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Abstract

Heart rate variability (HRV) has been analyzed using linear and nonlinear methods. In the framework of a controlled neonatal stress model, we applied Tone-Entropy (T-E) analysis at multiple lags to understand the influence of external stressors on healthy term neonates. Forty term neonates were included in the study. HRV was analyzed using multi-lag T-E at two resting and two stress phases (heel stimulation and a heel stick blood drawing phase). Higher mean entropy values and lower mean tone values when stressed showed a reduction in randomness with increased sympathetic and reduced parasympathetic activity. A ROC analysis was utilized to estimate the diagnostic performances of tone and entropy and combining both features. Comparing the resting and simulation phase separately, the performance of tone outperformed entropy, but combining the two in a quadratic linear regression model, resting from stress phases in neonates could be distinguished with high accuracy. This raises the possibility that when applied across short time segments, multi-lag T-E becomes an additional tool for more objective assessment of neonatal stress.

Keywords: heart rate variability, newborn, stress, tone-entropy, autonomic nervous system

INTRODUCTION

Neonatal stress is a special field of research and clinical practice that can be considered from a wide spectrum of perpectives [1-3]. Endocrinologically, a large excretion of hormones is generated to cope with the potentially life-threating event, further activating the autonomic nervous system, and producing significant changes on every body system – basically changing the body's homeostasis [4-6]. Clinically, neonates and especially those born prematurely can sometimes present with vague clinical signs and symptoms of disease. Stressors that do not affect adult humans might have a significant impact on the very young, altering their long term development [7, 8]. In addition to standard environmental stressors in the neonatal intensive care unit (NICU), if there is disease and or early gestational age at birth in this population, there is further stressors as a result of the multitude and invasive medical procedures they suffer daily [9].

Heart rate variability (HRV) is the variability of the duration between successive cardiac cycles that originates in the sinus node [10]. HRV has broad application in basic autonomic nervous science and clinical use, applying different mathematical and statistical methods. Up until today, many indices have been found generated from the routinely used time and spectral domain, measures of entropy and indices derived from chaos theory [11-14].

Among the various HRV parameters, tone-entropy (T-E) showed promising results in identifying patients with autonomic nervous system (ANS) dysfunction [15]. It uses successive R-R intervals with the implicit assumption that the current heartbeat is influenced by the immediately preceding beat. However, it has been reported that each heartbeat influences not only the beat immediately following it, but also up to 6–10 beats downstream, possibly as a consequence of respiratory sinus arrhythmia and baroreflex influence[16]. Multi-lag T-E analysis approach was

proposed to overcome the limitations of the single lag T-E analysis in HRV studies [15, 17]. A rationale for the use of T-E relies on the evidence that T-E is not influenced by the period of data collection or the baseline heart rate (HR).

SUBJECTS AND METHODS

The study protocol

Forty healthy term neonates (21 females and 19 males, birth weight 3542.05 ± 339.09 g), all of who were born through vaginal delivery, with an APGAR score >9/9, without any pre-, and perinatal risk factors, and not previously experiencing any external stress stimuli, were included in this study. The neonates were chosen by simple random sampling on a daily basis over a time period of two months in the NICU. The experimental paradigm was performed just prior discharge, in the maternity ward, at 72 hours of age, the recommended chronological age for routine metabolic screening. As described previously [18], the protocol is divided into three parts: a) dummy stimulation phase, b) the sharp pain - heel stick phase, c) the treatment phase, and only the first two parts were included in the study.

Part a) consisted of two phases: The first baseline phase, lasting 10 minutes (further named Phase 1), after which intermittent pressing of the newborn's heel was done, mimicking a heel stick blood drawing procedure (Phase 2). Phase 2 lasted 90 seconds, which was the average time for the nurse to perform the actual procedure. The end of Phase 2) is the starting point of Part b). Part b) also consisted of two sub-phases - Phase 3, which is the second baseline, lasting 10 minutes, followed by the actual heel stick blood sampling procedure (Phase 4).

