Point Process Heartbeat Dynamics Assessment of Neurocardiogenic Syncope in Children

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Abstract

The underlying mechanisms that lead to syncope are still unclear, especially in children. In this work, we applied a novel point-process model to study time-varying heartbeat dynamics and to characterize autonomic changes that occur prior to a syncopal event. Twenty-six children with history compatible with neurocardiogenic syncope (NCS) and a positive head up tilt table test (HUT) were included in the study. ECG and blood pressure signals were recorded during rest and the diagnostic HUT. Using self-developed software, a decrease of $> 30\%$ of the median systolic blood pressure during HUT compared to rest was selected as the onset of the syncopal event. After ECG peak detection and correction of ectopic beats, we modeled the time between R-wave events as a history dependent inverse Gaussian (IG) and applied the point-process framework to compute several measures related with HRV. We tested for significant changes in these measures for three consecutive two-minute time intervals previous to the syncopal event. Of all measures, only the mean of the heart rate probability density function, μ_{HR}, and the scale parameter of the IG probability density function, $\xi_0(t)$, presented a statistically significant increase prior to syncope, providing novel features associated with the statistical properties of heartbeat generation that could be critical to predict and explain the occurrence of syncope.

1. Introduction

Neurocardiogenic syncope (NCS) is the most common cause of unexplained syncope in children and adolescents [1]. Although the underlying mechanisms that lead to loss of consciousness due to blood pressure drop are still unclear, syncope is known to be associated with an imbalance of the autonomic nervous system (ANS) [2, 3]. Heart rate variability (HRV) provides a non invasive measure of cardiovascular regulation by the ANS, and it can been used to investigate changes in the sympathetic and parasympathetic activity. Several studies have analyzed HRV during head-up tilt table test (HUT) in children using time and frequency domain parameters [4, 5]. Despite some important studies performed with adults on the time-varying autonomic evolution leading to syncope [6, 7], none of the pediatric studies considered instantaneous estimates of HRV measures to characterize transient changes associated with syncope. No study has yet characterized time-varying statistical properties of heartbeat dynamics before syncope.

The objective of this paper is to study time-varying ANS dynamics during HUT in children and to identify changes that occur before a syncope or presyncope by applying a novel point-process model of heartbeat dynamics. In addition to instantaneous measures of HRV, the point process model is also able to give an instantaneous characterization of the generative statistical properties of the heartbeat. In particular, we look at the evolution of the shape parameter of the inverse Gaussian probability density function (PDF) used to describe the integrate-and-fire model for the ventricular contraction onsets, and assess its changes prior to syncope.

2. Materials and methods

2.1. Study population

We selected 26 subjects between 10 and 18 years of age who had experienced unexplained syncope and were referred to an autonomic physiology laboratory to perform a diagnostic HUT. All of them reported at least one syncopal episode and several presyncopal events during the previous six months and presented a positive response to HUT. Subjects with chronic diseases (diabetes mellitus or cardiac or

neurological diseases) and those who were taking medications known to affect heart rate or to cause orthostatic hypotension were excluded from the study. Informed consents were obtained from all children and their caretakers.

2.2. Experimental protocol

Continuous ECG and beat-to beat blood pressure (BP) signals were recorded with a Finometer device (Finapress Medical System, The Netherlands) during rest and during the diagnostic HUT. Baseline measures of ECG and BP were acquired for 10 minutes with the subject in supine position (*rest* record). Then, 20 min after venous cannulation, subjects were tilted to a 60° upright position for 30 min using an electrical driven tilt table with footboard support. If subjects did not present syncope or presyncope during a first HUT, they underwent a second tilt with administration of sublingual nitroglycerin, 200 mcg at the minute 15. A positive test was defined as syncope or presyncope associated with a decrease in systolic arterial blood pressure with or without associated bradycardia.

2.3. Syncope detection

For the present analysis a self-developed software was used to detect a decrease of $> 30\%$ of the median systolic blood pressure during HUT compared to rest. This point was considered as the onset of the syncopal event for all subjects. All records were visually inspected by a physician and were correlated with the clinical symptoms presented by the subjects during the exam.

2.4. Point process model

ECG peak detection and correction of ectopic beats was performed with an automatic technique previously described in [8]. Then, a point process model was applied to the RR intervals [9].

