M, Howard K, Thompson DK, Warfield SK, Inder TE. Reduction in cerebellar volumes in preterm infants: relationship to white matter injury and neurodevelopment at two years of age. Pediatr Res 2006 Jul;60(1):97-102.
Shekhawat PS, Sasidharan P, Lewis DA. Myocardial performance and baroreceptor reflexes in preterm neonates: an echocardiographic evaluation using the tilt-table test. Pediatr Cardiol 2001 Nov-Dec;22(6):465-470.
Siebold C, Anagnostou E, Glasauer S, Glonti L, Kleine JF, Tchelidze T, Buttner U. Canal-otolith interaction in the fastigial nucleus of the alert monkey. Exp Brain Res 2001 Jan;136(2):169-178.
Sindberg Eriksen P, Marsal K. Acute effects of maternal smoking on fetal blood flow. Acta Obstet Gynecol Scand 1984;63(5):391-397.
Slotkin TA. Cholinergic systems in brain development and disruption by neurotoxicants: nicotine, environmental tobacco smoke, organophosphates. Toxicol Appl Pharmacol 2004 Jul 15;198(2):132-151.
Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? J Pharmacol Exp Ther 1998 Jun;285(3):931-945.
Smith GC, Wood AM, Pell JP, White IR, Crossley JA, Dobbie R. Second-trimester maternal serum levels of alpha-fetoprotein and the subsequent risk of sudden infant death syndrome. N Engl J Med 2004 Sep 2;351(10):978-986.
Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993 Feb 4;328(5):303-307.
Southall DP, Stevens V, Franks CI, Newcombe RG, Shinebourne EA, Wilson AJ. Sinus tachycardia in term infants preceding sudden infant death. Eur J Pediatr 1988 Jan;147(1):74-78.
Sowter B, Doyle LW, Morley CJ, Altmann A, Halliday J. Is sudden infant death syndrome still more common in very low birthweight infants in the 1990s? Med J Aust 1999 Oct 18;171(8):411-413.
Spencer N, Logan S. Sudden unexpected death in infancy and socioeconomic status: a systematic review. J Epidemiol Community Health 2004 May;58(5):366-373.
Sprangers RL, Veerman DP, Karemaker JM, Wieling W. Initial circulatory responses to changes in posture: influence of the angle and speed of tilt. Clin Physiol 1991 May;11(3):211-220.
Stephan-Blanchard E, Telliez F, Leke A, Djeddi D, Bach V, Libert JP, Chardon K. The influence of in utero exposure to smoking on sleep patterns in preterm neonates. Sleep 2008 Dec 1;31(12):1683-1689.
Storm H, Nylander G, Saugstad OD. The amount of brainstem gliosis in sudden infant death syndrome (SIDS) victims correlates with maternal cigarette smoking during pregnancy. Acta Paediatr 1999 Jan;88(1):13-18.
Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. Thorax 1998 Mar;53(3):204-212.

Strachan DP, Cook DG. Health effects of passive smoking. 1. Parental smoking and lower respiratory illness in infancy and early childhood. Thorax 1997 Oct;52(10):905-914.
Stumper O. Hypoplastic left heart syndrome. Postgrad Med J 2010 Mar;86(1013):183-188.
Tabbutt S, Nord AS, Jarvik GP, Bernbaum J, Wernovsky G, Gerdes M, Zackai E, Clancy RR, Nicolson SC, Spray TL, Gaynor JW. Neurodevelopmental outcomes after staged palliation for hypoplastic left heart syndrome. Pediatrics 2008 Mar;121(3):476-483.
Takashima S, Becker LE. Developmental abnormalities of medullary "respiratory centers" in sudden infant death syndrome. Exp Neurol 1985 Dec;90(3):580-587.
Tamisier R, Pepin JL, Remy J, Baguet JP, Taylor JA, Weiss JW, Levy P. 14 Nights of Intermittent Hypoxia Elevate Daytime Blood Pressure and Sympathetic Activity in Healthy Humans. Eur Respir J 2011 Jan;37(1):119-128.
Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996 Mar;17(3):354-381.
Task Force on Sudden Infant Death Syndrome, Moon RY. SIDS and other sleep-related infant deaths: expansion of recommendations for a safe infant sleeping environment. Pediatrics 2011 Nov;128(5):1030-1039.
