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Heart period variability during vagal nerve stimulation

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Vagal nerve stimulation is an emerging therapy for epilepsy, yet little is known regarding the effects of this stimulation on heart period variability. We selected 10 patients (two female, eight male) who were receiving high-frequency, high-intensity left vagal nerve stimulation for intractable epilepsy. Electrocardiogram data were recorded for a 7 min baseline, 2.5 min of stimulation and a 7 min post-stimulation period. We found no significant changes in average heart period, instantaneous changes of successive R-to-R intervals greater than 50 ms or fractal dimension. We also found no significant changes in the total power in the 0.0–0.04 Hz, 0.04–0.12 Hz and 0.2–0.4 Hz bands with stimulation of the left vagus nerve. This study suggests that left vagal nerve stimulation has little acute effect on the cardiac rhythm or heart period variability.

Key words: autonomic nervous system; vagal nerve stimulation; heart rate; heart period variability; parasympathetic activity; epilepsy.

INTRODUCTION

Direct vagal nerve stimulation (VNS) has emerged as a treatment for intractable epilepsy. Studies have shown a reduction in seizure frequency with high-frequency (HF) (typically 30 Hz) stimulation of the left vagus nerve at maximum tolerable intensity (high intensity)[1]. The left vagus nerve was chosen because it has minimal direct cardiac efferent activity[2].

Traditional methods of evaluating cardiac functions during VNS have been inconclusive. The vagus nerve contains 10% efferent fibres which innervate the stomach, intestines, lungs and heart[3]. The input from the left vagus nerve has a minimal effect on the atrioventricular node and no influence over the sinoatrial node[4]. Kolman[5], studying dogs, reported that VNS produced a change in the repolarization of the canine ventricle. Holder *et al*[1] and Uthman *et al*[2] found that left vagal stimulation in humans produced no significant changes in heart rate. Ramsay[6] found no effect on cardiac function after ambulatory Holter monitoring. Kamath *et al*[4] studied heart rate variability in patients implanted with vagal nerve stimulators at two stimulation frequencies and found that in four patients the high-frequency, high-intensity setting resulted in a significant increase in the 0.2–0.5 Hz frequency band of the power spectrum[4].

The autonomic nervous system and neurohumoral influences modulate heart rate[7]. Heart period variability (HPV) is a sensitive, noninvasive method of quantifying dynamic autonomic influences over the heart period. Many studies have documented the variation of heart rate on a beat-to-beat basis in patients with obstructive sleep apnoea, Alzheimer's disease, Parkinson's disease, epilepsy and sleep states[8–12]. Beat-to-beat variations quantified by the contributions of each frequency band gives clues to these influences[7,13–16]. The low-frequency band (0.00–0.04 Hz) is related to neurohumoral and thermal regulatory influences and is increased with angiotensin converting enzyme inhibitors[13,16]. The mid-frequency band (0.04–0.12 Hz) is related to a mixture of sympathetic and parasympathetic influences and can be partially blocked by propranolol. The HF band (0.2–0.4 Hz) is principally related to respiration utilizing vagal mediated pathways and can be blocked by atropine[13,16–18].

Since increased power in the HF band of the power spectra is related to parasympathetic input, we felt that analysis of the HPV would be a valuable tool for studying the effect of left VNS on the cardiac cycle.

MATERIALS AND METHODS

Ten patients (two female, eight male) with intractable epilepsy who have been instrumented with left vagoafferent electrical stimulators (Cyberonics Model

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100 (Cybertronics, Inc., Webster, Texas, USA)) were selected for study. All of these patients were part of the open-label continuation study (Cyberonics XE5 protocol) with vagal stimulator settings of 30 Hz, pulse width of 750 μs, on-time of 30 s, and off-time of 5 min. Current was set at the maximum tolerable level (a high-intensity setting) for a minimum of 1 month prior to our study.

For this study additional data were collected which were separate from the Cyberonics XE5 protocol described above. During data collection for heart period analysis, patients were awake, in the supine position, and asked not to speak. A 7 min baseline segment was recorded with the vagal nerve stimulator inactivated. The stimulator was then activated for five sequential 30 s stimulation periods for a total continuous stimulation period of 2.5 min. Stimulation was verified by the subject noting the presence of the sensation of stimulation. Following the stimulation period, the vagal nerve stimulator was inactivated for a 7 min post-stimulation period.

