ORIGINAL ARTICLE

Cardiovascular and respiratory status in mechanically ventilated asphyxiated term infants: comparison between hypothermic and control group

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Abstract. *Objective:* To evaluate cardiorespiratory changes in hypothermic asphyxiated ventilated infants compared with controls. *Study Design:* Retrospective chart analysis with historical controls. Cardiorespiratory status of 10 asphyxiated newborns in hypothermia (H) (32°-34°C) (H group) was compared with that one of 11 asphyxiated newborns [control group, (C group)]. *Results:* 3/10 patients in H group needed an increased mean tidal volume (from 5.8 to 8 ml/Kg) during hypothermia when temperature reached a value of 32°C, to maintain adequate gas exchange. Length of mechanical ventilation was similar in the two groups (H=5.4±4.4 vs C=2.8±2.7 days, p=ns). Heart rate, similar at the baseline (H group: 129±11 beats/min; C group: 129±12 beats/min), dropped to an average of 102±10 beats/min ($p<0.05$) during cooling in H group, while it remained stable in C group. Mean arterial blood pressure, comparable at birth, increased by a median of 8 mmHg during hypothermia (p=ns). *Conclusions:* Hypothermia induces mild changes in cardiovascular status and in lung mechanics.

Key words: Hypothermia, heart rate, tidal volume, blood-pressure

Introduction

Perinatal asphyxia, affecting 2-4 out of 1.000 liveborn term infants, contributes to 21% of all death in neonatal age and up to 25% of neurological sequelae (epilepsy, cerebral palsy, mental retardation and other learning disabilities) (1-3).

The most important mechanisms leading to neuronal death following hypoxia-ischemia-reperfusion are started by energy failure, accumulation of extracellular glutamate, and activation of glutamate receptors. This event (Ca^{++} mediated), which evolves over many hours, sets off a cascade of pathologic events in the different districts of the body (3).

Currently, available data concerning the pathophysiology of neuronal damage secondary to acute phase of hypoxic-ischemic encephalopathy (HIE) suggest that adequate preventive interventions may reduce cerebral lesions (4-6).

Period between the hypoxic ischemic event and the onset of cerebral reperfusion seems to be the only window of opportunity for neuroprotection, in order to limit the cascade of biochemical events (3).

Promising experimental and clinical data are now available for the use of mild hypothermia (33°-34°C) for neonatal encephalopathy in infants suffering perinatal asphyxia (7-15).

Although the protective mechanism of hypothermia on asphyxiated brain is not totally elucidated, it seems to interrupt the biochemical cascades leading to cerebral damage by: 1) reducing cellular metabolic demands by 5% for each degree of diminished body temperature (4); 2) lowering phosphate depletion; 3) delaying membrane depolarization (6,16-18); 4) redu-

cing free radicals or cytotoxins (19-22) or decreasing programmed cell death, known as apoptosis, secondary to the suppression of intracellular pathways (23).

Many asphyxiated infants require endotracheal intubation and mechanical ventilation because of severe respiratory failure (acquired respiratory distress syndrome, persistent pulmonary hypertension), cardiac dysfunction (myocardial ischemia) or decreased spontaneous breathing following HIE.

Even if a normal body temperature manteinance is usually recommended in the management of newborns, nevertheless in case of perinatal asphyxia cooling may be already helpful during neonatal resuscitation.

Many authors studied the changes in systemic haemodynamic variables (e.g. mean arterial pressure, heart rate) and in ventilatory settings (e.g. minute ventilation and tidal volume) during moderate hypothermia in animals. Heart rate was significantly reduced below 33°C while the mean arterial blood pressure (MABP) remained stable at different levels of hypothermia. Minute ventilation (VE) was generally reduced, starting at 35°C and below, because of decreasing of respiratory drive and increasing of respiratory time, without significant changes in tidal volume (Vt) (24-26). Minimal cardiovascular changes without side effects were documented in a clinical trial of mild cooling (34-35°C) in asphyxiated term infants (27).

Since therapeutic cooling in course of mechanical ventilation can induce changes in cardiovascular and respiratory status, an accurate monitoring is recommended in order to avoid further sequelae in newborn infants.

Aim of the study

To assess cardiac and respiratory status in asphyxiated infants during mild therapeutic hypothermia and to compare it with that one of asphyxiated newborns not receiving hypothermia.

