HEART RATE VARIABILITY ANALYSIS OF CHILDREN WITH REFRACTORY EPILEPSY BEFORE AND AFTER THE VAGUS NERVE STIMULATION

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Abstract: Vagus nerve stimulation (VNS) is a well-known therapeutic option for patients with refractory epilepsy who do not respond to adequate anti-epileptic drugs. Heart rate variability (HRV) is mediated by sympathetic and parasympathetic efferent activities which always interact towards the heart. Our goal was to describe the link between autonomic nervous system (ANS) and HRV. In 18 epileptic children, ECG data were obtained before and after implantation of the VNS. HRV was measured by linear and nonlinear parameters during 50 minute epochs during phase 2 of sleep and deep sleep. Results of the patients were compared with those of an age and sex matched control group. We were able to confirm that vagus nerve stimulation do not influence heart rate in children with refractory epilepsy. After the VNS implantation, there is a shift in sympathovagal balance towards sympathetic predominance in phase 2 of sleep ($p=0.177$) and also during deep sleep ($p=0.035$). This study suggests that left vagus nerve stimulation has little effect on heart rate variability as measured by nonlinear parameters.

1 INTRODUCTION

The subjects with refractory epilepsy do not respond to adequate anti-epileptic drugs (30-40%) and they are prone to autonomic dysfunction. Stimulation of the vagus nerve is a valuable option for these subjects. Their heart rate (HR) and autonomic nervous system (ANS) have been changed due to the vagus nerve stimulation (VNS). Since the ANS affects heart rate by continued interaction between his two branches, sympathetic and parasympathetic, heart rate variability (HRV) can be used as a noninvasive tool to show information about the functional state of the ANS (TASK FORCE, 1996).

Autonomic modulation of heart rate is often studied by linear parameters, but nonlinear parameters have opened a new approach for studying and understanding the characteristics of cardiovascular dynamics. They give additional information about the nonlinear dynamics in the cardiovascular system, like the quality, scaling and correlation properties, which cannot be reflected by standard HRV analysis.

Changes in HR and HRV after the VNS implementation have been studied using linear parameters for short-term epochs (5 minutes) by Setty et al. (1998). Nonlinear HRV analysis on long-term epochs (50 minutes) of the ECG signals of children with refractory epilepsy were never done to our knowledge. Also HRV analysis was never done in this field for two stages of sleep separately.

The aim of this study is to investigate HRV parameters of 50 minutes ECG recordings before and after implantation of the VNS in epileptic children and to compare these results with the results of the control group for both sleep stages. Emphasis will be on how the VNS influences the autonomic nervous system.

2 METHODS

2.1 Subjects

Originally, 18 subjects (age 2-16 years, 13 males) with refractory epilepsy participated in this study. However, only data of 17 subjects could finally be used. Each subject was measured at two different time moments, before and long enough after the implantation of the VNS, being sure of stabilized conditions.

2.2 Data Collection and Preprocessing

ECG recordings were obtained using two leads with a sample rate of 250 Hz on a PC based platform. Two epochs of 50 minutes (one for phase 2 of sleep and one for deep sleep) were selected manually. The data length had to be equal in both epochs as well as for all subjects (epileptic and control) in order to extract consistent and reliable HRV parameters (TASK FORCE, 1996). For each recording, a file containing the consecutive RR intervals, derived from the ECG signal, was exported and checked manually before preprocessing. Extra ventricular beats were replaced by a 20%-filter, meaning that every RR interval that differs more than 20% of the previous one is replaced by an average value of the 5 previous and 5 next RR intervals.

2.3 Linear HRV Parameters

All standard HRV parameters are calculated in agreement with the standards of measurement proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (TASK FORCE, 1996). As time domain measures, we calculated mean RR interval, SDNN, SDANN, RMSSD and pNN50. After resampling the tachogram at 4 Hz with the use of a cubic spline approximation, power spectra were obtained by using the Welch method. The direct current component was removed by subtracting the mean value of the data set. A sliding Hamming window of 1024 points with 50% overlap was used. Three frequency bands were defined: a very low frequency (VLF) band from 0 to 0.04 Hz, a low frequency (LF) band from 0.04 to 0.15 Hz and a high frequency (HF) band from 0.15 to 0.40 Hz. Within each frequency band the spectral power was expressed in absolute values (in ms^2) as well as in normalized units (n.u.) which represent the relative value of each power component in proportion to the total power minus the VLF component. Additionally, a low-to-high frequency power ratio (LF/HF) is calculated to reflect the sympathovagal balance.