The EKG was amplified, displayed and digitized at 500 Hz. The peak of each QRS complex was identified and the sequential R-to-R intervals were calculated. The digitized EKG was reviewed off-line to ensure that no beats were improperly marked, no beats were missed, and no artifacts were detected as R waves. The time domain data were presented on the computer graphics screen for visual verification prior to analysis[12, 20, 21].

The data were divided into baseline, stimulation and post-stimulation data sets for each patient. For each data set, the mean and standard deviation of the heart period, fractal dimension and the average number of beat-to-beat variations which exceeded 50 ms (BB50) per 128 R-to-R intervals were calculated. The heart period was defined as the time between two consecutive QRS waves. The BB50 was defined as the number of R-to-R intervals that have a greater than 50 ms change from the previous interval for each 128 beat epoch. The 128 interval epochs were chosen for this calculation to equate the unequal time periods of prestimulation, stimulation and post-stimulation. The fractal dimension provides a concise way to express the complexity of the variation in the heart period. The fractal dimension was calculated as a ratio of the sum of the distance between all data points in the period or epoch divided by the distance between the first and the most distant data point. The time domain data were essential for proper interpretation of the frequency domain analysis and was required to avoid including nonstationary data in the frequency analysis. For each data set, the R-to-R intervals were divided into sequential 128 R-to-R interval epochs. Each data set from each patient was averaged together to derive the average power in each of three frequency bands for the baseline, stimulation and post-stimulation periods. The three frequency bands were 0.0–0.04, 0.04–0.12 and 0.2–0.4 Hz. Since the spectral power of a set of data is proportional to the variance of the data in the time domain, the average power in these frequency bands was used for statistical purposes to determine the significance of changes in HPV. The units of power for HPV are $s^2/s^2/Hz$. The same calculations were performed on all frequency bands. The F test for equal variances was used as a measure of the significance between the three data sets in each individual. Changes at the 0.05 level, using two tails, were considered to be significant for each time period[12]. Repeated measures univariate analysis of variance with the dependent variables of HPV, BB50, FD and the three frequency bands of 0.0–0.04, 0.04–0.12 and 0.2–0.4 were calculated across the three measurement points of baseline, stimulation and post-stimulation. An alpha level of 0.01 was chosen to reduce error as multiple comparisons were completed.

The relationship between clinical effectiveness (defined as a reduction in seizure frequency of 50%) and HPV changes were analysed using Student's *t*-test. Additionally, HPV changes from patients with maximum tolerable current settings of 2.0 mA or greater were compared with those with output currents of less than 2.0 mA using Student's *t*-test.

RESULTS

Ten subjects, aged 14–46 (average 28 years; eight male, two female) were diagnosed with intractable complex partial epilepsy defined as failure to respond to three or more conventional anticonvulsants. All patients averaged six or more seizures per month and were receiving anticonvulsant therapy. None of the patients had undergone cerebral surgery. One patient had a history of head trauma as the presumed aetiology for epilepsy. The remaining nine did not have definable aetiologies for their seizures.

Time domain

The average heart period of the 10 subjects did not change significantly during stimulation or post-stimulation periods when compared with the prestimulation period (Table 1). The results of the BB50 and fractal dimension analysis did not reveal any significant changes either. Finally, visual analysis of the time domain was without apparent changes (Fig. 1). Repeated measures analysis of variance for the average heart period, BB50 and fractal dimension were all nonsignificant.

