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ORIGINAL ARTICLE

Changes of cardiovascular regulation during rewarming in newborns undergoing whole-body hypothermia

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Abstract

OBJECTIVES: The aim of the study was to determine changes of oxygenation and cardiovascular parameters during body temperature recovery in newborns undergoing therapeutic hypothermia.
DESIGN AND SETTINGS: Three full-term newborns treated by whole-body hypothermia according to TOBY trial were included in the study. They were cooled to body temperature of 33.5 °C for 72 hours, thereafter gradual rewarming was initiated. During rewarming period following parameters were measured: heart rate and heart rate variability, blood pressure, core body temperature, blood oxygen saturation, cerebral and splanchnic tissue oxygenation. In one of the infants Doppler sonography examination of truncus coeliacus and arteria mesenterica superior was performed to assess blood flow in these arteries.
RESULTS: During rewarming period the heart rate increased, whereas blood pressure tended to decrease. It was observed ascending trend in parameters of heart rate variability (MSSD and total spectral power) due to increasing spectral activity in LF and also HF bands. Blood oxygen saturation and cerebral tissue oxygenation remained stable, but significant decrease of splanchnic tissue oxygenation was noticed. This finding corresponded to Doppler sonography parameters in arteria mesenterica superior.
THE MAIN FINDING: Therapeutic hypothermia and subsequent rewarming in newborns influenced cardiovascular regulation (blood pressure, heart rate, heart rate variability). Body temperature recovery was accompanied by reduction in splanchnic oxygenation and blood flow in superior mesenteric artery.
CONCLUSIONS: Body temperature recovery in neonates led to changes in autonomic cardiovascular regulation resulting in redistribution of blood flow to vital organs. Reduction of blood flow to splanchnic organs during heating is a finding that has not been described yet. Further studies are needed to confirm these findings.

Abbreviations:

AMS	- arteria mesenterica superior
BP	- blood pressure
CSOR	- cerebro - splanchnic oxygenation ratio
EDV	- end diastolic velocity
FoE CNS	- fractional oxygen extraction of cerebral tissue
FoE Spl	- fractional oxygen extraction of splanchnic tissue
HF	- high frequency band
HIE	- hypoxic – ischemic encephalopathy
HR	- heart rate
HRV	- heart rate variability
LF	- low frequency band
MSSD	- mean square of successive differences
NIRS	- near infrared spectroscopy
PSV	- peak systolic velocity
RI	- resistive index
SpO2	- blood oxygen saturation
StO2 CNS	- cerebral tissue oxygenation
StO2 Spl	- splanchnic tissue oxygenation
TC	- truncus coeliacus
Tot P	- total spectral power
VLF	- very low frequency band

INTRODUCTION

Encephalopathy caused by hypoxic-ischemic insult during perinatal period remains one of the major causes of death and severe disability in children. Reported overall mortality rate is approximately 20% and the frequency of poor neurodevelopmental outcome in surviving newborns is around 30%. Incidence and severity of impairment depend on severity of hypoxic-ischemic encephalopathy (HIE) in affected infants (Cloherty, 2012). Recent randomised controlled trials have shown that selective head cooling and whole-body hypothermia reduce mortality and long-term neurodevelopmental morbidity in neonates with moderate and severe HIE (Gluckman *et al.* 2005; Shankaran *et al.* 2005; Azzopardi *et al.* 2009). Despite the improvement in outcome of newborns undergoing therapeutic hypothermia, approximately half of cooled infants suffer from death or severe disability.

Effects of hypothermia and gradual rewarming on regional oxygenation and functions of cardiovascular system in newborns are not well known yet. Above mentioned trials referred a reversible decrease of heart rate (HR) in asphyxiated newborns during cooling. Heart rate variability (HRV) is considered to be a strong early biophysical indicator of autonomic regulation failure during development of several pathological conditions, as proved by many studies (Fairchild & O´Shea, 2009; Golder *et al.* 2013; Yiallourou *et al.* 2013). It is known, that HRV may be affected in newborns with HIE due to direct effect of asphyxia on the heart or secondary due to impaired central cardiovascular regulation but most likely combination of both conditions (Matić *et al.* 2013). In the current literature, there are several reports on the effects of hypothermia and rewarming on HRV in neonates (Lasky *et al.* 2009; Aliefendioglu *et al.* 2012; Matić *et al.* 2013; Massaro *et al.* 2014), and cerebral oxygenation (StO2 CNS) (Ancora *et al.* 2013; Shellhaas *et al.* 2013; Dehaes *et al.* 2014) in neonates, but complex data including splanchnic oxygenation (StO2 Spl) and haemodynamic changes during body temperature recovery is still lacking.

Tab. 1. Characterization of newborns included in the study.

