Poincaré Plot Indices as a Marker for Acute Pain Response in Newborns

Šapina, Matej; Kramarić, Karolina; Milas, Krešimir; Milas, Vesna; Vujčić, Dunja; Dobrić, Hana; Pirić, Marko; Brdarić, Dario; Pušeljić, Silvija

Source / Izvornik: **Signa vitae : journal for intesive care and emergency medicine, 2017, 13, 33 - 36**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:239:118009

SIGNA VITAE 2017; 13(SUPPL 4): 33-36

Poincaré plot indices as a marker for acute pain response in newborns

MATEJ ŠAPINA[1,2], KAROLINA KRAMARIĆ[1,2], KREŠIMIR MILAS[1,2], VESNA MILAS[1,2], DUNJA VUJČIĆ[2,3], HANA DOBRIĆ[1,2], MARKO PIRIĆ[2], DARIO BRDARIĆ[4], SILVIJA PUŠELJIĆ[1,2]

1 University hospital Osijek, Pediatric Clinic, Osijek, Croatia
2 Medical faculty Osijek, Osijek, Croatia
3 University hospital Osijek, Department of nephrology and dyalisis, Osijek, Croatia
4 Institute for Public Health for the Osijek-Baranya County, Osijek, Croatia

Corresponding author:
Matej Šapina
J. Huttlera 4, 31000 Osijek, Croatia
Phone: 00 385 95 556 78 76
E-mail: sapina.matej@yahoo.com

ABSTRACT

Traditional views on neonatal pain neglected long neglected the neonates' capability of feeling pain. Newborn infants experience at least one painful procedure during their first days of life, but with a lower gestational age, invasive procedures become more frequent and invasive. The modulation of the autonomic nervous system (ANS) is significantly changed during painful procedures. The analysis of the heart rate variability is shown to be a reliable tool in analyzing the ANS. In this study, the dynamic of the system has been examined by applying the Poincaré plot analysis, a primer of nonlinear methods used in the analysis of the ANS. The aim of this study is to assess the occurrence of changes in linear heart rate variability parameters, to determine the changes in the Poincaré plot indices and to evaluate the correlation between their differences in healthy newborns. The results have shown a significant increase in the heart rate, a reduction of the duration of RR intervals, and the square root of the mean squared differences between successive RR intervals (RMSSD), as well as a decrease in the short-term variability (SD1) of the Poincare plot. The results highlight the need for studying the application of nonlinear analyses of the HRV on the effects of pain on the ANS and its long-term effects on the infant.

Key words: autonomic nervous system, pain, poincare plot, nonlinear analysis, heart rate variability

INTRODUCTION

Much effort is given defining pain. According to the International Association for the Study of Pain (IASP), pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms such damage". It is foremost a subjective phenomenon and for numerous reasons objectifying it in newborns is harder than in adults. The apparent lack of defining pain as such is updated by saying that the inability to communicate verbally does not negate the possibility that an individual is experiencing pain. (1)
Traditional views on neonatal pain neglected the capability of neonates feeling pain. This view was supported by the decortication paradigm, further explaining the lack of memories of painful experiences. (2) In an evolutionary context, an explanation of higher threshold of pain stimuli was proposed, by hypothesizing how an extremely high pain threshold was protecting infants during labor. (3, 4) However, during the eighties, in spite of the numerous hypotheses and metaphysical explanations of neonatal pain perception, Anand changed the traditional view by proving that pathways for pain transmission are developed even during fetal development. (5)
A lot of effort has been given to objectify pain, but the far most common way to assess it is by using various neonatal pain scales. (6, 7)
In reality, almost every healthy infant will be experiencing at least one iatrogenic pain stimuli. Usually, a heel stick blood sampling, for metabolic screening purposes. With a lower gestational age, pain stimuli become more frequent and more invasive. (8) The heel stick blood sampling is the most common used procedure of neonatal blood sampling, with low risk of complications. The method is important because it represents the simplest model of pain stimuli, which can be used for the purpose of investigating other, more invasive procedures.