Methods

This study was performed in the neonatal intensive care unit (NICU) of the "Vittore Buzzi" Children's Hospital, Milan, Italy, with the approval of the hospital ethics committee.

We compared, by retrospective chart analysis, the cardiovascular and respiratory status of two groups of asphyxiated inborn term infants (37- 42 weeks' gestation).

The first group (historic control = C), included 11 consecutive newborns (5 females and 6 males), admitted to the NICU from September 1998 to September 1999; the second group (hypothermic group= H) included 10 consecutive newborns (3 females and 7 males) admitted to the NICU from October 1999 to October 2000.

All term infants met the criteria for the definition of asphyxia as established by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (28), in particular:

- arterial cord blood sample pH <7.0 with base excess (BE) at birth;
- Apgar score below 5 for more than 5 min;
- neurological signs of encephalopathy in the early postnatal period: e.g. seizures, hypotonia, coma or HIE grades II or III according to criteria of Sarnat and Sarnat within 6 hours of life (29).

We excluded infants with lethal congenital anomalies, encephalopathy unrelated to asphyxia, sepsis or suspected infections and severe haematological disorders.

Statistical analysis: the unpaired t-test was performed between the two groups. Outcome data were analysed by Fisher's test. Statistical significance was considered at $p<0.05$.

Clinical care and monitoring

All infants were resuscitated according to the international guidelines for neonatal resuscitation (30). Immediately after resuscitation and stabilization, they were transferred to the NICU and underwent mechanical ventilation [synchronized intermittent positive pressure ventilation (SIPPV) regimen] because of severe respiratory distress.

In both groups at the baseline we set the minimal peak inspiratory pressure (PIP) to deliver a target Vt =

5-6 ml/Kg, with a mean positive end expiratory pressure (PEEP) of 4-5 cmH_2O, a minimal fractional inspired oxygen concentration (FiO_2) to maintain oxygen saturation ($SatO_2$) 90-96%, a mean 0.4"-0.45" of inspiratory time (IT), an inspiratory flow allowing to reach plateau pressure within the first third of IT (mean 7 l/min) and a respiratory rate of 40 bpm to maintain pCO_2 at 40-55 Torr.

Lung mechanics were studied during sleep or quiet alert state for four 20-30 min periods (each day for 3 days), using a prototype ventilator (Dräger Babylog 8000plus® software version 5.n, Lubeck, Germany), with trigger sensitivity set at the maximum level (0.3 ml). The ventilator's flow sensor was calibrated at the beginning of the study. At the end of each monitoring period, data for about 500 breaths were downloaded from the ventilator pressure and volume-monitoring module, (software Lufu3, Dräger®) and so transferred into computer. For each patient we monitored during the first 3 days of life: mean values of Vt, VE , respiratory and heart rate, systemic blood pressure and oxygen saturation.

A 2D echocardiographic study was daily performed in all cases in order to exclude structural heart defects and to identify persistent pulmonary hypertension (PPHN).

Intensive care was conducted according to usual practice for the different pathologies of the patients. In case of renal failure a fluid restriction (by monitoring urine output) was associated with dopamine by continuous infusion i.v. at low dose (2.5-5 g/Kg/min) until renal function returned to normal values. In case of altered coagulation, plasma (10 ml/Kg/dose i. v.) was administered. Seizures (whether noted on EEG or clinically) were treated with phenobarbitone (20 mg/Kg i.v. followed by 5 mg/Kg/day i.v.).

Hypothermic treatment

Hypothermic treatment was started in term infants with clinical features of birth asphyxia and EEG anomalies, only after obtaining parental consent.

In the H group, we applied whole body hypothermia started within 6 hours of life (mean 3 h and 50 min), gradually obtained in a mean time of 2 hours and maintained using a commercial air cooling system (Polar Air, Augustine Medical INC, model 600) that induces blowing cool air through a translucent perforated paper blanket placed around the the infant's shoulders. Air temperature was continuously adjusted to maintain the rectal temperature between 32 and 34°C for 72 h. The system is not servo-controlled but the air temperature can be regulated by the operator. Infants were then rewarmed at 0.5°C/h (total approximately 12 h).

Rectal temperature was continuously recorded by a rectal probe (Vital Temp) during hypothermic treatment until the infants were rewarmed (31, 32).

Rectal probe was connected to the cardiomonitor Datascope® Passport (model EL), in order to control respiratory and heart rate, blood pressure and oxygen saturation.

