The Effect of Caffeine on the Heart Rate Variability in Newborns

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Research Article

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Abstract

Background:

Neonatal apnoea has been treated with caffeine, which affects the central nervous and the cardiovascular system. Heart rate variability (HRV) reflects the activity of the autonomic nervous system (ANS), and might be used as a measure of ANS maturation in newborns. We aimed to establish the effect of caffeine on HRV in newborns, and saught for a potential correlation between HRV and the postmenstrual age.

Methods:

In 25 newborns, hospitalized due to apnoea and treated with caffeine (2.5 mg/kg), we assessed breathing frequency, arterial oxygen saturation, body temperature, and the heart rate while they were sleeping in two bed positions (0° tilt and 30° head-up tilt). We assessed HRV by spectral analysis using fast Fourier transformation. The same protocol was reapplied 100 hours after caffeine withdrawal to assess control parameters.

Results:

Caffeine increased breathing frequency (p=0.023), but did not affect any other parameter assessed including HRV. We established a positive correlation between postmenstrual age and HRV during treatment with caffeine in a 30° head-up tilt position (total power: p=0.044; low-frequency band: p=0.039).

Conclusions:

Apparently, the maintenance dose of caffeine is too low to affect heart rate and HRV. A positive correlation between postmenstrual age and HRV might reflect maturation of ANS.

Trial registration:

NCT04869176, retrospectively registered on April 27th 2021.

Background

Neonatal apnoea is a life-threatening complication in newborns. Treatment with caffeine and other methylxanthines (aminophylline, theophylline) decreases its incidence as well as the need for mechanical ventilation [1]. Caffeine has become the drug of choice to treat neonatal apnoea due to its efficacy, tolerability, large therapeutic window and safety margin. Caffeine stimulates the respiratory centre in the central nervous system, thus increasing breathing frequency (BF) and tidal volume, improves the breathing pattern, and increases the blood flow rate in the pulmonary circulation [2]. It also affects the cardiovascular system (CVS): in the heart, it increases the heart rate (HR), cardiac contractility and stroke volume, consequently increasing cardiac output and mean arterial blood pressure [2, 3]. As for the

vascular system, caffeine exerts vasodilative effects in the pulmonary and most vessels of the systemic circulation but induces vasoconstriction in the cerebral circulation. Besides from the aforelisted effects, caffeine also augments the metabolic rate, neuromuscular transmission and catecholamine release [4].

HR is modulated by sympathetic and parasympathetic branches of the autonomic nervous system (ANS) on the sinoatrial node, and is subjected to beat-to-beat variability that could be assessed by measuring the time interval between consecutive heartbeats [5, 6]. While the effect of the parasympathetic nervous system (PNS) on the HR is expressed quickly, the effect of the sympathetic nervous system (SNS) takes longer for its full expression. These different time frames of the action of the PNS and the SNS on the sinoatrial node may partly be explained by the corresponding neurotransmitter kinetics [7].

A relevant clinical tool for a non-invasive assessment of the ANS maturation in newborns, as well as the effects of the ANS on newborn's heart, is spectral analysis of heart rate variability (HRV) [7]. Accordingly, HRV could be separated into typical frequency spectra, most usually high frequency (HF), and low frequency (LF) spectrum, respectively. HF is suggested to reflect PNS activity, whereas LF still undergoes controversial interpretations; by some, LF is considered as a marker of SNS activity, and by others as a product of both SNS and PNS activity [5].

In general, a higher HRV is suggested to be linked to decreased cardiovascular risk and consequently decreased mortality in adults [8–11], and with well-being and decreased mortality in newborns [12–14]. Studies performed in newborns found an increased HRV in term compared to preterm newborns [15–17], which might point to a more mature ANS, especially the PNS branch, in terms. It has been reported that PNS develops optimally after 37 weeks of postmenstrual age (PMA) [18, 19]. Moreover, it has been suggested that HRV in newborns is affected by sleeping position. We have previously shown an increased HRV in supine compared to prone position suggesting that supine is more favourable regarding well-being of the newborns. HRV was also increased while lying in a bed with 30° head-up tilt compared to 0° tilt [20].