Thach BT. The role of respiratory control disorders in SIDS. Respir Physiol Neurobiol 2005 Nov 15;149(1-3):343-353.
Thompson DK, Warfield SK, Carlin JB, Pavlovic M, Wang HX, Bear M, Kean MJ, Doyle LW, Egan GF, Inder TE. Perinatal risk factors altering regional brain structure in the preterm infant. Brain 2007 Mar;130(Pt 3):667-677.
Thompson FJ, Yates BJ, Franzen O, Wald JR. Lumbar spinal cord responses to limb vein distention. J Auton Nerv Syst 1983 Nov;9(2-3):531-546.
Thompson JM, Mitchell EA, New Zealand Cot Death Study Group. Are the risk factors for SIDS different for preterm and term infants? Arch Dis Child 2006 Feb;91(2):107-111.
Thoresen M, Cowan F, Walloe L. Cardiovascular responses to tilting in healthy newborn babies. Early Hum Dev 1991 Oct;26(3):213-222.
Timmers HJ, Wieling W, Karemaker JM, Lenders JW. Denervation of carotid baro- and chemoreceptors in humans. J Physiol 2003 Nov 15;553(Pt 1):3-11.
Trinder J, Allen N, Kleiman J, Kralevski V, Kleverlaan D, Anson K, Kim Y. On the nature of cardiovascular activation at an arousal from sleep. Sleep 2003 Aug 1;26(5):543-551.
Ulm MR, Plockinger B, Pirich C, Gryglewski RJ, Sinzinger HF. Umbilical arteries of babies born to cigarette smokers generate less prostacyclin and contain less arginine and citrulline compared with those of babies born to control subjects. Am J Obstet Gynecol 1995 May;172(5):1485-1487.
Valdes-Dapena M. The sudden infant death syndrome: pathologic findings. Clin Perinatol 1992 Dec;19(4):701-716.
Van Reempts PJ, Wouters A, De Cock W, Van Acker KJ. Stress responses to tilting and odor stimulus in preterm neonates after intrauterine conditions associated with chronic stress. Physiol Behav 1997 Mar;61(3):419-424.
van Sleuwen BE, Engelberts AC, Boere-Boonekamp MM, Kuis W, Schulpen TW, L'Hoir MP. Swaddling: a systematic review. Pediatrics 2007 Oct;120(4):e1097-106.
Vege A, Rognum TO, Scott H, Aasen AO, Saugstad OD. SIDS cases have increased levels of interleukin-6 in cerebrospinal fluid. Acta Paediatr 1995 Feb;84(2):193-196.
Vennemann MM, Hoffgen M, Bajanowski T, Hense HW, Mitchell EA. Do immunisations reduce the risk for SIDS? A meta-analysis. Vaccine 2007 Jun 21;25(26):4875-4879.
Vennemann MM, Findeisen M, Butterfass-Bahloul T, Jorch G, Brinkmann B, Kopcke W, Bajanowski T, Mitchell EA, GeSID Group. Modifiable risk factors for SIDS in Germany: results of GeSID. Acta Paediatr 2005 Jun;94(6):655-660.
Wade JG, Larson CP,Jr, Hickey RF, Ehrenfeld WK, Severinghaus JW. Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. N Engl J Med 1970 Apr 9;282(15):823-829.
Waldman S, Krauss AN, Auld PA. Baroreceptors in preterm infants: their relationship to maturity and disease. Dev Med Child Neurol 1979 Dec;21(6):714-722.
Wang X, Tager IB, Van Vunakis H, Speizer FE, Hanrahan JP. Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes. A prospective cohort study. Int J Epidemiol 1997 Oct;26(5):978-988.
Warner HR. The frequency-dependent nature of blood pressure regulation by the carotid sinus studied with an electric analog. Circ Res 1958 Jan;6(1):35-40.
Waters KA, Meehan B, Huang JQ, Gravel RA, Michaud J, Cote A. Neuronal apoptosis in sudden infant death syndrome. Pediatr Res 1999 Feb;45(2):166-172.
Weimer LH. Autonomic testing: common techniques and clinical applications. Neurologist 2010 Jul;16(4):215-222.