2.4 Nonlinear HRV Parameters

Nonlinear HRV techniques have not been standardized as the linear ones. They give additional information about the nonlinear dynamics in the cardiovascular system which cannot be reflected by standard HRV analysis. The most commonly used nonlinear parameters are computed in this study.

The *1/f* slope of the log(power) – log(frequency) plot was obtained from the linear regression from 10^{-4} to 10^{-2} Hz (Kobayashi and Musha, 1982). A slope of -1 is an indication of scaling behaviour.

Fractal dimension is based on the algorithm of Katz (1988), which describes the planar extent of the time series. The higher the FD, the more irregular signal.

Detrended fluctuation analysis quantifies fractal like correlation properties of the time series and uncovers short-range and long-range correlations. The root mean square fluctuation of the integrated and detrended data are measured within observation windows of various sizes and then plotted against window size on a log-log scale (Peng et al., 1996). The scaling exponent DFA α indicates the slope of this line, which relates log(fluctuation) to log(window size). Both the short-term (4–11 beats) DFA α_1 and the long-term (>11 beats) DFA α_2 scaling exponents were calculated. Values of α around 1 are an indication of scaling behaviour.

Sample entropy measures the likelihood that runs of patterns that are close will remain close for subsequent incremental comparisons. SampEn was calculated according to the formula of Richman and Moorman (2000) with fixed input variables $m = 2$ and $r = 0.2$ (m being the length of compared runs and r the tolerance level). Higher values of SampEn indicate a more complex structure in the time series.

Noise titration is currently the only algorithm available that provides a sufficient test for chaotic dynamics in noise-contaminated signals (Deng et al., 2006). It measures chaos by controlled neutralization with added noise. The output noise limit (NL) > 0 indicates the presence of chaos, and the value of NL also gives an estimate of its relative intensity. We calculated two parameters to investigate nonlinear properties: NLmean (average of NL values measured in 5 minute windows slid each 30 s) and NLdr (corresponding detection rate).

2.5 Statistical Analysis

To compare HRV parameters pairwise between the different stages of sleep, the nonparametric Wilcoxon signed rank test was used, as well as to investigate the before-after VNS differences. For the comparisons between epileptic and control groups, Wilcoxon rank sum test was used.

Using those tests, p values were obtained to examine the similarity between adequate groups for each HRV parameter. In general, $p<0.05$ was considered statistically significant.

3 RESULTS

On all 50 minute segments, during phase 2 of sleep as well as during deep sleep, all HRV parameters described in the previous sections were calculated.

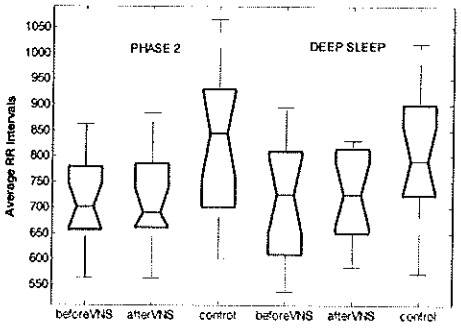

Figure 1: Boxplots for average RR intervals for phase 2 (first 3 boxes: epileptic subjects before and after the implantation of the VNS, and their controls) and deep sleep (last 3 boxes), respectively.

Detailed information about the mean RR intervals is shown in Figure 1. Heart rate is significantly lower for the control group in both stages of sleep, phase 2 and deep sleep, compared to the epileptic group, before ($p=0.009$ and $p=0.008$, respectively) and after ($p=0.042$ and $p=0.036$, respectively) implantation of the VNS. On the other hand, VNS therapy doesn't affect heart rate ($p=0.554$ for phase 2 and $p=0.795$ for deep sleep).