Assuming history dependence, the probability distribution of the waiting time $t - u_j$ until the next R-wave event u_{j-1} follows an inverse Gaussian model [9]:

$$f(t|H_t,\xi(t)) = \left[\frac{\xi_0(t)}{2\pi(t-u_j)^3}\right]^{\frac{1}{2}} \cdot \exp\left\{-\frac{1}{2}\frac{\xi_0(t)[t-u_j-\mu_{RR}(t,H_t,\xi(t))]^2}{\mu_{RR}(t,H_t,\xi(t))^2(t-u_j)}\right\} \quad (1)$$

with the instantaneous mean RR defined as:

$$\mu_{\text{RR}}(t,H_t,\xi(t)) = \text{RR}_{j-1} + \gamma_0(t) + \sum_{i=1}^{p}\gamma_1(i,t)RR_{j-i-1} \quad (2)$$

where $H_t = (u_j, \text{RR}_j, \text{RR}_{j-1})$ is the history of events and $\xi(t) = [\xi_0(t), \gamma_0(t), ..., \gamma_1(t)]$ is the parameter vector. Of note, as the shape parameter tends to infinity, the inverse Gaussian distribution becomes more like a normal (Gaussian) distribution.

For parameter estimation, a local maximum likelihood method using a sliding window of duration $W = 90\,\text{s}$ was used to estimate the unknown time-varying parameter set [9]. After parameter estimation, instantaneous RR and heart rate (HR) variability indexes, as well as conventional spectral HRV measures (total spectral power, low frequency power (0.04 – 0.15 Hz, LF), high frequency power (0.15 – 0.45 Hz, HF), RR interval variability) were estimated in an instantaneous manner from the parameter vector [9], [10].

We determined the optimal order p based on the Akaike Information Criterion (AIC) and by prefitting the point process model goodness-of-fit to a subset of the data. Model goodness-of-fit is based on the Kolmogorov-Smirnov (KS) test and associated KS statistics [9], [11]. Autocorrelation plots were also considered to test the independence of the model-transformed intervals [9]. Once the order p was determined, the initial coefficients were estimated by the method of least squares [10].

2.5. Statistical analysis

Point process measures were first calculated for each subject independently and then, after aligning the episodes by the time of the syncope onset, the median and the confidence intervals of each of the measures were computed to analyze intersubject trends. In order to assess the changes occurring before the syncope, we analyzed three two-minute intervals starting six (*int3*), four (*int2*) and two (*int1*) minutes before a reference point 10 s prior to the syncope onset, and checked for differences between groups. As the data did not pass the Kolmogorov-Smirnov normality test, Kruskal Wallis and Wilcoxon rank sum test were used.

3. Results

Panels (A) and (B) of Fig.1 show representative results for (A) one single subject and (B) the median of all the subjects. After a preliminary analysis we present the following most relevant measures: systolic and diastolic BP (plotted in red and blue, respectively), RR intervals and the mean of the estimated RR interval PDF (μ_{RR}), the mean of the estimated HR PDF (μ_{HR}) the ratio LF/HF, and the scale parameter of the RR interval PDF, $\xi_0(t)$. Although the effects of orthostatic stress were not the focus of this study (no statistical comparisons are presented), the differences between tilt before syncope and rest confirm the expected autonomic changes with tilt. Considering dy-