The effect of caffeine on HRV remains controversial. However, studies conducted in adult healthy subjects showed an increase in HRV after caffeine administration [21–24]. Only a few studies assessed HRV in newborns; even less is known about potential influence of caffeine on ANS as assessed by spectral analysis of HRV. To this end, the aim of our study was to evaluate the impact of caffeine treatment on HRV in newborns. In addition, we sought for a potential association between caffeine treatment and the BF, the HR, the arterial oxygen saturation (SaO_2), and the body temperature (T). We compared the values of the aforementioned variables as well as the values of HRV parameters at two different bed positions (0° tilt and 30° head-up tilt). We further correlated the parameters of HRV with PMA, during as well as after caffeine treatment.

Methods

Patients

A prospective clinical intervention study was performed in 25 newborns with apnoea who had been admitted to the Neonatal Department of University Medical Centre Ljubljana, Division of Paediatrics, in the period 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 (i.e. 10 mg/kg caffeine), followed by a daily maintenance dose of 5 mg/kg (i.e. 2.5 mg/kg caffeine) after 24 hours. The newborns were treated for 9.5 days on average, either orally or intravenously, regarding their clinical state. It has previously been shown that the route of administration does not affect the pharmacokinetics of caffeine as there is almost complete bioavailability after oral or intravenous administration [25].

Exclusion criteria were severe perinatal hypoxia, infection, liver or renal insufficiency, neurological disorders, and congenital anomalies. Newborns whose data could not be used for spectral analysis due to artefacts of the recordings were also excluded from the study.

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, while the state of newborns' alertness was 1 or 2 as determined according to Prechtl [26]. We simultaneously assessed newborn's BF, SaO_2, T, and ECG. The bed was initially placed horizontally (0° tilt), and was tilted for 30° head-up after 20 minutes of continuous tracing (Fig. 1).

BF, SaO_2 and T were measured three times during the suitable alertness state of the newborn for each bed tilt. BF was determined manually by observing the chest movement. SaO_2 was performed by a pulse oximeter (IntelliVue MP 50, Philips, Germany) attached to the right hand. T was measured by a frontal non-contact infrared thermometer (Veratemp, USA).

As for the ECG tracing, five precordial ECG electrodes (ECG Holter, Vision 5L, Burdick, Milwaukee, USA) 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 suitable alertness state (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 (Cardiac Science Corp., Waukesha, Wisconsin, USA) and Nevrokard (Nevrokard, Izola, Slovenia). 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, a frequency domain linear method of assessing HRV. In addition to the total power spectrum (TP), two frequency bands were assessed: one for LF (in the range of 0.04–0.15 Hz) and one for HF (in the range of 0.15–1.0 Hz). We selected a segment which corresponded to the suitable alertness state of each newborn. Mean HR value was obtained from the corresponding analysed segment.

Statistical analysis

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 (SD) for a normal (HR, BF, T), or median (Me) and interquartile range (IQR) for an abnormal distribution (SaO_2, HRV parameters), respectively.

We compared variables according to the presence of caffeine ('on-' or 'off-treatment') 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°'). We 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°').

We assessed potential correlation between PMA and HRV parameters regarding the presence and absence of caffeine. We correlated the data from the first measurement (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.

Results

The newborns were homogenous regarding PMA, birth weight, head circumference, Apgar score, and discharge diagnose at the time of performing the measurements. Out of 25 included newborns, 17 were preterm and 8 were term. Both groups were of similar PMA at the time of measurements. The newborns had been treated with caffeine after being diagnosed with neonatal apnoea. The treatment was discontinued at 37 ± 2 weeks of PMA. In the subsequent analysis on potential effects of caffeine, we

included only 17 newborns in whom the measurements could be repeated after withdrawal of caffeine. The demographic data of the newborns are shown in Table 1.

