Early Human Development 91 (2015) 565–568

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

The effect of caffeine citrate on neural breathing pattern in preterm infants

Vilhelmiina Parikka [a,*], Jennifer Beck [b,c,d], Qian Zhai [b], Juha Leppäsalo [a], Liisa Lehtonen [a], Hanna Soukka [a]

[a] Department of Pediatrics, Turku University Hospital, University of Turku, Turku, Finland
[b] Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Canada
[c] Department of Critical Care, St. Michael's Hospital, Toronto, Canada
[d] Department of Pediatrics, University of Toronto, Toronto, Canada

ARTICLE INFO

Article history:
Received 10 November 2014
Received in revised form 16 June 2015
Accepted 22 June 2015

Keywords:
Apnea
Diaphragm electrical activity
Neurally adjusted ventilation
NAVA

ABSTRACT

Background: Caffeine citrate is widely used to prevent and treat prematurity-associated apnea.
Aims: The aim of this study was to characterize the effect of caffeine citrate on the neural control of breathing, especially central apnea, in premature infants.
Study design: Preterm infants were evaluated for 30 min before and 30 min after caffeine citrate loading (20 mg/kg). A feeding tube including miniaturized sensors was used to measure the diaphragm electrical activity (Edi) waveform. Central apnea was defined as any period where the Edi waveform was flat for >5 s.
Subjects: Seventeen preterm infants with a mean age of three days and mean birth weight of 900 grams were evaluated.
Outcome measures: In addition to central apnea, several parameters including neural inspiratory time, neural respiratory rate, peak Edi, delta inspiratory change in Edi (phasic Edi) and minimum Edi on exhalation were measured.
Results: The majority of the apnea were short (5 to 10 s) and the number of apnea correlated with birth weight ($p = 0.039$). Caffeine citrate reduced significantly the number of 5-to-10-second-long central apnea during the 30-minute periods (12 ± 11 to 7 ± 7; $p = 0.02$). Caffeine citrate increased both peak and phasic Edi leading to a significant increase in the diaphragm energy expenditure.
Conclusions: Edi signal can be reliably measured and processed to study changes in premature infants' neural breathing. The beneficial effect of caffeine citrate on the reduction of the number of apnea is mediated through stimulated neural breathing increasing the diaphragm energy expenditure.

1. Introduction

The immature neural control of breathing in preterm infants leads to pauses in breathing, known as central apnea. Apnea may be associated with bradycardia and oxygen desaturation, the former occurring more frequently when duration of apnea increases [1–3]. Although long-term consequences of apnea are difficult to assess due to comorbidity, there are concerns about hypoxic–ischemic brain injury and possible risks for later neurodevelopmental impairment.

Caffeine has successfully been used in clinical practice to reduce the apnea of prematurity for almost 40 years [4–6]. Its prophylactic use also decreases the rate of extubation failure and reduces intubation times as well as the need for supplemental oxygen [7–9]. In addition to the immediate effects, caffeine citrate therapy is associated with a reduced incidence of bronchopulmonary dysplasia [9] and improves the rate of survival without neurodevelopmental disability in very low birth weight infants at 18 to 21 months [10]. The beneficial effect of neonatal caffeine citrate treatment on neurodevelopment can be still found at 5 years of age [11].

The mechanism of action of Xanthines involves competing with adenosine receptors, overriding the inhibitory action of adenosine on central nervous system. Binding to these receptors, caffeine stimulates breathing and reduces the hypoxia-induced respiratory depression by increasing minute ventilation and the response to CO_2 [12,13]. Caffeine also increases diaphragm activity [14], but the direct effect of caffeine on the central respiratory control and diaphragm electrical activation has not been previously demonstrated. The neural signals for breathing can be inferred by measurement of the electrical activity of the diaphragm (Edi) [15,16]. This method has been validated and

Abbreviations: Edi, the electrical activity of the diaphragm; NAVA, neurally adjusted ventilatory assist.

* Corresponding author at: Department of Pediatrics, Turku University Hospital and University of Turku, Kiinamyllynkatu 4-8, PO Box 52, FI-20521 Turku, Finland. Tel.: +358 2 3133667.
E-mail address: vilpar@utu.fi (V. Parikka).

http://dx.doi.org/10.1016/j.earlhumdev.2015.06.007
0378-3782/

standardized also in preterm infants [17]. It involves the use of microsensors placed on a nasogastric feeding tube thereby imposing no additional level of invasiveness on preterm infants who require tube feeding.

The aim of this study was to characterize the effect of caffeine citrate on neural control of breathing, especially central apnea, in premature infants using the Edi signal. We hypothesized that caffeine citrate treatment reduces central apnea and increases neural breathing efforts interpreted from the Edi waveform.

2. Patients and methods

2.1. Subjects

Twenty preterm infants were enrolled in the study. Infants with gestational age less than 34 weeks who received caffeine citrate therapy for prevention or treatment of central apnea were eligible. Infants with severe congenital anomalies and those with apnea potentially caused by other reasons than prematurity (like intraventricular hemorrhage) were excluded. Three recordings were excluded due to unsuccessful recording and the final study group consisted of 17 infants.