Werthammer J, Brown ER, Neff RK, Taeusch HW,Jr. Sudden infant death syndrome in infants with bronchopulmonary dysplasia. Pediatrics 1982 Mar;69(3):301-304.
Wieling W, Van Lieshout JJ, Ten Harkel AD. Dynamics of circulatory adjustments to head-up tilt and tilt-back in healthy and sympathetically denervated subjects. Clin Sci (Lond) 1998 Apr;94(4):347-352.
Wilkinson AR, Brosi DM, Jiang ZD. Functional impairment of the brainstem in infants with bronchopulmonary dysplasia. Pediatrics 2007 Aug;120(2):362-371.
Williams GM, O'Callaghan M, Najman JM, Bor W, Andersen MJ, Richards D, U C. Maternal cigarette smoking and child psychiatric morbidity: a longitudinal study. Pediatrics 1998 Jul;102(1):e11.
Witcombe NB, Yiallourou SR, Walker AM, Horne RS. Delayed blood pressure recovery after head-up tilting during sleep in preterm infants. J Sleep Res 2010 Mar;19(1 Pt 1):93-102.
Witcombe NB, Yiallourou SR, Walker AM, Horne RS. Blood pressure and heart rate patterns during sleep are altered in preterm-born infants: implications for sudden infant death syndrome. Pediatrics 2008 Dec;122(6):e1242-8.
Woodring SF, Rossiter CD, Yates BJ. Pressor response elicited by nose-up vestibular stimulation in cats. Exp Brain Res 1997 Jan;113(1):165-168.

Yates BJ, Bronstein AM. The effects of vestibular system lesions on autonomic regulation: observations, mechanisms, and clinical implications. J Vestib Res 2005;15(3):119-129.
Yates BJ, Holmes MJ, Jian BJ. Adaptive plasticity in vestibular influences on cardiovascular control. Brain Res Bull 2000 Sep 1;53(1):3-9.
Yates BJ, Aoki M, Burchill P, Bronstein AM, Gresty MA. Cardiovascular responses elicited by linear acceleration in humans. Exp Brain Res 1999 Apr;125(4):476-484.
Yates BJ. Vestibular influences on the autonomic nervous system. Ann N Y Acad Sci 1996 Jun 19;781:458-473.
Yates BJ. Vestibular influences on the sympathetic nervous system. Brain Res Brain Res Rev 1992 Jan-Apr;17(1):51-59.
Yates BJ, Mickle JP, Hedden WJ, Thompson FJ. Tracing of afferent pathways from the femoral-saphenous vein to the dorsal root ganglia using transport of horseradish peroxidase. J Auton Nerv Syst 1987 Jul;20(1):1-11.
Yiallourou SR, Sands SA, Walker AM, Horne RS. Postnatal development of baroreflex sensitivity in infancy. J Physiol 2010 Jun 15;588(Pt 12):2193-2203.
Yiallourou SR, Walker AM, Horne RS. Effects of sleeping position on development of infant cardiovascular control. Arch Dis Child 2008 Oct;93(10):868-872.
Yiallourou SR, Walker AM, Horne RS. Validation of a new noninvasive method to measure blood pressure and assess baroreflex sensitivity in preterm infants during sleep. Sleep 2006 Aug 1;29(8):1083-1088.
Ykeda DS, Lorenzi-Filho G, Lopes AA, Alves RS. Sleep in infants with congenital heart disease. Clinics (Sao Paulo) 2009;64(12):1205-1210.
Young IM, Holland WW. Some physiological responses of neonatal arterial blood pressure and pulse rate. Br Med J 1958 Aug 2;2(5091):276-278.
Young M, Cottom D. Arterial and venous blood pressure responses during a reduction in blood volume and hypoxia and hypercapnia in infants during the first two days of life. Pediatrics 1966 May;37(5):733-742.
Zacharia A, Zimine S, Lovblad KO, Warfield S, Thoeny H, Ozdoba C, Bossi E, Kreis R, Boesch C, Schroth G, Huppi PS. Early assessment of brain maturation by MR imaging segmentation in neonates and premature infants. AJNR Am J Neuroradiol 2006 May;27(5):972-977.
Zhou W, Tang BF, King WM. Responses of rostral fastigial neurons to linear acceleration in an alert monkey. Exp Brain Res 2001 Jul;139(1):111-115.