Analysis of the heart rate variability

The analysis of the heart rate variability (HRV) to assess the autonomic nervous system and its reduction has been shown to be a likely risk factor for mortality in adults. (9) Although it is widely used in the adult population, its use in the neonatal and premature newborn population is not yet that widely appreciated. In recent neonatology studies, HRV analysis has been shown to be a useful marker of neonatal sepsis. (10)
Many quantitative HRV analysis methods have been described, but the two main methods can be divided into temporal and frequency domain analyses. Due to their insufficiency to describe the whole beat to beat variability, nonlinear methods are used for further understanding of the complexity of the heart rhythm regulation. (9)
Then, considering the nonlinear nature of organic systems, a nonlinear analysis is necessary, because some information may be lost if only analyzed by linear methods. These techniques have been shown to be powerful tools for characterization of complex systems, like complexity and fractal scaling properties of the cardiac interbeat series. (9)

Poincaré plots

The Poincaré plot (return maps) is a two-dimensional phase space scatter plot of the correlation between consecutive RR inter-

vals, in which a successive RRj+1 interval is plotted as a function of the previous RRj interval. As a result, the plot appears as a cloud of points dispersed along the line of identity (RRj+1=RRj). Further, an ellipse is fitted, where it's width and length are determined by the standard deviations perpendicular (SD1) and parallel (SD2) to the line of identity (11). SD1 represents instantaneous, or short-term variability, whereas SD2 is a measure of long-term variability. SD1 and SD2 correlate with parameters of the spectral frequency powers, while their ratio SD1/SD2 has been associated with the randomness of the HRV signal, and has a strong association with mortality in adults. (12)

By describing the nonlinear dynamics of a phenomenon that can recognize the hidden correlation patterns of a time series signal, this method is considered to be a nonlinear. (11, 13)

Due to the lack of studies investigating Poincaré plot analysis in neonates, the specific aim of this study is to apply it in acute neonatal pain, by hypothesizing that pain will cause a reduction of short-term variability.

MATERIALS AND METHODS

This study is a part of a larger ongoing research project on the relation of neonatal pain and the autonomic nervous system reactivity. Simple random sampling was used to obtain the subjects. Only healthy infants with APGAR >9/9, born through vaginal delivery, without congenital malformations, were included in the study. 14 male and 11 female participants, mean birth mass 3311.6±438.3 g, and 72 hours old, participated in the study. This age was chosen because the phenylketonuria screening is done at the third day of life. Before the testing, infants were fed and placed in supine position. The study environment has been without excessive noise pollution.

The heart rate intervals were recorded the during the whole procedure, which was divided into two parts. At the beginning of the study, at the baseline (control) phase, infants were monitored for 10 minutes, without manipulation, which was followed by the intervention phase. At this point, a registered nurse did the heel prick blood sampling.

A Firstbeat Bodyguard 2 (Firstbeat Technologies Ltd, Jyvaskyla, Finland) was used for monitoring the heart rate variability. It is a lightweight device, with a high-resolution sampling rate of 1024 Hz. The raw data was further transferred, visually inspected, corrected for artifacts and analyzed with the Kubios software(14). In addition to the Poincaré plot descriptors, the standard deviation of all RR intervals (SDNN), the standard deviation of instantaneous heart rate values (STDHR) and the square root of the mean squared differences between successive RR intervals (RMSSD).

The data was analyzed with the R software (www.r-project.org). The normality of the distributions of numerical variables was assessed by the Kolmogorov Smirnov test. If the data met the assumption of normality, the values were descriptively presented with means and standard deviations, otherwise with median and interquartile range. Group differences were assessed with the paired Student t-test, and Wilcoxon matched pair test. The Pearson's correlation test was used to test the associations between variables. P values less than 0.05 were considered statistically significant.

RESULTS

The first objective of this study was to assess the occurrence of changes in linear heart rate variability parameters. At the baseline, the mean RR interval was 460.06±74.13 ms, the mean HR 136.31±24.9 bpm, the median RMSSD 10.8 (8.2-14.7) ms. At the intervention time, the mean RR interval and the median RMSSD decreased to 403.44±60.33 ms and 9.1 (7.4-11.9) ms, respectively, whereas the HR rose to 154.83±22.97 bpm. Statistically significant decreases of -56.7±72.03 ms of the RR interval (p=0.001) and the RMSSD (-3.19±7.26 ms, p=0.039) were observed. The mean HR rose for 19.07±25.71 bpm (p=0.002).