Table 1
The demographic data of the newborns.

		Mean ± SD or Me (IQR)
Gestational age (weeks)	N = 25	34 ± 5
Birth weight (g)		2353 ± 914
Birth length (cm)		46 ± 7
Head circumference (cm)		31 ± 4
Apgar score 1 min		8.0 (7.5–9.0)
Apgar score 5 min		9.0 (7.0–9.0)
Postmenstrual age[a] (weeks)		37 ± 4
Body mass[a] (g)		2659 ± 676
Head circumference[a] (cm)		33 ± 3
Caffeine - loading dose (mg/kg BM/day)		9.84 (5.65–9.93)
Postmenstrual age[b] (weeks)		37 ± 3
Body mass[b] (g)		2786 ± 560
Head circumference[b] (cm)		34 ± 2
Caffeine - maintenance dose (mg/kg BM/day)		2.55 (2.31–2.67)
Postmenstrual age[c] (weeks)	N = 17	37 ± 2
Body mass[c] (g)		2745 ± 512
Head circumference[c] (cm)		34 ± 3

N, number of newborns; [a], measurements at the time of loading dose of caffeine; [b], measurement while on maintenance dose of caffeine treatment; [c], measurement while off caffeine treatment; BM, body mass; SD, standard deviation; Me, median; IQR, interquartile range.

The effect of caffeine on heart rate, breathing frequency, arterial oxygen saturation and body temperature

The BF was significantly higher during the caffeine treatment, and higher while tilted 0° than 30° head-up. No significant differences in the HR, SaO_2 or T were found between the treatment ('on caffeine') and post-

treatment ('off caffeine') (Table 2). No differences in any parameter between the term and preterm newborns were found.

Table 2
Physiological variables during ('on') and after ('off') caffeine treatment, and in two different bed positions.

	HR (beats/min)		BF (breaths/min)		SaO_2 (%)		T (°C)	
0° TILT (N = 17)		p		p		p		p
On caffeine	138.6 ± 12.0	1	56.2 ± 12.5	**0.023***	99 (97–100)	0.477	36.7 ± 0.4	0.332
Off caffeine	138.6 ± 13.1		50.7 ± 13.2		99 (97–100)		36.8 ± 0.3	
30° TILT (N = 17)								
On caffeine	138.5 ± 12.4	0.715	53.3 ± 11.5	0.704	98 (97–99)	0.376	36.7 ± 0.4	0.332
Off caffeine	139.6 ± 13.3		52.1 ± 14.6		98 (96–99)		36.8 ± 0.3	

Comparisons were made separately for each bed tilt. Data are presented as arithmetic mean and SD (HR, BF, T), or as median and IQR (SaO_2). '0° tilt' and '30° head-up tilt' refer to bed tilt; * $p < 0.05$; HR, heart rate; BF, breathing frequency; SaO_2, arterial oxygen saturation; T, body temperature.

The effect of caffeine on HRV

No association between caffeine treatment and any of the HRV parameters were found. The HRV parameters were compared depending on the presence of caffeine treatment for both bed tilts (Table 3).

Table 3
The HRV parameters during ('on') and after ('off') caffeine treatment, and in two different bed positions.

	TP (ms^2)		LF (ms^2)		HF (ms^2)	
0° TILT (N = 17)		p		p		p
On caffeine	522 (286–1399)	0.653	219 (99–357)	0.435	107 (66–272)	0.523
Off caffeine	732 (228–1270)		232 (85–598)		145 (57–268)	
30° TILT (N = 17)						
On caffeine	545 (358–1042)	0.906	195 (105–361)	0.776	114 (66–273)	0.723
Off caffeine	381 (241–1054)		179 (93–281)		67 (42–154)	

Comparisons were made separately for each bed tilt. Data are presented as median and IQR. HRV parameters of the wide-range are given. '0° tilt' and '30° head-up tilt' refer to bed tilt; TP, total power; LF, low frequency; HF, high frequency; N, number of newborns.

