NONLINEAR ANALYSIS OF HEART RATE VARIABILITY IN INFANTS WITH APPARENT LIFE-THREATENING EVENTS

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1. ABSTRACT

Some studies have shown that neonates having experienced an Apparent Life-Threatening Event (ALTE) have an increased risk of dying of the Sudden Infant Death Syndrome (SIDS) [1]. In this study the heart rate variability in neonates has been analyzed through a study of the long range correlations and scale invariance (self-similarity) in their cardiac rhythm. The goal is to see whether it is possible to distinguish normal infants from infants with ALTEs using the previously mentioned nonlinear measures of the heart rate variability.

Twelve ALTE infants are included in this study. To determine the degree to which these neonates suffer from ALTEs two examinations are performed: a polysomnography[1] and home monitoring. Using the nonlinear measures obtained from the nonlinear analysis of the heart rate variability, the group suffering most from ALTEs can clearly be separated from the other neonates.

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[1] i.e. the simultaneous recording of physiological signals, such as ECG, heart rate, peripheral oxygen saturation, respiration, EEG, EOG and EMG, during 8 to 12 hours.

2. INTRODUCTION

Some studies have indicated that the occurrence of ALTEs is a risk factor for SIDS. Therefore, a measure predicting the degree to which a neonate suffers from ALTEs could be used as a measure to predict the risk for a neonate to die of SIDS.
In this study twelve ALTE infants are included. Two examinations are performed in order to determine in an objective way the degree to which a neonate suffers from ALTEs: a polysomnography in the hospital and home monitoring as follow-up. In this way the group of ALTE neonates can be split up into four classes: AA (abnormal polysomnography, abnormal follow-up (3 babies)), NA (normal polysomnography, abnormal follow-up (1 baby)), AN (abnormal polysomnography, normal follow-up (2 babies)) NN: normal polysomnography, normal follow-up (6 babies)). A polysomnography is defined as being abnormal when one of the following events occur during the examination:

- a bradycardia of less than 50 bpm for at least 4 seconds
- an obstructive apnea of at least 15 seconds with a concurrent bradycardia of less than 60 bpm and/or concurrent oxygen desaturation of less than 80%.

An abnormal follow-up (i.e. home monitoring) is defined as the occurrence of a bradycardia of less than 50 bpm during the follow-up.
In addition a control group of 7 healthy infants is included. It is clear that the neonates most at risk for ALTEs are those in class AA. The heart rate variability is analyzed by means of the Detrended Fluctuation Analysis (DFA)[2,3] of the RR time series, which consists of the duration of the time intervals between successive R peaks in the electrocardiogram (ECG). As explained in the next section, four numbers are derived from the obtained DFA function. They correspond to the very short term (α_0), the short term (α_1), the long term (α_2) and the very long term (α_3) scale-invariant (fractal) correlation property of the RR time series. The rationale behind this approach is the following. Recent research[4] indicated that a deficit in the arcuate nucleus may be partially responsible for some SIDS deaths. Further research[5] suggested the existence of cellular connections between the arcuate nucleus and the caudal raphe, a region implicated in cardiorespiratory control. Deficiencies in cardiorespiratory control will be reflected in the RR time series and thus it makes sense to analyze this time series as possible source of information about SIDS.

3. METHODS

3.1. Derivation of RR time series

Due to the long duration of the ECG recordings (on average 8 hours) the RR time series has to be extracted in an automated way from the ECG. The R peaks are detected using the second order derivatives of the ECG followed by an automated validation/correction of the obtained RR time series.

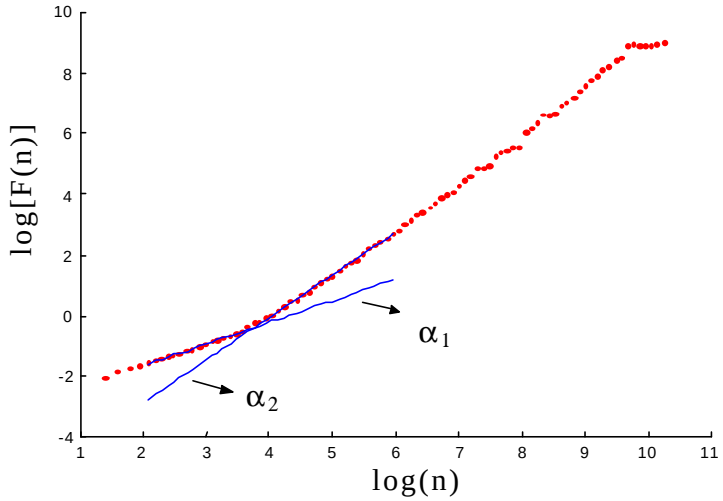

Figure 1. This figure shows the DFA function F(n) as a function of the frame length. Straight lines indicate self-similarity.

