Short Term Prediction of Severe Bradycardia in Premature Newborns

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Abstract

Premature newborns show frequent episodes of bradycardia due to the immaturity of their autonomic nervous system. There is a need for developing methods which may alert physicians as soon as early signs of bradycardia are detected. In this paper we studied the RR Interval (RRI) series using data mining methods to detect early signs of bradycardia. We employed principal components analysis (PCA) and hierarchical ascending classification (HAC) according to the generalised Ward's method. Time domain and frequency domain parameters as well as non-linear indices based on entropy were extracted from 13 stationary RRI series 3 minutes preceding the bradycardias. The projection of observations on the first factorial plan demonstrated a well defined path: clustering of observations appeared approaching the bradycardia (in 10/13 cases). These results suggest that the RRI contains information that can be employed to predict the onset of the bradycardia event.

1. Introduction

In premature infants recurrent bradycardias associated or not to apnea and desaturation have emerged as particularly troublesome problem. The repetition of episodes of bradycardia may compromise oxygenation and tissue perfusion and quick nursing intervention is usually required to prevent severe and permanent damage to the infant. Indeed, for infants with frequent and severe bradycardia there have been few effective alternatives to intubation for intracheal-ventilation.

Some studies assessed the efficiency of kinesthetic stimulation to the treatment of apnea and bradycardia [1][2][3]. These studies enrolled preterm infants with established apnea with exclusion of secondary causes and not on any treatment with a respiratory stimulant. The type of kinesthetic stimulation differed between the trials: irregularly oscillating water bed, regularly rocking bed tray, blood pressure cuff placed under the thorax. These methods of kinesthetic stimulation were judged efficient in reducing the frequency of episodes of apnea/bradycardia but not for preventing reintubation.

Even if algorithms for bradycardia detection have been developed, they are inefficient and usually produce false or late alarms. There is also a need for developing methods which may alert physicians as soon as early signs of bradycardia are detected. A new method of early on line prediction of severe bradycardia is presented in this communication: it associates parameter measurements of RR Interval (RRI) series and principal components analysis. As the episodes of bradycardia in newborns may be due to the immaturity of their Autonomic Nervous System (ANS), RRI variability seems to be the appropriate tool to investigate it. In fact, RRI carries relevant information about ANS status. It has been documented [4] that power spectral analysis reveals two main spectral components: the High Frequency (HF) component, which is mainly modulated by vagal tone, and the Low Frequency (LF) one, which is found to increase in presence of increased sympathetic tone. It has been also shown that the RRI signal is not simply linear, but it involves non-linear contributions. Therefore in this paper, we will investigate both linear and non-linear indexes of RRI variability and we will explore them by PCA in order to detect those metrics which contain early signs of bradycardia and may help in predicting it.

2. Method

Experimental protocol. The investigation was carried out in the neonatal intensive care unit of the department of paediatrics at the University Hospital of Rennes. We retrospectively studied the recordings of 5 premature infants who had required for polygraphic monitoring in their clinical management because of severe and recurrent bradycardia. The median gestational age at birth was 26.9 weeks (26 to 30.3) and birth weight was 905g (650 to 1470g). Absence of structural anomalies of the heart had been checked in all babies by echocardiography in the first days of life. On the day of recording, all the babies were spontaneously breathing room air and treated by caffeine. Their median post conceptional age (gestational + postnatal ages) was 29.6 weeks (27.1 to

31.6) and median weight was 895g (685 to 1280g). Three babies were provided continuous positive airway pressure by a nasal prong. Three babies were at the onset of a systemic infection (increase in C-reactive protein and bacterial evidence on blood cultures). The two others had no sign of infection. The polygraphic monitoring consisted of two ECG leads, two EEG leads, one pulse oxymetry saturation and respiration recordings.