The correlation between postmenstrual age and the parameters of HRV

We found a positive correlation between some of the HRV parameters and PMA (Fig. 2). During caffeine treatment, we found a positive correlation of moderate strength between PMA and LF (Pearson correlation coefficient = 0.42 ; p = 0.039), and between PMA and TP (Pearson correlation coefficient = 0.41 ; p = 0.044). Both correlations were found while tilted 30°, but not while tilted 0°. No correlation between PMA and any other parameter of HRV was found.

After the cessation of the caffeine treatment, a positive and moderately strong significant correlation was found between PMA and LF (Pearson correlation coefficient = 0.57 ; p = 0.017), and between PMA and TP (Pearson correlation coefficient = 0.5 ; p = 0.041) while tilted 30°, but not while tilted 0° (Fig. 2).

Discussion

The main finding of our study is that treatment with caffeine does not affect HRV in newborns. Moreover, caffeine did not induce any significant changes in HR, SaO_2 or T but did increase BF. Apparently, the maintenance dose of 2.5 mg/kg body mass to treat apnoea is not sufficient to exert any measurable effects on the above parameters, except for an expected increase in BF. To the best of our knowledge, our study is the first to have assessed the effect of caffeine on HRV in postmenstrually 37-week-old newborns.

The preterm newborns included in the only two available studies were significantly younger.

The only parameter that was affected by caffeine was BF. The increase of BF after the caffeine treatment was expected, as caffeine is a known stimulant of the respiratory centre. Contrary to our expectations, the

association was only found at a 0° tilt, but not 30° head-up tilt, for which we have no feasible explanation; a continuous measurement of BF might have yielded a significant correlation also in a tilted position.

In our study, the values of SaO_2 were comparable during and after the cessation of caffeine treatment. As the values were in physiological limits after the cessation of treatment, caffeine could have hardly induced an additional increase.

Caffeine reportedly increases the rate of metabolism and could thus potentially induce an increase in temperature. Nevertheless, the maintenance dose used in our study apparently was not sufficient to induce any measurable effects of caffeine on T since we found no differences in T during versus after the caffeine treatment. In fact, this is a favourable outcome in regard to interpretation of the HRV data; an elevated T namely affects HR and if this was the case in our study, it would interfere with the interpretation of the effects of caffeine on HRV.

In our study, the HR and HRV parameters obtained during caffeine treatment were comparable to the parameters after discontinuation of treatment. Since cardiogenic effects in terms of tachycardia only occur when applying toxic doses of caffeine, we conclude that a maintenance dose is not sufficient to impact the HR in newborns. Our results regarding the effect of caffeine on HR and HRV are in accordance with the study of Ulanovsky et al. who also didn't show any impact of caffeine (applied in a loading dose 15–20 mg/kg/day, followed by a maintenance dose of 5–10 mg/kg/day) either on the HR or HRV in premature newborns. Yet, their sample may not be comparable to ours, as the newborns in their study [1] as well as in Huvanandana's [3] were younger than our newborns (gestational age 30.3 ± 2.5 weeks and 27.0 (23.6–33.3) weeks compared to 34 ± 5 weeks in our study) and also had significantly lower birth weight (1397 ± 458 g and 934 (552–2100) g compared to 2353 ± 914 g in our study) [1, 3]. On the other hand, Huvanandana et al. who compared the results of the linear and non-linear measurements of HRV in preterm newborns prior to and two hours after a loading caffeine dose, reported an increased HRV after caffeine administration when using non-linear, but not when using linear modelling, as it was analysed in our study. They suspected that linear metrics might not adequately capture potentially altered dynamics in the HR control [3]. Moreover, the influences of caffeine on the heart and the activity of ANS seem controversial as caffeine has also been shown to increase the HF component of HRV in adults, apparently increasing PNS activity [21, 27].