2.2. Study protocol

Study infants were recruited between June 2012 and February 2014 in the neonatal intensive care unit of the Turku University Hospital (level III NICU). According to the routine treatment protocol, the infants born before 29 gestational weeks received an intravenous loading dose of 20 mg/kg caffeine citrate (Citrate de Caféine Cooper, Laboratoire Cooper) prophylactically if not needing invasive ventilation or when the patient was either switched from synchronized intermittent mechanical ventilation (SIMV) to neurally adjusted ventilatory assist (NAVA) ventilation or extubation was planned. Infants born ≥29 gestational weeks received caffeine citrate only if presenting several clinically significant apnea. The study was approved by the ethics committee of the Hospital District of Southwest Finland. All parents were informed and asked a written consent for participation in the study.

2.3. Recordings

The electrical activity of the diaphragm (Edi) was measured with an Edi catheter, which was also used as a feeding tube (Maquet, Solna, Sweden), including nine miniaturized electrodes and positioned in the esophagus at the level of the diaphragm. The signal was recorded by a ventilator (Servo-I with NAVA option; Maquet, Sweden), displayed as a waveform and transferred into a computer with Servo-tracker software (Maquet, Sweden). Oxygen saturation was monitored concurrently using Masimo pulse oximeter (Irvine, CA).

The Edi waveform was recorded continuously for 30 min before caffeine citrate infusion and 30 min after the end of the infusion. The patient was not fed and no changes were done in a mode of respiratory support during the recording. If the child was ventilated in NAVA, apnea time was set to 5 ($n = 2$) to 10 s and the other settings were determined by the attending neonatologist. When the duration of apnea exceeded apnea time, NAVA ventilation automatically switched to backup ventilation. NAVA ventilation resumed immediately from the first Edi signal exceeding the signal threshold. The primary outcome variable was the number of central apnea of different lengths. Central apnea was defined as any period where the Edi waveform was flat for >5 s. Heart rate was measured by Edi catheter and calculated as an instantaneous value just prior and at the end of the central apnea.

2.4. Data analysis

The Edi waveform was quantified, as previously described [3]. The 30 minute periods were analyzed breath-by-breath by placing three time cursors on each Edi breath: [1] onset of neural inspiration, [2] the highest point in the Edi breath, and [3] onset of the next inspiratory signal.

The period from onset to peak Edi signal was identified as the neural inspiratory time and used to calculate the peak phasic Edi during inspiration. The period from peak Edi to the onset of the next inspiratory Edi signal was identified as the neural expiration time. Neural respiratory rate was calculated using the above identified neural inspiratory and expiratory times. The Edi-time product (an indication of diaphragm energy expenditure) was calculated per minute as the product of the mean inspiratory phasic Edi, the neural inspiratory time and the neural respiratory rate. SigmaStat was used for statistical analyses (Sigmastat, Jandel Scientific, CA). Paired t-tests were used to compare variables before and after caffeine infusion. Mean ± SD are reported.

3. Results

A total of 17 preterm infants were studied, 12 of them were boys. All infants were born before 32 gestational weeks and 10 of them before 28 weeks all having extremely low or very low birth weight (Table 1). The prematurity related diagnoses, treatments and the type of respiratory support are presented in Table 2. One of the infants had also Down syndrome, one had an ileal perforation and one had renal and cardiac insufficiency.

3.1. The influence of caffeine citrate

The number of central apnea in study infants correlated with birth weight ($p = 0.0394$, $r = -0.5$). The majority of the apnea (55% before caffeine loading) lasted for 5 to 10 s. Before caffeine citrate, the intubated infants on NAVA ventilation had 22 (±17) apnea during the 30-minute recording whereas the infants on nCPAP/high-flow nasal cannula (HFNC) had 7 (±4) 5- to 10-second-long apnea, $p = 0.076$. Caffeine citrate significantly reduced the number of these 5- to 10-second-long central apnea ($p = 0.02$; Table 3). The effect varied between individual patients but most of those with frequent apnea showed a clear response (Fig. 1). Caffeine citrate did not change the mean duration of the apnea which lasted longer than 5 s.

In addition to the effect on central apnea, caffeine citrate increased peak Edi as well as the phasic Edi during the 30-minute recording period (Table 3). The effect on the phasic Edi varied between individual patients but majority showed a clear response to caffeine citrate (Fig. 2). Although caffeine citrate did not alter the neural respiratory rate, it increased the diaphragm energy expenditure (Edi time product; Table 3). As expected, caffeine citrate increased the heart rate ($p = 0.02$).

4. Discussion

Our study showed a significant reduction in central apnea after the caffeine citrate loading in very preterm infants. This was demonstrated by using a novel technique which detects the neural respiratory stimulus as the electrical activity of the diaphragm (Edi). With this technique, we showed that caffeine citrate stimulates neural breathing and reduced the number but not the length of apnea.

The stimulatory effect of caffeine citrate on breathing has been suggested to be mediated through both the central nervous system and peripheral chemoreceptors [18]. Our data show for the first time

Table 1
Demographic characteristics of the 17 study infants.

	Mean	Range
Gestational age at birth (weeks)	27 + 4	23 + 5–31 + 6
Age at recording (days)	3.0	0.8–9.9
Birth weight (g)	900	610–1440
Weight at recording (g)	893	602–1270