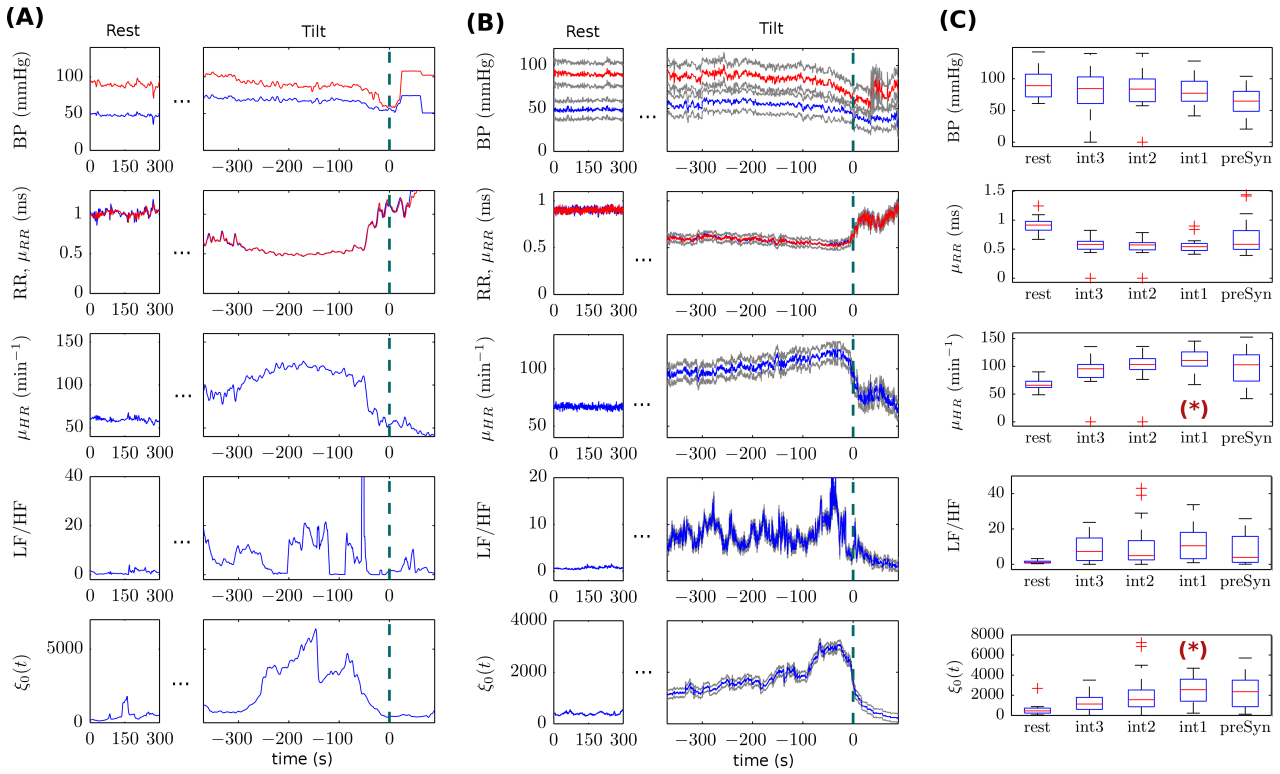

Figure 1. Representative hearbeat dynamics measures (A) for one of the subjects in the dataset, (B) averaged across subjects (confidence intervals shown in gray) and (C), boxplots related to changes in the measures before the syncope onset. In (A) and (B) 300 s of the measures during rest are shown in the left panel, and an interval of the tilt starting 360 s before the syncope in the right panel. In (C), measures during rest are visually compared with three two-minute intervals starting six (*int3*), four (*int2*) and two (*int1*) minutes before the reference point (10 s prior to the syncope onset) and with the measures during the last 10 s. Only int1, int2 and int3 are statistically tested with Kruskal-Wallis test. Measures that change significantly before the syncope are marked with an asterisk.

namics starting from 360 s before syncope, it is possible to observe a slow steady increase in μ_{RR}, a burst-like increase in LF/HF, and a steady step-like significant increase in $\xi_0(t)$. Of note, all measures reverse their trends a few seconds before syncope. Panel (C) shows boxplots for all the considered measures during rest, during the three analyzed intervals, and during the ten seconds previous to the syncope (*preSyn*). The statistical comparison among int1, int2 and int3 showed statistically significant differences only between int1 and int3 for μ_{HR} and $\xi_0(t)$.

4. Discussion

Previous studies have reported conflicting results in relation to the autonomic changes observed during orthosthatism in NCS [4, 12–14]. One reason for these discrepancies could be the lack of consensus as to the most appropriate time points for recording HRV and the limitations of the traditional HRV analysis methods in providing continuous indexes. Our study is the first in reporting a continuous estimation of autonomic indexes during HUT in children with NCS. We used self-developed software to automatically identify the onset of the syncopal event. The syncope was identified when the systolic blood pressure decreased $> 30\%$ of the median value observed during the baseline measurements acquired with the subject in supine position. We found that using the median instead of the maximum value as a reference was more robust against artifacts in the BP signal, and that the rest record provided a more stable reference than the tilt one. This method correctly identified syncope onset for all the records.

We modeled the stochastic structure of heartbeat intervals as a history-dependent inverse Gaussian process and derived from this model several time-varying measures to analyze transient changes in heartbeat dynamics. Our results confirmed previous findings in adults. In particular, they revealed an exaggerated sympathetic response in the minutes previous to the syncopal event followed by an abrupt drop of this activity (note the peak in LF/HF

ratio in Fig.1, panel (B)). These changes were correlated with the hemodynamic changes and clinical symptoms observed during syncope. However, this measure did not show significant differences for the time intervals compared in this study. Although the LF/HF presents a peak before the syncope, this signal could be too noisy to provide a precise indication as precursor of syncope onset. Of note, the mean of the estimated HR PDF, μ_{HR}, was the only autonomic index with statistically significant changes prior to syncope, thus providing a potential measure for syncope detection.

A critical finding of the present study was the evolution in time of the scale parameter, $\xi_0(t)$, associated with the RR interval PDF, which presents a highly significant increase in the two minutes prior to syncope. An increase in this measure means that the inverse Gaussian distribution modeling the R-R intervals becomes more like a normal (Gaussian) distribution. This measure decreases again during the last 10 s prior to syncope. We speculate that the change in probability structure is due to a disruption of the normal integrate-and-fire properties of the sinus node as they are generated under a wide range of sympatovagal influences [9]. This disruption might be one of the causes of malfunction of the compensatory action of the ANS in the maintenance of blood pressure levels in response to orthostatism. Future studies will be performed to determine the predictive value of this index on determination of syncope onset. For example, a threshold could be established to detect the initial disruption of the system.

In conclusion, our results provide new insights into the ANS alterations underlying the hemodynamic responses to HUT in children with NCS, and reveal new measures that could be used to characterize and possibly predict syncopal events.

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