Subject	1	2	3
Gestational age (weeks)	39	39	37
Birth weight (g)	3350	3860	2420
Gender	M	F	M
Apgar score (1st min.)	1	1	1
Apgar score (5th min.)	4	5	2
Apgar score (10th min.)	4	6	2
Initial pH	7.03	6.97	7.01
Initial base excess	–22.0	–20.2	–11.5
Grade of the encephalopathy	moderate	moderate	moderate
Clinical seizures	yes	no	yes
aEEG seizures	yes	no	no

Legend: aEEG – amplitude integrated electroencephalography, g – grams, min. – minute, M – male, F – female

MATERIAL & METHODS:

This clinical pilot study was approved by the Ethical Committee at Jessenius Medical Faculty in Martin and contains data of three asphyxiated newborns (Table 1) admitted to the Department of Neonatology, University Hospital in Martin, after meeting the conditions for whole-body hypothermia according to TOBY trial (Azzopardi *et al.* 2009). Informed consent was obtained from parents of all participants included in the study.

Therapeutic hypothermia was carried out according to the protocol corresponding to TOBY trial (Azzopardi *et al.* 2009). Neonates were cooled to target rectal body temperature of 33.5 °C. Rewarming to physiological value of rectal body temperature 36.9 °C was initiated after 72 hours. All infants were mechanically ventilated. Selected oxygenation (SpO2, StO2 CNS, StO2 Spl) and cardiovascular parameters (ECG, HR, HRV and systemic blood pressure) were monitored continuously and evaluated in intervals corresponding to the increase in body temperature by approximately 1.0 °C. SpO2 was monitored by pulse oximetry (Masimo®), StO2 CNS and StO2 Spl were recorded using near infrared spectroscopy (NIRS) device FORE – SIGHT (CAS Medical Systems, Branford, CT, USA). ECG, HR and HRV were recorded by means of VarCor PF 7 System (Dimea, Olomouc) with bipolar horizontal thoracic ECG belt. ECG signal and beat-to-beat (RR) intervals (2576–3293 in one segment) were analysed in time and frequency domains. The data was sampled at frequency of 1000 Hz. The power spectrum parameters were com-

puted using the Fast Fourier transform (window length of 256 samples) and calculated in very low frequency (VLF; 0.02–0.04 Hz) low-frequency (LF; 0.04–0.15 Hz) and in high-frequency (HF; 0.15–1.0 Hz) bands.

Average values (arithmetic means) of mentioned parameters of all probands for each selected body temperature level (I – 33.6 °C, II – 34.5 °C, III – 35.6 °C, IV – 36.7 °C) were calculated. Because of low number of subjects, no statistical evaluation excluding arithmetic mean was applied. In one neonate the Doppler sonography of truncus coeliacus (TC) and arteria mesenterica superior (AMS) was performed to assess the blood flow in these arteries under the certain values of body temperature.

RESULTS

During body temperature recovery SpO2 and StO2 CNS were relatively stable, whereas significant decrease in StO2 Spl was noticed. Fractional oxygen extraction of cerebral tissue (FoE CNS) did not change, while fractional oxygen extraction of splanchnic tissue (StO2 Spl) increased rapidly. Cerebro-splanchnic oxygenation ratio (CSOR) have shown a slight descending trend (Table 2).

Finding of a decrease in StO2 Spl correlated with Doppler flow parameters in AMS. Along with heating, peak systolic velocity (PSV) in AMS raised from initial 50.4 cm/s during hypothermia to 119.1 cm/s after temperature recovery, while end diastolic velocity (EDV) did not change significantly. Values of resistive index (RI) remained relatively high (from 0.83 to 1.0). The opposite phenomenon was found in Doppler parameters in TC. While PSV increased slightly (from 102.3 to 127.5 cm/s), values of EDV elevated markedly from 28.1 to 62.9 cm/s and RI values declined (from 0.73 to 0.5).

With the increase of body temperature, HR accelerated gradually, whereas systolic, diastolic and mean BP tended to decrease. HRV parameters – MSSD and total spectral power have shown an ascending trend due to an increase in all spectral bands. The LF/HF ratio had a diminishing tendency during BT recovery (Table 3).

DISCUSSION

To our knowledge, this study is the first report concerning changes of tissue oxygenation, cardiovascular and Doppler sonography parameters during period of body temperature recovery in newborns. There are several papers in the literature focusing on StO2 CNS evaluation, especially in relation to short and long term outcome prediction in neonates with encephalopathy (Ancora *et al.* 2013; Dehaes *et al.* 2014). Up to date, no reports about StO2 Spl measurements in the context of hypothermia and rewarming of asphyxiated neonates were published.

Changes of HR and systemic BP caused by hypothermia and heating are well known yet (Thoresen & Whitelaw, 2000; Cavallaro *et al.* 2013). Our findings are consistent with these studies. However, the first published case study regarding changes of HRV during temperature recovery in neonates has shown a descending trend of the HRV parameters (Lasky *et al.*

Tab. 2. Oxygenation parametres in individual probands (1, 2, 3) and average values (AV) during temperature recovery.