Although all parameters in our study were measured after the newborns were fed, and during the first 40 minutes of sleep, the HRV measurements could also be dependent on the sleep phase which we did not assess. Namely, the sleep onset in newborns corresponds to a REM phase, one sleep cycle lasts for about 50 minutes, and consists of equal consequent proportions of REM and non-REM sleep [28, 29]. Yiallourou et al., who assessed HRV in preterm and term newborns, found significantly increased values of both LF and TP spectra during REM compared to non-REM sleep [16]. Similarly, Takatani et al. showed higher LF and HF during REM than during non-REM in newborns [17]. To this end, assessing the phase of sleep in our newborns might be valuable for further interpretation.

We found a positive correlation between HRV (LF and TP but not HF) and PMA. A positive correlation between PMA and HRV supports the idea of ANS maturation with increasing age; yet, due to the narrow time frame (100 ± 26 hours) between the consecutive measurements the results should be interpreted with caution. Our results are accordant with our previous study [20], and with the study of Sahni et al., who showed a significant increase in HRV with increasing PMA in growing low birth weight infants, and implied an important role of ANS maturation in the control of cardiac activity [30]. Based on our observation, it seems that the maturation of ANS proceeds independently of caffeine. Contrary to our hypothesis and our observation from our previous study [20], where the study population was on average four weeks older, the HF did not significantly increase with increasing PMA in the present study. The discrepant findings could be due to limitations of the spectral analysis. In the present study, the mean HR was about 139 beats per minute. The Nyquist frequency of our sample was therefore 69.5 per minute, which is approximately 1.16 Hz. The upper limit of HF range, used for our analysis, was 1 Hz. Anything above this value was therefore a part of HF score that fell out of the analysis. Besides, the influence of respiratory sinus arrhythmia on HRV should be taken into consideration. As PNS has a much shorter delay than SNS on the heart that covariates with respiration, PNS is the main factor contributing to respiratory sinus arrhythmia. Many reports have confirmed that a considerable part of HRV, affected by PNS, actually arises from the respiratory sinus arrhythmia [18, 31], yet this phenomenon has not been adequately studied in newborns so far. We can speculate that HF did not significantly increase with PMA due to higher BF in newborns as compared to BF in adults. PNS, not fully developed in preterm newborns, thus contributes less to HRV. Moreover, our newborns presented with neonatal apnoea which is connected with respiratory disorder, increased work of breathing, or even abnormal breathing patterns; therefore, their breathing pattern might differently affect HF than the pattern in healthy newborns.

The limitation of our study is a small sample size. Another limitation is a rather long half-life of caffeine in preterm newborns – 87 ± 25 hours at 35 weeks PMA [32]. A prolonged half-life of caffeine could persist up to 38 weeks PMA due to immature liver function [33]. Accordingly, caffeine concentration might have been elevated in some newborns by the time of the control measurements. Unfortunately, we could not exceed this time frame due to limited duration of hospitalisations; however, by ensuring that 100 hours on average passed between the last dose of caffeine and the second measurement, this option seems rather unlikely. Furthermore, HF values above 1 Hz could not be included in the analyses due to the upper limit of the frequency range. As stated above, our study could be improved by a continuous measurement of BF, as well as blood pressure monitoring, and by measuring also EEG to determine the phase of sleep which might have impacted the outcome. Finally, a note should be given on the study design: a more reliable estimation of potential impact of caffeine on HRV would be obtained causally, i.e. by first assessing the parameters before caffeine was applied, and subsequently during the application of caffeine. As our newborns needed a treatment for apnoea, such design was not feasible. Another approach would be to check the effect of caffeine in healthy newborns which would enable a successive regimen of measurements; yet, application of caffeine in healthy is not acceptable from ethical point of view.