Results

The two groups of newborns had comparable gestational age at delivery, Apgar scores at 5 min, arterial cord values of pH (<7.09), BE (<10 mmol/L) and lactate (>2 mmol/L). Data were collected by the same operator.

Table 1 shows clinical characteristics and biochemical findings of infants; we did not observe significant differences between the two groups in the first 3 hours of life (p=ns).

The admission rectal temperatures were 36.2-36.5°C (H group) and 36.3-36.5°C (C group). The mean rectal temperature during hypothermia was 33°C ± 0.8.

Respiratory status and ventilatory settings

We did not find any significant difference in number of breaths examined from each study infant.

In H group, 3/10 patients needed the transient increase of set Vt during hypothermia (Vt baseline: 5.8 ml/Kg; Vt in course of hypothermia: 8 ml/Kg) to maintain an adequate gas exchange.

In these patients, the set respiratory rate (RR) was not modified, but we observed a reduction in the spontaneous respiratory rate in course of hypothermia

Table 1. Clinical characteristics and laboratory findings at birth of infants in the two groups (values expressed as means±SD)

Group	H (n°10)	C (n°11)
Gestational Age (wks)	38.8±1. 4	39.5±1. 9
Birth Weight (g)	3295±700	3500±500
pH	6.81±0. 1	6.80±0. 2
BE (mmol/L)	19.6±7	19.5±6
Lac (mEq/L)	9.8±4.6	7.6±4.4
EEG anomalies (n° neonates)	10/10	11/11
ALT - AST (UI/L)	482±644 - 131±142	261±278 - 157±163
PK(UI/L)	2716±2241	1390±1128
LDH (UI/L)	1880±1557	1980±900
Platelets x 1000	254±87	221±65
PT (%)- APTT (sec)	40±12 - 60±11	54±11 - 60±9
CRP (n.v.<0.8)	<0.8	< 0.8
Glucose (mg/dl)	79±30	72±26
Ca^{++}(mmol/L)	1.1±0.2	1±0.2
K^{+} (mEq/L)	3.6±0.4	3.9±0.5

p=ns
EEG anomalies: burst suppression patterns, isoelectric tracing, and mild to severe depression.
PT: prothrombin time
APTT: activated partial thromboplastin time
CRP: C reaction protein

(mean RR: 64 breath/min at baseline; 40 breath/min at reached temperature of 32°C). This effect was strictly related to hypothermia, since during the rewarming phase it was possible to reduce set Vt and we observed a growth in spontaneous respiratory activity. On the contrary in C group the mean Vt and RR remained stable during mechanical ventilation. In 2/10 patients (H group) and in 1/11 (C group) we registered a PPHN that was drastically resolved by nitric oxide administration (10 ppm for 24 h). In 1/10 patient (H group) and in 1/11 (C group) we performed a bronchopulmonary lavage with diluted surfactant to treat a meconium aspiration syndrome.

We did not observe significative differences in length of mechanical ventilation even if there was a trend of longer ventilation in H group (H=5.4±4.4 days vs C=2.8±2.7 days, p=0.12). $SatO_2$ remained stable during hypothermic treatment with no need of increasing FiO_2 administration (table 2)

Cardiovascular findings

Heart rate was similar in both groups at the beginning of the study (H group: 129±11 beats/min; C group: 129±12 beats/min), dropped to an average of 102±10 beats/min (p<0.05) during hypothermia in H group and it remained stable in C group. No arrhythmia was observed during the study in both groups.

Mean arterial blood pressure (MABP) was comparable in infants of both groups at admission (H group: 45±9 mmHg; C group: 46±10 mmHg) and increased by a median of 8 mmHg during hypothermia in the H group (p=ns).

Need of sympathomimetic amine therapy was similar in both groups (dopamine: 9/10 in H group, 10/11 in C group; dobutamine: 5/10 in H group, 2/11 in C group) (p =ns) without significative difference in length of treatment (dopamine: 8.9±5.7 days in H group, 3.2±2.2 days in C group; dobutamine: 13±3.3 days in H group, 2±1.4 days in C group).

All the newborns that developed transient mild renal failure (9/10 in H group and 10/11 in C group) were treated with dopamine for a better renal perfusion and fluid restriction with rapid normalization of renal function; nevertheless no infants required dialysis.