The second objective was to determine the changes in the Poincaré plot indices. The median values of SD1 at the baseline was 7.6, which decreased to 6 (p=0.029). Similarly, a decrease of the SD2 was observed from 21.7 to 19.5 (p=0.088). (Table 1)

A further objective of the study was to assess the correlation between the differences of linear HRV and Poincaré plot indices. Significant positive correlations were found between the differences of the mean RR and SD1 (r=0.77), SD2 (r=0.74), between RMSSD and SD1 (r=1), and SD2 (r=0.91). Also, significant negative correlations were found between the mean HR and SD1 (r=-0.73) and SD2 (r=-0.69) (Table 2)

DISCUSSION

Based on previous research, a Poincaré plots have been marked as an accurate method of quantifying autonomic nervous system reactivity. (15) Pain causes physiological changes, which are shown in the results, with the significant increase in heart rate. Due to their inverse relation, a reduction in RR interval and heart rate variability, reflected by RMSSD, is observed.

The physiological interpretation of SD1 is related to the vagal mediated activity on the sinus node, which results in instanta-

Table 1. Summary of the most relevant findings

	Control	Intervention	Δ(t2-t1)	p
Mean RR	460.06±74.13	403.44±60.33	-56.7±72.03	0.001
STD RR	20.09±10.52	16.04±6.54	-4.56±10.48	0.049
Mean HR	136.31±24.9	154.83±22.97	19.07±25.71	0.002
STD HR	6.04±1.75	5.95±1.85	-0.31±2.23	0.506
RMSSD	10.8 (8.2-14.7)	9.1 (7.4-11.9)	-3.19±7.26	0.027
SD1	7.6 (5.8-10.4)	6.5 (5.2-8.4)	-2.25±5.14	0.029
SD2	22.6 (19.6-29.8)	19.8 (15.7-26.5)	-6.09±14.04	0.088
SD1/SD2	0.31 (0.29-0.39)	0.33 (0.28-0.38)	0.01±0.09	0.443

RR - rr interval, STD - standard deviation, HR - heart rate, SD1 - short axis, SD2 - long axis, t1 - baseline time, t2 - intervention time

Table 2. Correlations between the differences (Δ(t2-t1)) of the most significant variables

	Δ Mean RR	Δ STD RR	Δ Mean HR	Δ STD HR	Δ RMSSD	Δ SD1	Δ SD2	Δ SD1/SD2
Δ Mean RR	1							
Δ STD RR	0.74*	1						
Δ Mean HR	-0.98*	-0.68*	1					
Δ STD HR	0.33	0.81*	-0.29	1				
Δ RMSSD	0.72*	0.85*	-0.65*	0.54*	1			
Δ SD1	0.72*	0.85*	-0.65*	0.54*	1.00*	1		
Δ SD2	0.71*	0.99*	-0.67*	0.83*	0.78*	0.78*	1	
Δ SD1/SD2	-0.02	-0.36	0.07	-0.52*	0.14	0.15	-0.47*	1

RR - rr interval, STD - standard deviation, HR - heart rate, SD1 - short axis, SD2 - long axis, Δ t1 - baseline time, t2 - intervention time, *p<0.05

neous beat to beat variability. (12, 16) The vagal effect on the sinus node develops faster than the sympathetically mediated effect. SD2 is a result of both sympathetic and parasympathetic influence. Therefore, the changes in SD1 during the pain intervention show mostly a change in the parasympathetic autonomic nervous system.

The SD1/SD2 ratio is a marker of nonlinear information of the HRV, whit a strong correlation with various nonlinear variables. (17) Our results showed no change in SD1/SD2, meaning that there is no statistically significant change in nonlinear information in the pain response of a healthy newborn.

The perfect correlation of ΔSD1 and ΔRMSSD is a result of a known relationship between SD1 and RMSSD: RMSSD = $\sqrt{2}\times$ SD1 (2). Although these two parameters are mathematical equivalents, their origin is different. (13) Thus, RMSSD has the same interpretation as SD1. (18) The differences of SD2 were best correlated with the STDRR, which shows a relationship of total HRV to long-term HRV in short recordings.