A lightweight, high-resolution device, with a high sampling rate (1024 Hz) was used (Firstbeat Bodyguard 2, Firstbeat TechnologiesLtd, Jyvaskyla, Finland). After visual inspection and artifact removal, the data were analyzed. To reduce movement artifacts and ensure quality of the recordings, the infants were positioned supine after breast- or formula feeding in a quiet room.

Multi-lag T-E analysis of HRV signal

The RR interval is defined as the time difference between two consecutive R peaks of the electrocardiogram (ECG) signal and the RR intervals in time series (RR_i) are defined as:

$$RR \equiv (RR_1, RR_2, \cdots, RR_N)$$

where, N is the number of RR_i. HR acceleration and inhibition can be determined from the difference of consecutive RR_i. If RR_{i+1} becomes shorter than RR_i then it is an acceleration of HR. Therefore, acceleration of the heart is expressed as a plus difference and inhibition as a minus difference of RR_i. However, to reduce the impact of HR variation over a wide range of time and different subjects, normalized variation in RR_i is preferred to monitor the variability. This normalized variation is measured by percentile change (percentage index (PI)) and defined as:

$$PI_i^m = \frac{RR_i - RR_{i+m}}{RR_i} \times 100 \qquad (1)$$

where, m is an integer and represents the lag used for measuring the PI. The detailed methodology of multi-lag T-E analysis has been described in previous report [15]. The $Tone$ at lag m ($Tone^m$)is defined as a first order moment (arithmetic average) of this $\boldsymbol{PI^m}$ time series as:

$$Tone^m = \frac{1}{N-m}\sum_{i=1}^{N-m} PI_i^m \qquad (2)$$

The *Entropy* at lag m is defined from the probability distribution of $\boldsymbol{PI^m}$ by using Shannon's formula [19]:

$$Entropy^m = -\sum_{i=1}^{n} p(i)\, log_2\, p(i) \qquad (3)$$

where, $p(i)$ is a probability that $PI_n^m(n)$ has a value in the range,, i is an integer. The $Entropy^m$ evaluates total acceleration–inhibition activities, or total heart period variations, in a familiar unit of bit.

Statistical analysis

The data were analyzed with the Matlab R2007a software. The Kolmogorov-Smirnov test was used to test the normality of distributions. The data are descriptively presented with means and standard deviations. Group differences were assessed with a repeated measures ANOVA, followed by a pairwise post hoc test. A ROC curve analysis was used to test the diagnostic properties of the T-E comparing the stress phases to the first baseline. P-values less than 0.05 were considered statistically significant.

Ethical statement

Our research was accepted by our institution's ethical committee, and informed consents were obtained from all research participant's parents or guardians.

RESULTS

There were statistically significant differences when comparing both the tone and entropy values across the four phases during the first ten lags (Table 1). The values for tone of each lag are negative at the baseline phases, while at the stress phases the values are positive. The values of entropy at the baseline phases were always higher than at the stress phases. Post hoc pairwise comparisons of tone show statistically significant differences between the resting and both stress phases. Similarly, comparing the stimulation and heel stick blood sampling phases, the tone differed between all lags, but lag 1, while entropy values showed no differences.

Comparing Phase 1 to Phases 2 and 4, using ROC analyses, reported as AUC and 95% confidence intervals (Table 2 and Figure 1). In the comparison of AUC (tone) shows consistency with increasing lags for both Phase 1 vs. Phase 2 and Phase 1 vs. Phase 4. Tone showed better performance in discriminating Phases 1 and 2 with higher AUC values for each lag than between Phases 1 and 4.

In both cases, the discriminating performance of entropy increased with increasing lags, plateauing at lag 5. At higher lag values, entropy showed better performance than tone when comparing Phases 1 and 4. While comparing Phases 1 and 2, AUC values of tone were always greater.