Data selection and measurements. In this study, the dataset was composed of linear and non-linear parameters of Heart Rate Variability (HRV). Particularly, we computed spectral parameters of RRI variability such as Low Frequency power (LF band: 0-0.2 Hz), High Frequency power (HF band: 0.2-2 Hz) and the LF/HF ratio [4]. In addition non-linear indexes were computed: they include Approximated Entropy (ApEn) and Spectral Entropy (SE) measurements [5][6].

Data were computed and averaged in sliding temporal window (20 seconds lengths, overlap 15 seconds) starting from 3 minutes before the bradycardia up to the onset of the event.

Episodes of bradycardia were selected by an expert physician according to the following criteria: only isolated (normal rhythm in the 5 minutes preceding the bradycardia) and severe (RR > 750 ms) bradycardia episodes were included in this study. Globally, we analysed 13 events.

Principal Components Analysis (PCA). Statistical Factorial methods may give a synthetic representation of a large set of observations and PCA is a useful tool to reduce the dimensions of this original dataset. The m-multidimensional data cloud is represented using a smaller set of orthogonal axes, called principal factors, trying to catch the largest part of the information hidden in the original data. Usually, the original m-multidimensional dataset is reduced to less than 3 dimensions.

As our data were not homogeneous, they were normalized by subtracting the population mean and dividing by its standard deviation, let:

$$x_{ij} = \frac{r_{ij} - \bar{r}_j}{s_j \sqrt{n}} \qquad (1)$$

After applying the PCA analysis, we found that the first and the second factors were sufficient to provide a meaningful description of the data (third factor or higher had inertia < 1).

The choice of a pair of principal factors makes possible a planar and intuitive representation of the data in both the individuals and variables plane.

Hierarchical Ascending Classification (HAC) HAC is an useful tool able to evidence the presence of classes of individuals in a given dataset. In our case, classification was performed on the dataset obtained by PCA (i.e. variables projected into the principal factorial plane).

HAC creates, at each step, a partition obtained by the aggregation of the two nearest elements. Elements can be both individuals and groups of individuals (classes). The hierarchy of partitions can be easily represented in a partition-tree called dendrogram [7].The main problem in the construction of the dendrogram is the huge number of operations involved. In order to reduce computation time, we used the reciprocal neighbours algorithm introduced by McQuitty [8]. Several aggregation criteria have been proposed [7]: we used the generalised Ward's criterion [9]. This criterion is founded on the idea that the global quality of a partition is bound to the homogeneity inside the classes. Inertia can be subdivided in two components, according to Huygen's formula: inertia intra-classes and inertia inter-classes. To obtain a good classification, the Ward's criterion minimizes the intra-classes inertia (or, dually, maximises the inter-classes inertia). The inertia jumps through the classification can be considered as new indexes of dissimilarity called level index. Obviously the summation of all the level indexes equals the global Inertia (I) of the dataset:

$$I = \sum_{i}^{n} m_i \|\mathbf{x_i} - \mathbf{g}\|^2 = \sum_{q} m_q \|\mathbf{g_q} - \mathbf{g}\|^2 + \sum_{q}\sum_{i \in q} m_i \|\mathbf{x_i} - \mathbf{g_q}\|^2$$

where $m = \sum_{i}^{n} m_i$ is the total dataset's mass, $m_q = \sum_{i \in q} m_i$ is the q-th class' mass, $\mathbf{g} = \frac{1}{m}\sum_{i}^{n} m_i \mathbf{x_i}$ is the baricenter of the total dataset's mass and $\mathbf{g_q} = \frac{1}{m_q}\sum_{i \in q} m_i \mathbf{x_i}$ is the baricenter of the q-th class' mass.