There are a few studies focused on the relation of neonatal HRV and pain response. In a HRV study after heart surgery, researchers have shown that postoperative pain is associated with changes of HRV in terms of short-term and variability and its ratio in newborn infants. (19) In another pain related study, the Poincaré plot was used in a different way (20), using the area of the plot as descriptors. A study similarly designed to ours, varying in baseline and intervention duration showed comparable results to ours. (21) The findings suggest that there is a reduction of vagal tone after acute pain stimuli, reflected by the SD1.

CONCLUSION

Although there are limitations of this study, these preliminary results suggest that Poincaré plot analysis might be efficient in objectifying pain responses as other linear heart rate variability parameters, highlighting the need for further studies in neonatal pain (patho)physiology. As the simplest way in studying pain using nonlinear methods, the results of this study show that Poincaré plot analysis might have a promising value in pain research. Although there are questions still remaining, further research is needed to evaluate the long-term effects of pain stimuli on nonlinear aspects of the human heart rate and autonomic nervous system.

REFERENCES

1. Merksey H, Bogduk N. Classification of chronic pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Term. 1994:59-71.
2. McGraw MB. The neuromuscular maturation of the human infant. 1943.
3. Levy DM. The infant's earliest memory of inoculation: a contribution to public health procedures. The Journal of genetic psychology. 1960;96(1):3-46.
4. Merskey H. On the development of pain. Headache: The Journal of Head and Face Pain. 1970;10(3):116-23.
5. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. N Engl j Med. 1987;317(21):1321-9.
6. Krechel SW, BILDNER J. CRIES: a new neonatal postoperative pain measurement score. Initial testing of validity and reliability. Pediatric Anesthesia. 1995;5(1):53-61.
7. Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. Neonatal network: NN. 1993;12(6):59-66.
8. Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. Jama. 2008;300(1):60-70.
9. Cardiology TFotESo. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. circulation. 1996;93:1043-65.
10. Care PEE. Neonatal, Paediatric and Child Health Nursing. 2011.
11. Karmakar CK, Gubbi J, Khandoker AH, Palaniswami M. Analyzing temporal variability of standard descriptors of Poincaré plots. Journal of electrocardiology. 2010;43(6):719-24.
12. Tulppo MP, Makikallio T, Takala T, Seppanen T, Huikuri HV. Quantitative beat-to-beat analysis of heart rate dynamics during exercise. American journal of physiology-heart and circulatory physiology. 1996;271(1):H244-H52.
13. Brennan M, Palaniswami M, Kamen P. Do existing measures of Poincare plot geometry reflect nonlinear features of heart rate vari-

ability? IEEE transactions on biomedical engineering. 2001;48(11):1342-7.
14. Tarvainen MP, Niskanen J-P, Lipponen JA, Ranta-Aho PO, Karjalainen PA. Kubios HRV–heart rate variability analysis software. Computer methods and programs in biomedicine. 2014;113(1):210-20.
15. Kamen PW, Krum H, Tonkin AM. Poincare plot of heart rate variability allows quantitative display of parasympathetic nervous activity in humans. Clinical science. 1996;91(2):201-8.
16. Tulppo MP, Mäkikallio TH, Seppänen T, Laukkanen RT, Huikuri HV. Vagal modulation of heart rate during exercise: effects of age and physical fitness. American Journal of Physiology-Heart and Circulatory Physiology. 1998;274(2):H424-H9.
17. Hoshi RA, Pastre CM, Vanderlei LCM, Godoy MF. Poincaré plot indexes of heart rate variability: relationships with other nonlinear variables. Autonomic Neuroscience. 2013;177(2):271-4.
18. Ciccone AB, Siedlik JA, Wecht JM, Deckert JA, Nguyen ND, Weir JP. Reminder: RMSSD and SD1 are Identical Heart Rate Variability Metrics. Muscle & Nerve. 2017.
19. Smith R, Wathen E, Abaci PC, Von Bergen N, Law I, Dick M, et al., editors. Analyzing heart rate variability in infants using non-linear Poincaré techniques. Computers in Cardiology, 2009; 2009: IEEE.
20. Lindh V, Wiklund U, Blomquist HK, Håkansson S. EMLA® cream and oral glucose for immunization pain in 3-month-old infants. Pain. 2003;104(1):381-8.
21. Weissman A, Zimmer EZ, Aranovitch M, Blazer S. Heart rate dynamics during acute pain in newborns. Pflügers Archiv-European Journal of Physiology. 2012;464(6):593-9.