AUC values obtained using both tone and entropy features at each lag using linear regression, show consistency and high AUC values (AUC>0.9) comparing Phases 1 and 2 (Table 3., Figure 2.). An increase of AUC with increasing lags was observed comparing Phases 1 and 4 performing best at lags 6 and 9 (AUC=0.87).

DISCUSSION

The multi-lag T-E method efficiently shows the changes in the ANS balance that can be used even with short time series. The physiological interpretation of both tone and entropy has been reported in different experimental settings [15, 20-22]. A lower tone (negative values) indicates the parasympathetic predominance while a higher tone and lower entropy indicate a decrease in the parasympathetic and an increase or sympathetic predominance [15]. Although there is limited research on neonatal pain and stress applying HRV measures, this is the first study investigating multi-lag T-E in a neonatal stress framework [23, 24].

It has been previously reported that healthy adults at rest have higher mean levels of entropy and lower and negative mean tone levels at different lags, showing a predominance in the parasympathetic branch of the ANS [14, 15]. Our findings are comparable to that of adults, showing the same distribution of mean tone and entropy levels indicating a predominance of parasympathetic activity in neonates when at rest [25, 26].

Compared to the stress phases, at baseline, higher mean entropy values were observed than in the heel stick blood sampling phase, showing a reduction in randomness with increased sympathetic activity. Mean tone values are lower in the baseline phases compared to the stress phases, showing a predominance in parasympathetic activity at baselines, and an increase in the sympathetic activity at both stress phases.

Statistically, entropy is related to uncertainty. The decrease of entropy during stress phases indicates that the series is less erratic or less uncertain. It is consistent with previous findings, that have been seen in HRV of neonates in stress phases: 1) an increasing part of mean-reversion effect compared to random fluctuations, 2) an increasing negative scaling exponent, which

depicts a higher autocorrelation of the accelerations in the RR_i series. This higher autocorrelation, acting as a fractional integral, smooths the series and thus reduces fluctuations [18, 27].

The multi-lag part of our method is intended to take into account long-range influence of the baroreflex. This generalization of the T-E method to lags higher than one is consistent with many other methods that incorporates long-term effects. The particularity of the multi-lag T-E approach compared to fractal methods is that it determines the one lag that is the most significant, independent to any model relating various lags as is often stated in the fractal models. This model-free analysis of the lags therefore seems more general.

Another aim of this study was to estimate the diagnostic performances of tone and entropy and when combining both features. When separately comparing the resting and simulation phase, the performance of tone outperformed entropy, but a slight reversion of performance, especially at higher lags was shown when comparing the resting and blood sampling phase. When combined in a quadratic linear regression model, the AUC values increased in both cases. The lower performance comparing Phase 1 and 4 to Phase 1 and 2 might be related to the duration and type of stress that was applied. When sampling blood, pressure to the heel is routinely applied intermittently; after lancing, pressure to the heel is just enough to collect the required amount of blood to do further laboratory tests and then to stop the bleeding. In Phase 2, intermittent pressure only was applied to the neonates' heel for 90 seconds while at Phase 4, pressure is applied after lancing for blood collection and for hemostasis. These findings imply that multi-lag T-E may be useful for differentiating the type, duration and intensity of stress in the newborn.

As compared to mature nervous systems, the findings in stressed and resting neonates match the distributions of tone and entropy to adults without and with cardiac autonomic neuropathy

(CAN) [14, 15, 20]. It is well known that in patients with CAN due to the nerve damage, the parasympathetic activity is diminished, and the sympathetic tone predominates [28]. These findings let us conclude that T-E can be used as a surrogate measure of ANS in neonates.