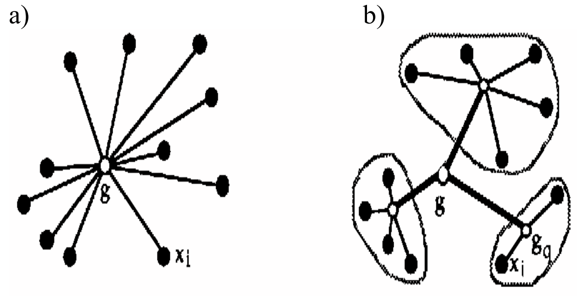

Figure 1. a) graphical representation of the total inertia concept; b) inertia intra-classes (referred to $\mathbf{g}_q$) and inter-classes (referred to $\mathbf{g}$).

The choice of the best level index in correspondence to which we can cut the dendrogram to obtain a good classification is not trivial. At lower levels all points tend to fall in separate classes, at higher levels all points tend to be grouped together. In our case, the cut of the dendrogram was made at the largest level index variation.

Next, the obtained classification was refined by Mobile Center Classification (MCC) method which is able to further increase the homogeneity of each class.

Finally, an automatic, quantitative description of the classes was derived in order to select the most distinctive variables of each class. We used the test-value criterion [7].

3. Results

An example of RRI series and the extracted parameters is shown in Figure 2.

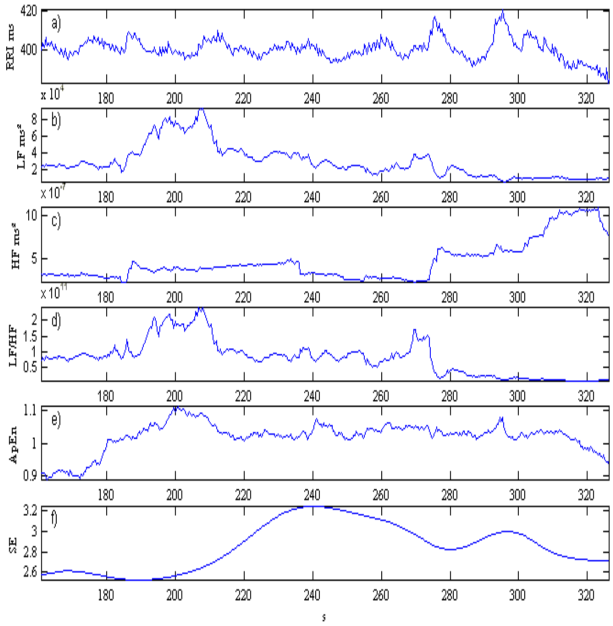

Figure 2. a) RR Interval series preceding the onset of bradycardia. Bradycardia starts on the last sample of the trend. b) to d) Spectral parameters of RRI variability (see text for details); e)-f) Entropy indexes. Note the progressive reduction of LF power and Entropy preceding toward the onset of the bradycardia (30-40 seconds before the event).

It is worth noting the decrease of the LF/HF ratio before the onset of the bradycardia, as well as the simultaneous decrease of LF components. Usually LF's trend is opposite to the HF's trend. This tendency demonstrates a reduction of sympathetic modulation and a synchronous increased vagal tone to the newborn's heart.

During the same period, ApEn and SE are found to progressively decrease proceeding toward the beginning of bradycardia. Such a reduction is in agreement with the hypothesis that the system before the bradycardia is becoming more regular and predictable, thus showing a reduced adaptability of the control mechanisms.

These trends were observed in several episodes and in different newborns even in presence of systemic infection.

Results of PCA and HAC classification are shown in Figure 3 and Figure 4. Figure 3 shows the projection of our data in the principal factorial plane. It can be observed that, proceeding towards the onset of bradycardia, points in the plane are moving aside toward a particular basin (in this case the basin is located in the right lower corner). This suggests possible peculiar properties of the last points in respect of the previous ones.

In agreement, the classification groups the last eight points preceding the bradycardia (corresponding to roughly 55s) together in a separate, homogeneous class. This grouping is evident in both the dendrogram (Figure 4) and in the individuals plane (Figure 3).