3.2. DFA

The DFA analysis derives a function F(n) from the RR time series r(i), i=1,…,N in the following way. First r(i) is integrated over time and shifted by its average r_{ave} over the N data points: y(k)= $\sum_{i=1}^{k} r(k) - r_{ave}$. Next the integrated time series y is divided into frames of equal length n. In each frame of length n, a straight line is fitted in least squares sense to y, yielding a new function $y_n(k)$, representing the local trend in each frame. Next the DFA function F(n) is obtained as the mean square fluctuation of the detrended integrated time series: $F(n) = \sqrt{\sum_{k=1}^{N} (y(k) - y_n(k))^2 / N}$. Note that the different steps described before are necessary to obtain information on the self-similarity of the RR time series while taking into account its nonstationary character. Furthermore, a linear relation on a double log graph (see figure 1) indicates the presence of self-similarity (i.e. fluctuations over small frames are related to fluctuations over large frames in a power-law fashion). The determination of $á_1$ and $á_2$ is done by selecting an index n_{break} such that the global mean square error of two straight lines fitted to F(n) over the intervals log(n)=[2 … n_{break}] and log(n)=[n_{break} …6] is as small as possible, where log stands for the natural logarithm. The slope of the straight line fitted on the first interval is $á_1$ whereas the slope of the straight line fitted on the second interval is $á_2$ (see figure 1). Two additional lines are fitted to the DFA function over the interval to the left of log(n)=2 and to the interval log(n)=[7 … 9.5], since their slopes $á_0$ and $á_3$ tend to deviate from respectively $á_1$ and $á_2$. Note that these different á's are called the scale-invariant (fractal) correlation properties of the RR time series.

4. EXPERIMENTAL RESULTS

4.1. Measurements

The polysomnography is acquired using a Hellige Servomed (Hellige Freiburg, Germany). The home monitoring is performed using two types of monitors: the Arvee 4800 (Arvee Medical, Austin, Texas, USA) and the Nellcor Edentec 336 (Nellcor Puritan Bennett, Eden Prairie, Minnesota, USA). Both monitors record the ECG as well as a respiratory signal. Home monitoring was performed during at least 2 and at most 18 months (the average being 5 months).

4.2. Results

Considering all possible pairs from the parameter set $\{a_0, a_1, a_2, a_3\}$, the combination of $á_1$ and $á_2$ turns out to be the best choice for distinguishing the AA group from the other infants. This is illustrated in figure 2. The neonates of group AA are represented by a "*", those of the NA group by a white disk, those of the NN group by a "+", those of the AN group by a "x" and those of the control group by a grey disk. The AA group is clearly characterized by a combination of higher $á_1$ values and lower $á_2$ values when compared to infants belonging to the other groups. Note however that there is one neonate of the AA group that has a significantly lower $á_1$ value than the other members of the AA group. It turned out that this neonate suffers from the long QT syndrome and should thus be considered as a special case. It should be mentioned that although some authors have indicated a long QT interval as one of the causes of SIDS[6] this hypothesis is rather controversial[7,8,9].

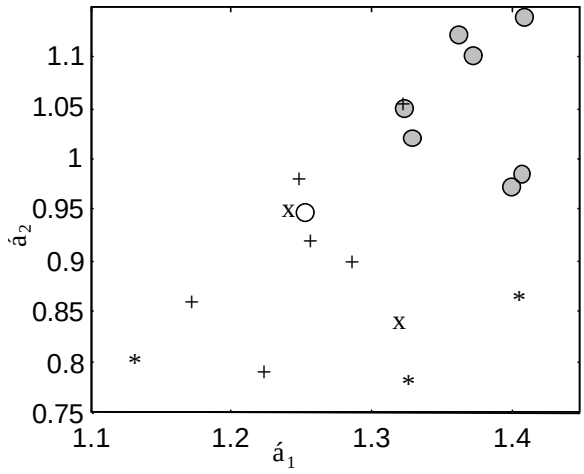

Figure 2. This figure illustrates the position of the members of the AA group ("*") , the NA group (white disk), the NN group ("+"), the AN group ("x") in the $á_1$- $á_2$ plane, where $á_1$ and $á_2$ are nonlinear measures derived from the RR time series.

5. CONCLUSIONS

Although the group of patients is too small for a statistical analysis, it is clear that a combination of α_1 and α_2 enables to distinguish healthy infants from infants suffering to a high degree from ALTEs (the AA group). While long-term correlations are most persistent for normal infants (α_2 close to 1), ALTE babies have a smaller α_2 index, pointing out a decreased long-term correlation, in particular for the AA group, which might indicate a higher risk for SIDS. Within the ALTE group, the NN group can be clearly separated from the AA group. The distinction between the NA, AN and AA groups is less clear. A larger follow-up study is needed to confirm the performance of the nonlinear measures, and to evaluate the predictive value of the different measures with respect to SIDS.

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