In another recent study, similar to ours though evaluating fetal HRV, the authors indirectly showed the evolution of the ANS [22]. Their results showed that tone increases and entropy decreases at all lags in the late term fetuses, compared to the younger estimated gestational ages reflecting the maturation of the sympathetic nervous system as the fetus approaches the delivery period. Our study can be thought as an extension of their work, showing the changes in the ANS in healthy term neonates. The transition from intrauterine to extrauterine life is the most complex adaptation in human life [29]. Significant changes occur in the cardiovascular system during the first hours or perhaps first days of life to to a transitional circulation that undergoes further development depending on the different circumstances of extrauterine life. Compared to our study, especially the baseline phases, at all lags, tone is higher both in the early and late fetuses, while entropy is higher in our study group. Such findings might indicate a maturation both in the sympathetic and parasympathetic branch of the ANS, further showing that in our stress phases, a higher sympathetic response is observed. Although the researchers hypothesized that the maturation of the sympathetic branch might indicate preparing for delivery, transition in the circulation plays a role in the ANS balance [29]. The higher dominance of the parasympathetic branch at rest might imply that at the third day after delivery, the stress response caused during vaginal delivery has finally calmed down.

In conclusion, we applied a novel, recently developed measure of HRV to a simple physiological model of acute neonatal stress. Multi-lag T-E provides new insight in the developing ANS and was able to distinguish resting from stressed neonates. The possibility to apply multi-lag T-E on

short time segments make it suitable as an additional tool for more objective assessment of neonatal stress.

Competing interests

We have no competing interests.

Author contributions

MS and CKK contributed equally to this study. MS, KK and KM designed the study, conducted the research and collected the data; MS, KK, KM, MP, DB did the data preprocessing, CKK developed the code required for analysis and analyzed the data; KK carried out both intervention phases; JY, DB, MP, DA interpreted the data, revised the draft and approved the final version; MS, CKK, MG, DA, wrote the first draft and final manuscript. All authors gave final approval for publication.

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TABLES

Table 1: Feature values and statistical comparison using ANOVA, followed by pairwise comparison.

