Effect of Caffeine on Heart Rate Variability in Newborns

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BACKGROUND

Caffeine is the drug of choice for neonatal apnoea, affecting respiratory and cardiovascular systems among others. Heart rate variability (HRV) reflects the change of duration of consecutive RR intervals. Spectral analysis of HRV is a significant clinical tool for evaluating the development and influence of the autonomic nervous system on the newborns' heart. A higher HRV reflects a better developed ANS.

The aim of our research was to establish whether caffeine affects cardiorespiratory parameters in newborns. By analyzing HRV, we indirectly assessed the activity of autonomic nervous system, also regarding the postmenstrual age (PMA).

METHODS

Study type: A prospective clinical intervention study.

Study design: 25 newborns with apnoea who had been admitted to the Neonatal Department of University Medical Centre Ljubljana, Division of Paediatrics, from November 2017 to August 2018, and treated with caffeine citrate.

The physiologic measurements were performed while the newborns were receiving caffeine citrate: the treatment regimen consisted of a loading dose of 20 mg/kg body mass, followed by a daily maintenance dose of 5 mg/kg after 24 hours. The newborns were treated for 9,5 days on average, either orally or intravenously, regarding their clinical state.

Inclusion Criteria:

- newborns with apnoea treated with caffeine citrate,
- newborns whose parents have signed the informed consent form.

Exclusion Criteria:

- severe perinatal hypoxia,
- infection,
- liver or renal insufficiency,
- neurological disorders,
- congenital anomalies.

In 17 of the 25 newborns, the measurements were repeated 100 ± 26 hours after the treatment with caffeine was withdrawn. These newborns served as controls. In eight newborns, we could not perform the control measurements due to technical difficulties.

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (0120-458/2016-3 KME 67/09/16) and complies with the principles of the Declaration of Helsinki, European Convention on Human Rights and Biomedicine, and the Slovenian Code of Medical Deontology. Written parental consent was obtained for all participants.

Study setting

Measurements were performed during sleep. We simultaneously assessed newborn's breathing frequency, arterial oxygen saturation, body temperature, and ECG. The bed was initially placed horizontally (0°-tilt) and was tilted for 30° head-up after 20 minutes of continuous tracing.

Breathing frequency, arterial oxygen saturation and body temperature were measured three times for each bed tilt during the newborn was sleeping. Breathing frequency was determined manually by observing the chest movement. Arterial oxygen saturation was performed by a pulse oximeter attached to the right hand. Body temperature was measured by a frontal non-contact infrared thermometer.

As for the ECG tracing, five precordial ECG electrodes were attached to the newborn's chest prior to feeding. After feeding, the newborn was placed supine in a bed and a 40-minute tracing was obtained during the sleep (initially at a 0°-tilt, and subsequently at a 30° – head-up tilt as described above). During the recordings, the heating was turned off to avoid potential interference with the ECG signal.

Data analysis

Data were extracted from ECG recordings using programmes Vision Premier ver. 3.4 and Nevrokard. For the analysis of each recording, a 5-minute segment was used. Data containing artefacts in more than 1% of the corresponding segment were removed from subsequent analyses.

ECG segments were analysed by using fast Fourier transformation. In addition to the total power spectrum, two frequency bands were assessed: one for low frequency (in the range of 0,04 – 0,15 Hz) and one for high frequency (in the range of 0,15 – 1,0 Hz). We selected a

segment which corresponded to the suitable alertness state of each newborn. Mean heart rate value was obtained from the corresponding analysed segment.

Statistical Analysis Plan

Statistical analysis was performed by Microsoft Excel 2010 and IBM SPSS Statistics 24. Data distribution was tested by the Shapiro-Wilk normality test. Numeric variables are shown either as arithmetic mean and standard deviation for a normal, or median and interquartile range for an abnormal distribution. Variables were compared according to the presence of caffeine at two bed positions: at a 0°-tilt ('on caffeine – 0°' vs. 'off caffeine – 0°') and at a 30°– head-up tilt ('on caffeine – 30°' vs. 'off caffeine – 30°'). The investigators also compared variables according to the bed tilt (0° or 30°) twice - while the newborns were treated with caffeine ('on caffeine – 0°' vs. 'on caffeine – 30°') and after the treatment has been withdrawn ('off caffeine – 0°' vs. 'off caffeine – 30°'). Potential correlation between PMA and HRV parameters was assessed regarding the presence and absence of caffeine. The data from the first measurement were correlated (PMA 'on caffeine' and HRV parameters 'on caffeine') for each bed tilt, i.e. 0° and 30°. The same comparisons were made for the second measurement (PMA 'off caffeine' and HRV parameters 'off caffeine'), again for each bed tilt. Student's t-test was used for comparisons of normally distributed variables, and Wilcoxon signed-rank test for abnormally distributed data. The correlation between HRV parameters and PMA was tested with the Pearson correlation coefficient. A significance level was set at $p \leq 0,05$. Correction factor was not used due to multiple testing.