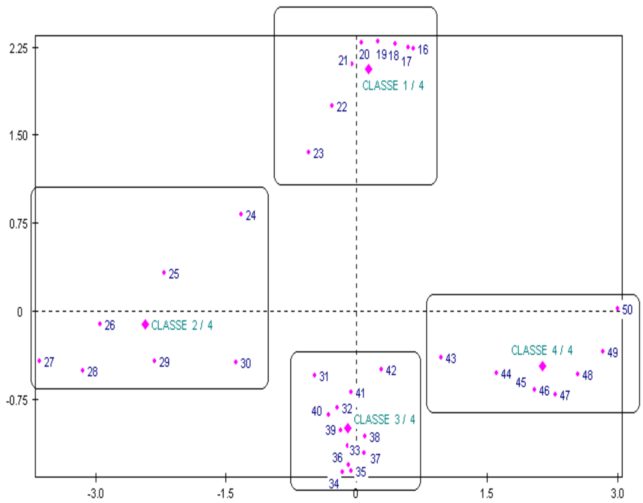

Figure 3. Trajectory of the projected dataset in the principal factorial plane. The number of each point increases toward the onset of bradycardia. Square boxes representing the clustering of points as obtained by HAC (see text for detail). It is worth noting that the points closer to bradycardia are grouped in a single class (class #4).

Similar patterns were observed in 10 of the 13 episodes considered. The last points were grouped in a single class including a varying number of points (ranging from 2 to 11 points) corresponding to temporal windows of 25 to 70 seconds.

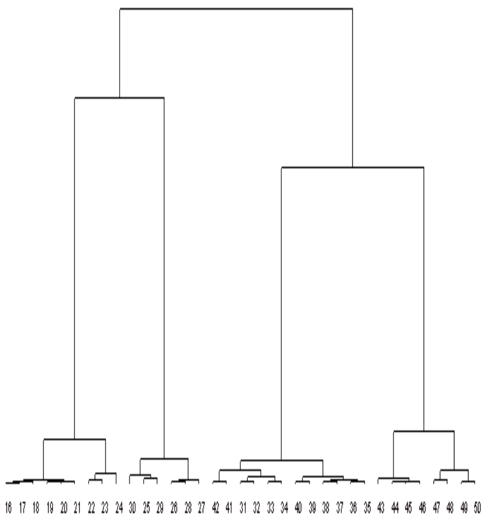

Figure 4. The dendrogram obtained for the same patient whose parameters are shown in Figure 3.

Despite the fact that similar patterns were observed in several newborns, it was not possible to identify a unique description of the classes (i.e. the most characterizing variables of each class were different among babies and episodes). The same observation stands for the principal axes. In fact, even if we observed that in many cases principal axes were obtained as a combination of ApEn and HF parameters, the influence of these parameters was not constant among the studied bradycardia.

These results demonstrate that none of the studied parameters is able to predict by itself the onset of bradycardia. Nevertheless, it appears that each one carries a bit of information which can contribute to the prediction of the events.

4. Discussion

In this manuscript we studied linear and non-linear parameters of RRI in the epoch preceding the onset of isolated bradycardia in newborns. The aim was to detect premature signs of bradycardia and to develop methods to alert physicians before the onset of the event. PCA was used to extract, among the studied parameters, those metrics carrying the relevant information about the incoming bradycardia. It was found that the projection of observations on the first factorial plan showed well defined paths: clustering of observations appeared approaching the bradycardia in 10 over 13 analyzed cases. These preliminary results, obtained on a limited number of episodes, evidenced that RRI variability contains early information about the bradycardia events. An interesting observation was that the prediction of the bradycardia was more reliable when all the studied parameters were included into the PCA. Therefore, we concluded that both linear and non-linear indexes of RRI variability carry a bit of information about incoming the bradycardia.

Further studies will include an homogeneous baby database in terms of clinical status (for example only newborns with sepsis without caffeine), the analysis of a larger database of episodes, the extraction of information from other biological signals (for examples the respiratory signal to assess bradycardia associated to apnea) and the developing of an automatic predictor of bradycardia.

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