Lag	Feature	Phase 1	Phase 2	Phase 3	Phase 4	p	p12	p13	p14	p23	p24	p34
1	Tone	-0.09 ± 0.10	0.04 ± 0.09	-0.09 ± 0.11	-0.02 ± 0.13	<0.001	<0.001	>0.999	0.015	<0.001	0.052	0.013
	Entropy	3.63 ± 0.63	3.11 ± 0.59	3.58 ± 0.74	3.22 ± 0.59	<0.001	0.002	0.99	0.023	0.005	0.863	0.055
2	Tone	-0.12 ± 0.10	0.11 ± 0.18	-0.12 ± 0.11	0.00 ± 0.19	<0.001	<0.001	>0.999	0.001	<0.001	0.008	0.001
	Entropy	3.96 ± 0.56	3.46 ± 0.59	3.93 ± 0.66	3.51 ± 0.58	<0.001	0.001	0.997	0.004	0.003	0.986	0.009
3	Tone	-0.17 ± 0.12	0.19 ± 0.27	-0.17 ± 0.15	0.03 ± 0.26	<0.001	<0.001	>0.999	<0.001	<0.001	0.005	<0.001
	Entropy	4.23 ± 0.53	3.65 ± 0.59	4.18 ± 0.65	3.69 ± 0.59	<0.001	<0.001	0.976	<0.001	<0.001	0.994	0.001
4	Tone	-0.20 ± 0.13	0.26 ± 0.37	-0.21 ± 0.17	0.05 ± 0.34	<0.001	<0.001	>0.999	<0.001	<0.001	0.003	<0.001
	Entropy	4.39 ± 0.51	3.80 ± 0.59	4.35 ± 0.63	3.85 ± 0.60	<0.001	<0.001	0.985	<0.001	<0.001	0.978	0.001
5	Tone	-0.24 ± 0.15	0.34 ± 0.47	-0.24 ± 0.20	0.08 ± 0.42	<0.001	<0.001	>0.999	<0.001	<0.001	0.003	<0.001
	Entropy	4.54 ± 0.49	3.93 ± 0.57	4.47 ± 0.63	3.96 ± 0.61	<0.001	<0.001	0.945	<0.001	<0.001	0.992	0.001
6	Tone	-0.27 ± 0.16	0.42 ± 0.56	-0.27 ± 0.22	0.11 ± 0.51	<0.001	<0.001	>0.999	<0.001	<0.001	0.004	<0.001
	Entropy	4.63 ± 0.48	4.02 ± 0.59	4.57 ± 0.62	4.05 ± 0.60	<0.001	<0.001	0.959	<0.001	<0.001	0.995	<0.001
7	Tone	-0.31 ± 0.17	0.49 ± 0.66	-0.30 ± 0.24	0.14 ± 0.60	<0.001	<0.001	>0.999	<0.001	<0.001	0.005	<0.001
	Entropy	4.72 ± 0.47	4.08 ± 0.59	4.64 ± 0.61	4.12 ± 0.61	<0.001	<0.001	0.931	<0.001	<0.001	0.987	<0.001
8	Tone	-0.33 ± 0.18	0.57 ± 0.76	-0.33 ± 0.26	0.17 ± 0.70	<0.001	<0.001	>0.999	<0.001	<0.001	0.006	<0.001
	Entropy	4.77 ± 0.47	4.15 ± 0.59	4.70 ± 0.60	4.18 ± 0.60	<0.001	<0.001	0.945	<0.001	<0.001	0.996	<0.001
9	Tone	-0.35 ± 0.19	0.64 ± 0.86	-0.35 ± 0.28	0.21 ± 0.81	<0.001	<0.001	>0.999	<0.001	<0.001	0.008	<0.001
	Entropy	4.82 ± 0.46	4.21 ± 0.59	4.75 ± 0.59	4.24 ± 0.60	<0.001	<0.001	0.932	<0.001	<0.001	0.99	<0.001
10	Tone	-0.38 ± 0.20	0.72 ± 0.96	-0.36 ± 0.29	0.24 ± 0.91	<0.001	<0.001	>0.999	<0.001	<0.001	0.008	<0.001
	Entropy	4.87 ± 0.46	4.26 ± 0.59	4.79 ± 0.58	4.28 ± 0.60	<0.001	<0.001	0.939	<0.001	<0.001	0.997	<0.001

Table 2: AUC values between two groups

		Phase 1 vs Phase 2		Phase 1 vs Phase 4	
Lag	Feature	AUC	95% C.I.	AUC	95% C.I.
1	Tone	0.89	0.80-0.95	0.76	0.63-0.83
	Entropy	0.74	0.62-0.82	0.69	0.54-0.80
2	Tone	0.88	0.74-0.95	0.76	0.67-0.87
	Entropy	0.74	0.62-0.83	0.72	0.55-0.84
3	Tone	0.89	0.80-0.97	0.78	0.67-0.89
	Entropy	0.77	0.68-0.86	0.75	0.62-0.83
4	Tone	0.89	0.70-0.95	0.77	0.63-0.88
	Entropy	0.78	0.63-0.85	0.76	0.65-0.90
5	Tone	0.89	0.74-0.95	0.76	0.65-0.87
	Entropy	0.79	0.68-0.89	0.78	0.66-0.90
6	Tone	0.88	0.78-0.97	0.77	0.65-0.88
	Entropy	0.78	0.66-0.86	0.78	0.68-0.87
7	Tone	0.88	0.72-0.95	0.78	0.60-0.88
	Entropy	0.8	0.69-0.87	0.78	0.68-0.88
8	Tone	0.87	0.74-0.94	0.77	0.61-0.84
	Entropy	0.79	0.68-0.88	0.79	0.67-0.86
9	Tone	0.87	0.75-0.95	0.77	0.63-0.88
	Entropy	0.79	0.64-0.87	0.78	0.62-0.86
10	Tone	0.87	0.72-0.93	0.77	0.58-0.85
	Entropy	0.79	0.69-0.86	0.78	0.65-0.88

Table 3: AUC values obtained using both Tone and Entropy features at each lag using linear regression (quadratic model).