Conclusions

This is the first study that assessed the impact of caffeine on HRV in postmenstrually 37-week-old newborns. The results of our study did not show any effects of caffeine on HRV in newborns. We assume that the maintenance dose of caffeine in newborns is too low to affect the HR and HRV. On the other hand, caffeine expectedly increased the BF. Furthermore, we showed a positive correlation between HRV and PMA, regardless of caffeine intake or bed tilt. While both TP and LF were higher with increasing PMA, HF did not significantly increase, assumingly because of the upper limit of the HF spectral band. An increased HRV with increasing PMA points to ANS maturation with age, and apparently is not subjected to any alterations induced by a standard treatment dose of caffeine. Our study implies safety of caffeine use in the prescribed dosage in newborns.

Abbreviations

ANS – autonomic nervous system

BF – breathing frequency

BM – body mass

CVS – cardiovascular system

ECG – electrocardiogram

HF – high frequency power spectrum

HR – heart rate

HRV – heart rate variability

IQR – interquartile range

LF – low frequency power spectrum

Me – median

NREM – non-rapid eye movement

PMA – postmenstrual age

PNS – parasympathetic nervous system

REM – rapid eye movement

SaO_2 – arterial oxygen saturation

SD – standard deviation

SNS – sympathetic nervous system

T – body temperature

TP – total power spectrum

Declarations

Competing interests: The authors declare they have no conflict of interest.

Ethics approval and consent to participate: Written parental consent was obtained for all participants.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

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Author Contributions: All authors collaborated and conceptualized the study, drafted the initial manuscript, and reviewed and revised the manuscript. Petja Fister coordinated the clinical conduction of the research. Helena Lenasi critically revised the manuscript for important physiological content. Eva Rihar and Jerneja Filipič conducted clinical research and methodologically analysed the data. Matjaž Klemenc performed spectral analysis of heart rate variability. All authors revised and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Supplementary Files

Supplementary Files are not available with this version.

Figures

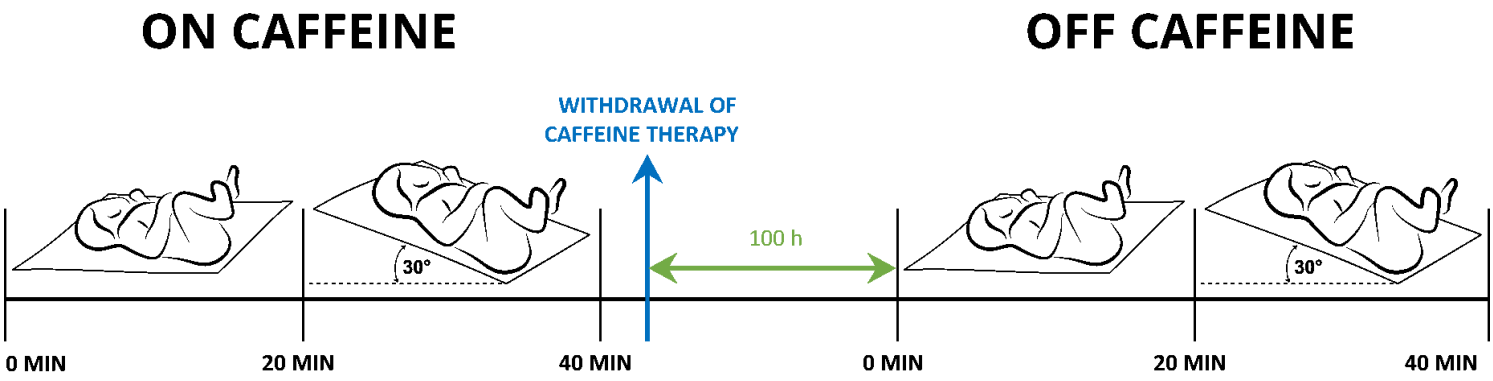

Figure 1

Timeline of the study protocol.