Since standard deviations for HRV parameters in the frequency domain are quite high, it is better to observe values in normalized units. For phase 2 of sleep, there is an increase of LFn.u. ($p=0.209$) and a slight decrease of HFn.u. ($p=0.309$) due to the VNS stimulation. There are no remarkable differences between epileptic (both before and after the VNS) and control groups, during phase 2. In contrast, during deep sleep phase, these changes are statistically significant. Again, HFn.u. ($p=0.019$) decreased, and LFn.u. ($p=0.019$) increased after the implantation of the VNS in epileptic subjects. Compared to the control group, even before the implantation of the VNS, epileptic subjects had significantly different LFn.u. ($p=0.023$) and HF.n.u. ($p=0.028$) parameters. After the start of the VNS, the epileptic group is rambled further more from their controls than before the VNS ($p=0.003$ for LFn.u. and $p=0.003$ for HFn.u.).

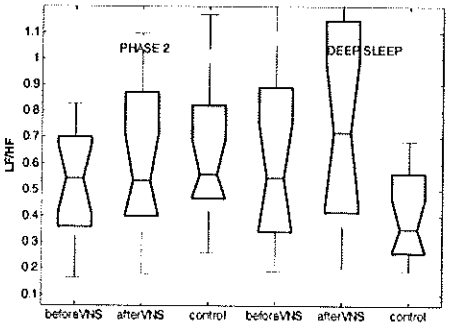

Figure 2: Boxplots for LF/HF ratio for phase 2 sleep and deep sleep, respectively.

There is an increase of LF/HF ratio in both stages of sleep after the VNS stimulation ($p=0.163$ and $p=0.049$, for phase 2 and deep sleep, respectively). This increase is higher during deep sleep. For phase 2, LF/HF ratio is closer to LF/HF ratio for the control group after VNS ($p=0.654$), while for the deep sleep it is higher in both conditions, before and after VNS ($p_{preVNS}=0.025$ and $p_{postVNS}=0.003$). Figure 2 gives boxplots for all groups for parameter LF/HF.

Coefficients α_1 and α_2 increase due to the implantation of the VNS, especially during deep sleep, when this increase is statistically significant. While DFA coefficients of the epileptic group are getting closer to their controls after the implantation of the VNS during phase 2 of sleep ($p=0.705$ and $p=0.945$, respectively), in deep sleep their values are statistically different ($p=0.012$ and $p=0.073$, respectively).

Noise titration is reported by the parameters NLmean and NLdr. During phase 2 of sleep, NLmean isn't statistically different when comparing pre-VNS versus post-VNS and compared to normal subjects. In epileptic subjects before the implantation of the VNS, NLdr is statistically higher compared to the control group ($p=0.046$). The same parameters, during deep sleep, don't demonstrate significant differences when comparing pre-VNS

versus post-VNS and epileptic versus control groups.

We found no significant changes in other parameters due to the VNS, and when compared to the control group.

4 DISCUSSION

As no remarkable difference was found between pre-VNS and post-VNS implantation in epileptic subjects, even when compared to the control group for the parameters SDNN, SDANN, RMSSD, *1/f* slope, FD and SampEn, no discussion is made.

The major previous studies regarding the effects of the VNS on HRV were performed during wakefulness. Setty et al. (1998) didn't find any significant effect of the VNS on the heart rate and heart rate variability. This study confirmed that VNS does not influence the heart rate in epileptic children (mean RR interval in the Figure 1), which is significantly higher compared to their controls. We found a reduction of vagal tone after long-term VNS during night-time, when autonomic control on heart rate should be mainly sustained by vagal influence (Pagani et al., 1997). This is however, in contrast to the study of Kamath et al. (1992), which reported significant increase in HF component of the power spectrum.

LF/HF ratio after the implantation of the VNS stimulation still remains below 1 for most of the children with refractory epilepsy, meaning that vagal modulation of the heart rate is still dominant. On the group level, there are changes in cardiac sympathovagal balance towards sympathetic predominance in phase 2 of sleep ($p=0.177$) and also during deep sleep ($p=0.035$) after the VNS implantation. These findings require further observations.

In addition, LF/HF and DFA coefficients have similar pattern of behaviour due to the implantation of the VNS and compared to the control group. In other nonlinear parameters, we found no significant changes due to the implantation of the VNS.

In conclusion, our data indicate that: (a) VNS do not influence heart rate during phase 2 of sleep and deep sleep; and (b) VNS affects cardiac sympathovagal balance.

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