	Phase 1 vs Phase 2		Phase 1 vs Phase 4	
Lag	AUC	95% C.I.	AUC	95% C.I.
1	0.93	0.85-0.97	0.78	0.62-0.87
2	0.93	0.85-0.97	0.84	0.72-0.92
3	0.94	0.85-0.97	0.86	0.76-0.93
4	0.95	0.89-0.98	0.86	0.74-0.92
5	0.94	0.86-0.97	0.86	0.77-0.94
6	0.95	0.87-0.98	0.87	0.73-0.93
7	0.95	0.87-0.99	0.88	0.75-0.94
8	0.95	0.88-0.98	0.87	0.77-0.93
9	0.95	0.88-0.98	0.86	0.77-0.93
10	0.95	0.81-0.98	0.86	0.75-0.93

FIGURES

Figure 1: Changes of Entropy values with increasing lag

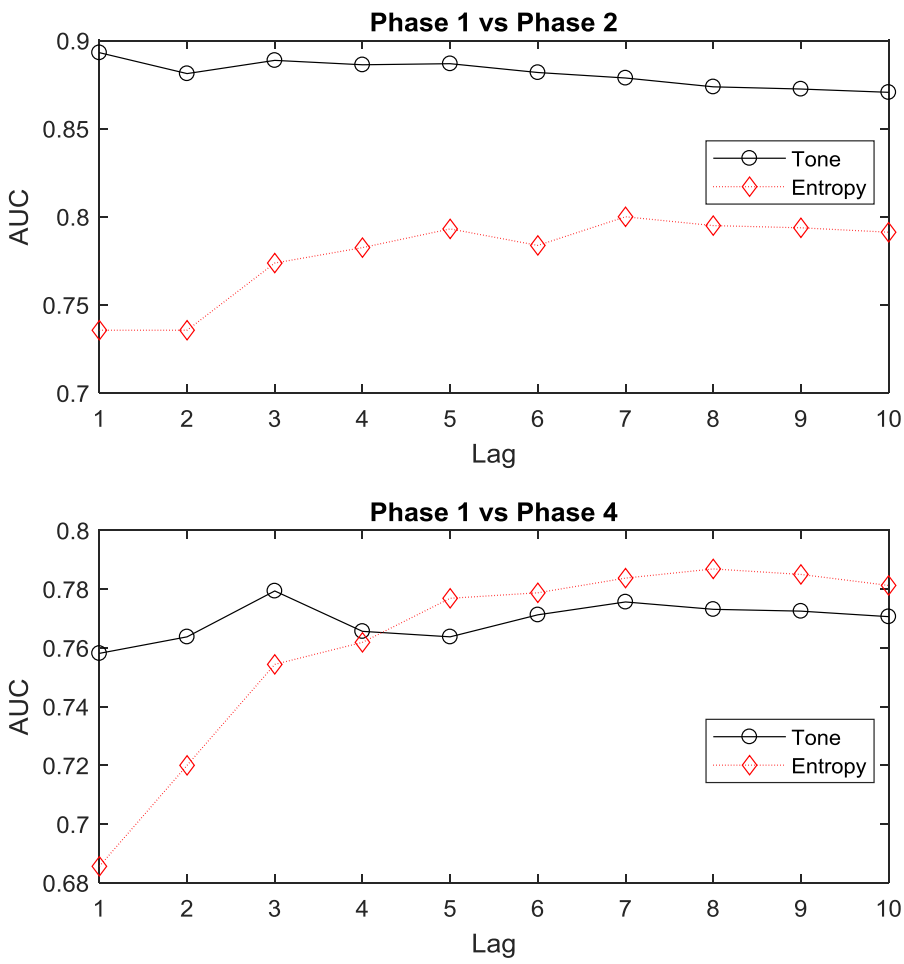

Figure 2: Variation in AUC values with varying lags.