BT (°C)	P	OXYGENATION PARAMETERS					
		SpO2 (%)	StO2 CNS (%)	StO2 Spl (%)	FoE CNS	FoE Spl	CSOR
33.6	1	99	78	94	0.21	0.05	1.20
	2	97	95	91	0.02	0.06	0.96
	3	94	71	86.8	0.24	0.07	1.22
	AV	96.6	81.3	90.6	0.16	0.06	1.12
34.5	1	99	79.3	91.2	0.19	0.07	1.15
	2	97	95	91.5	0.02	0.05	0.96
	3	92.5	68.4	77.2	0.26	0.16	1.12
	AV	96.2	80.9	86.6	0.16	0.09	1.07
35.6	1	98	79.5	91.2	0.18	0.07	1.15
	2	98	95	77.3	0.03	0.21	0.81
	3	94.5	70.2	86.4	0.25	0.08	1.23
	AV	96.8	81.6	85.0	0.15	0.12	1.06
36.7	1	98	80	93.7	0.18	0.04	1.17
	2	96	94.7	65.1	0.01	0.32	0.68
	3	92	70.8	83.8	0.23	0.08	1.18
	AV	95.3	81.8	80.9	0.14	0.15	1.01

Legend: BT – body temperature, P – probands, SpO2 – blood oxygen saturation, StO2 CNS – cerebral tissue oxygenation, StO2 Spl – splanchnic tissue oxygenation, FoE CNS – fractional oxygen extraction of cerebral tissues, FoE Spl – fractional oxygen extraction of splanchnic tissues, CSOR – cerebro-splanchnic oxygenation ratio

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Tab. 3. Parameters of HR, BP and HRV in individual probands (1, 2, 3) and average values (AV) of these parametres during body temperature recovery.

BT (°C)	P	CARDIOVASCULAR PARAMETERS									
		HR (/min)	BPs (mmHg)	BPd (mmHg)	BPm (mmHg)	MSSD	Tot P	VLF	LF	HF	LF/HF
33.6	1	111	75	49	61	14	35.5	13.2	18.6	3.7	5.0
	2	110	79.5	51	60.5	202	93.7	13.6	43.1	37.0	1.16
	3	127	72	47	56	20	29.5	6.0	18.7	4.8	3.9
	AV	116	75.5	49	59.2	78.6	52.9	10.9	26.8	15.1	3.35
34.5	1	114	59	38	48	51	28.4	3.0	12.8	12.6	1.0
	2	132	78.5	49.5	57.5	15	30.1	4.7	5.3	20.1	0.27
	3	138	77.5	46	54.5	53	102.4	20.4	54.2	27.8	1.94
	AV	128	71.6	44.5	53.3	39.6	53.6	9.3	24.1	20.1	1.07
35.6	1	121	69	45	56	44	174.5	83.8	71.5	19.2	3.7
	2	118	76	45	54	126	83.0	16.3	33.1	33.7	0.97
	3	135	72	46	55	26	72.0	1.8	53.6	16.7	3.24
	AV	124.6	72.3	45.3	55	65.3	109.8	33.9	52.7	23.2	2.63
36.7	1	132	51	46	49	19	33.7	5.8	20.9	7.1	3.3
	2	120	75	43.5	54	324	147.7	0.5	10.8	134.4	0.08
	3	135	69	35	48	22	206.3	74.7	112.3	19.4	5.8
	AV	129	65	41.5	50.3	121.6	129.2	27	48	53.6	3.06

Legend: BT – body temperature, P – probands, HR – heart rate, BPs – systolic blood pressure, BPd – diastolic blood pressure, BPm – mean blood preassure, MSSD – mean square of successive differences, Tot P – total spectral power, VLF – very low frequency band, LF– low frequency band, HF – high frequency band

2009). Our results of HRV parameters are in contrast to the mentioned paper. In our study, all HRV parameters increased at the end of rewarming indicating a better chronotropic cardiac regulation under normal body temperature. Probably the reason for this discrepancy may be the degree of encephalopathy and severity of the brain damage. This finding needs further evaluation by studies with higher number of probands.

According to the literature and our data we hypothesize that rewarming results in vasodilatation of peripheral vessels leading to a drop in blood pressure. Subsequent activation of cardiovascular regulatory mechanisms caused the increase in HR and HRV. Another concomitant effect was a redistribution of blood to vital organs, as it was confirmed by stable values of StO2 CNS and significant decrease of StO2 Spl. Doppler sonography revealed a preserved and adequate blood flow in TC, whereas the blood flow in AMS was diminished. The reduction of blood flow in AMS was caused by its vasoconstriction as documented by high vascular resistance (RI). The increasing metabolic demand of intestinal tissue as a consequence of ascending body temperature was probably the reason of increased fractional oxygen extraction in splanchnic region to compensate the mesenterial vasoconstriction. Reduction in mesenterial perfusion in neonates during heating after therapeutic hypothermia is a valuable finding that has not been described previously. It may be essential for optimal feeding management to avoid hypoxic intestinal injury after therapeutic hypothermia and rewarming procedure in newborns.

The main limitation of our study is a very small number of included infants and the results will need validation by other large trials.

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