On admission, altered coagulation was observed in 3/11 infants in the C group and in 7/10 infants in the H group. Coagulopathy was always treated with fresh frozen plasma at dose of 15 ml/kg: seven neonates showed a rapid normalization of coagulation parameters with no need of further correction, three in-

Table 2. Cardiovascular and respiratory parameters in course of mechanical ventilation of patients in the two groups (values expressed as means±SD)

Group	MABP (mmHg)	HR (b/min)	Vt (ml/Kg)	FiO_2 (%)	VE (ml/Kg/min)	Length of ventilation (days)
H (n° 10) baseline	45±9	129±11	5.8±1	38±10	305±100	5.4±4.4
H 12 hrs	51±10	102±10*	6.5±1	43±10	280±102	
C (n° 11) baseline	46±10	129±12	5.7±1	39±9	300±103	2.8±2.7
C 12 hrs	45±8	132±7	5.4±0	40±6	300±84	

* $p<0.05$ H in course vs pre
MABP: mean arterial blood pressure
HR: heart rate
Vt: Tidal Volume
FiO_2: fraction of inspired oxygen
VE: Minute Ventilation

fants died because of disseminated intravascular coagulation (DIC) (2 infants of the C group, in 3rd and 6th day of life, and 1 infant of the H group, in 5th day of life).

In the H group, 8/10 infants showed hypokalemia during hypothermia (the median and the lowest potassium levels were 2.8 and 2.2 mEq/L, respectively), as yet previously showed (14).

Discussion and conclusions

During the past decade, researchers have proceeded with caution in applying hypothermia, due to concern of possible side effects: cardiac arrythmias (33), blood viscosity effects (34, 35), pancreatic disorders (36), hypoglycemia (37) and sepsis (38-40).

Recent studies showed encouraging results of the treatment with whole body hypothermia for asphyxiated newborns (14, 15).

Some experimental trials regarding the effects of hypothermia on cardiovascular and respiratory systems reported a transient but significant reduction of heart rate and minute ventilation without severe side effects (24-26). Recently, a clinical trial demonstrated the reduction of heart rate and the increasing of MAPB in course of hypothermia: these changes were not hazardous, but worthy of monitoring in order to avoid potential adverse effects in newborns (27).

In this retrospective chart analysis we evaluated the cardiovascular and respiratory status in two groups of mechanically ventilated asphyxiated newborns: the first one received hypothermia treatment within the 6th hour of life (H group), the second one did not (C group).

In the H group, we applied body hypothermia instead of selective head cooling because the latter has not been proved yet to be able to reduce with success the temperature of the deep structures of the brain.

No life-threatening events or severe adverse effects, which could directly be attributed to induced hypothermia, were observed during cooling. Only physiologic abnormalities as hypokalemia and one episode of sinus bradycardia occurred during hypothermia; these two effects have been already observed (14). No arrhythmia or significant alterations of MAPB were seen during hypothermic therapy, as in a previous study (27, 41).

During hypothermia, when rectal temperature reached a value of 32°C, 3/10 newborns of H group needed the temporary increase of Vt by a median of 2.2 ml/Kg to maintain a normal lung filling and adequate gas exchange; mean VE remained stable in time (p=ns).

We speculated that hypothermia, besides reducing spontaneous respiratory drive, might also induce transient stiffness of the chest wall that requires sometimes the application of higher Vt in these patients when the temperature is strongly reduced (e.g. below 32°C). It was not completely defined if the PPHN observed in 2/10 patients of the H group was due to asphyxia or to hypothermic treatment: in these cases a short course of inhaled nitric oxide (at low dosage, 10 ppm) drastically resolved the PPHN.

Mortality rate was similar in both groups (2/11 in C group and 1/10 in H group) (p=ns).

Our data suggest that mild hypothermic therapy in mechanically ventilated asphyxiated term infants is safe even if it causes changes of cardiovascular and respiratory status; these modifications showed to be transient and without severe side effects if monitored and corrected step by step during cooling.

The small sample size of this study limits the power of our conclusions even if data we collected appear to be similar to those in previous studies.

Since perinatal asphyxia is rare, in order to demonstrate the real safety of hypothermic therapy, future research has to focus on large, randomized and multicenter trials; moreover, since the effects of hypothermia may go far beyond the immediate tissue recovering from hypoxic-ischemic damage, further studies should also be undertaken basing on prolonged pediatric and neurologic follow up.

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Received: 24 November 2003
Accepted in revised form: 30 May 2004
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