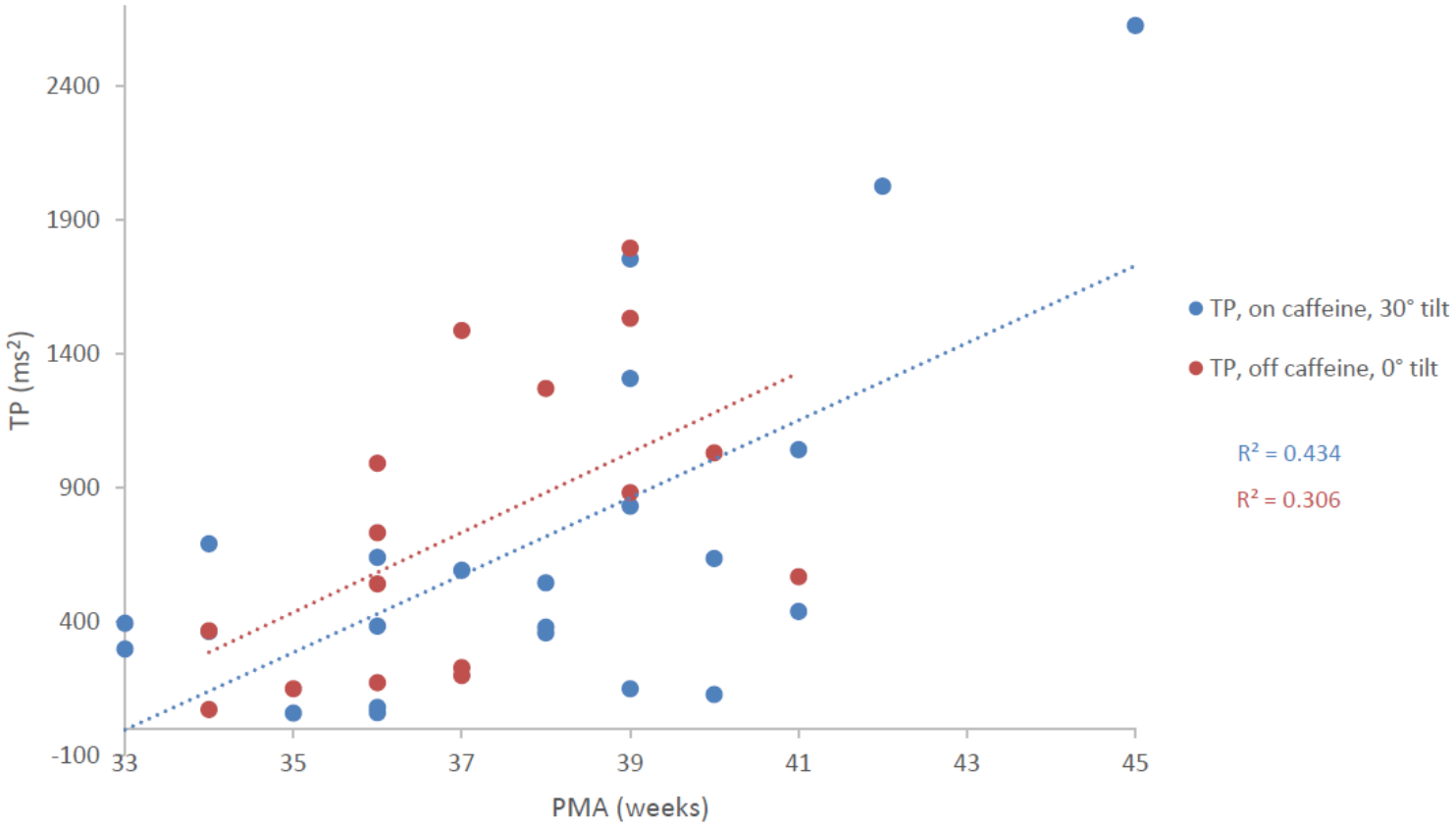

Figure 2

The correlation between the total power spectrum (TP) and the postmenstrual age (PMA). Linear regression was used. '0° tilt' and '30° head-up tilt' refer to bed tilt.