Table 1: Time domain results

	Baseline	SD	Stimulation	SD	Post stimulation	SD
Heart period (s)	0.728	0.097	0.7133	0.086	0.726	0.093
BB50 (instantaneous beat-to-beat changes greater than 50 ms/128 intervals)	6.15	6.77	4.45	4.43	4.47	6.71
Fractal dimension	1.67	0.331	1.66	0.253	1.66	0.269

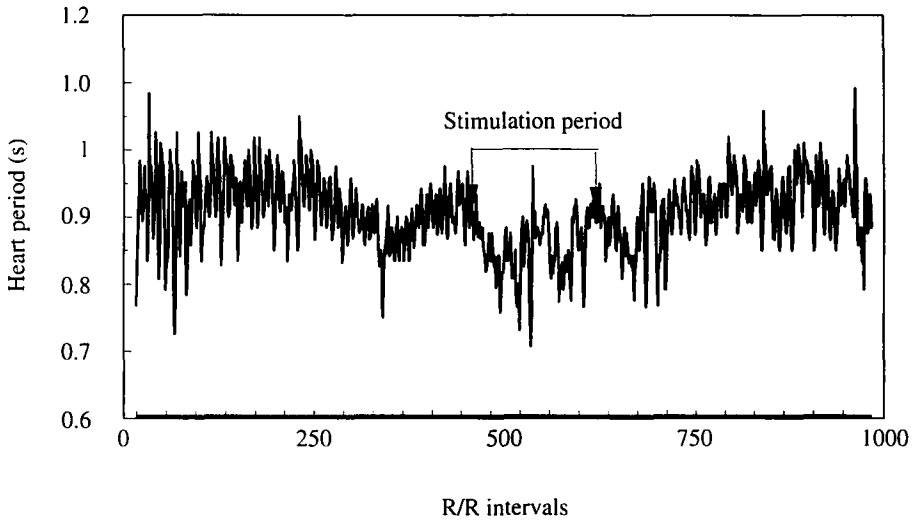

Fig. 1: Time domain depicting heart period vs. successive R-to-R intervals before, during and after VNS in one patient. The figure shows a decrease in the HF variation of heart period during stimulation. This observed change was not statistically significant among the 10 patients in this study.

Frequency domain

The power in each of the frequency bands showed no significant changes during or after direct left VNS when compared with the baseline (Table 2). Repeated measures analysis of variance found no significant differences across time from the baseline, stimulation and post-stimulation periods. The average power in the 0.0–0.4 Hz band appeared to increase in the post-stimulation period. This increase was not statistically significant and the majority of the increase was related to one patient (subject number 1 in Fig. 2).

A trend towards decreased total power in the HF band during stimulation occurred in four out of 10 patients. The decrease in total power in these four patients could not be accounted for by a shift in peak frequency or a move of power to another frequency band. Results were mixed for the remaining six patients. The overall decrease in power in the HF band was not significant (baseline to stimulation $p = 0.61$, baseline to post-stimulation $p = 0.30$). In only one patient (patient number 3 in Fig. 2), power in the HF band was increased during and after stimulation.

In addition, there was no relationship between clinical effectiveness after VNS (defined as a greater than 50% reduction in seizure frequency) and HPV changes. Considering the threshold activation currents suggested by Woodbury[25], we decided to look at the relationship between current intensity at maximum tolerable stimulation and HPV changes. We compared the HPV changes of patients whose maximum tolerable current settings were 2.0 mA or greater with those whose settings were below 2.0 mA. We found no relationship between stimulation settings and changes in power in the various frequency bands.

DISCUSSION

HPV is an excellent tool for assessing the neurohumoral and autonomic influences over the cardiac cycle. Previous studies have used indirect methods to assess the vagal effects upon HPV. Atropine has been shown to attenuate the HF component of HPV[13,16,18,19]. Studies on dogs have shown that vagotomy also decreases the HF component[15]. Our research differs from those studies in that we are directly stimulating only the left vagus nerve which innervates the atrioventricular node and has significantly less effect on heart rate than bilateral stimulation[4].

Table 2: Frequency domain results

	Baseline	SD	Stimulation	SD	Post stimulation	SD
0.0–0.04 Hz band (s^2/s^2/Hz)	1.77	1.82	2.69	2.21	3.68	5.65
0.04–0.12 Hz band (s^2/s^2/Hz)	1.23	1.25	1.93	2.01	1.95	2.02
0.2–0.4 Hz band (s^2/s^2/Hz)	0.805	0.089	0.621	0.541	0.779	1.23

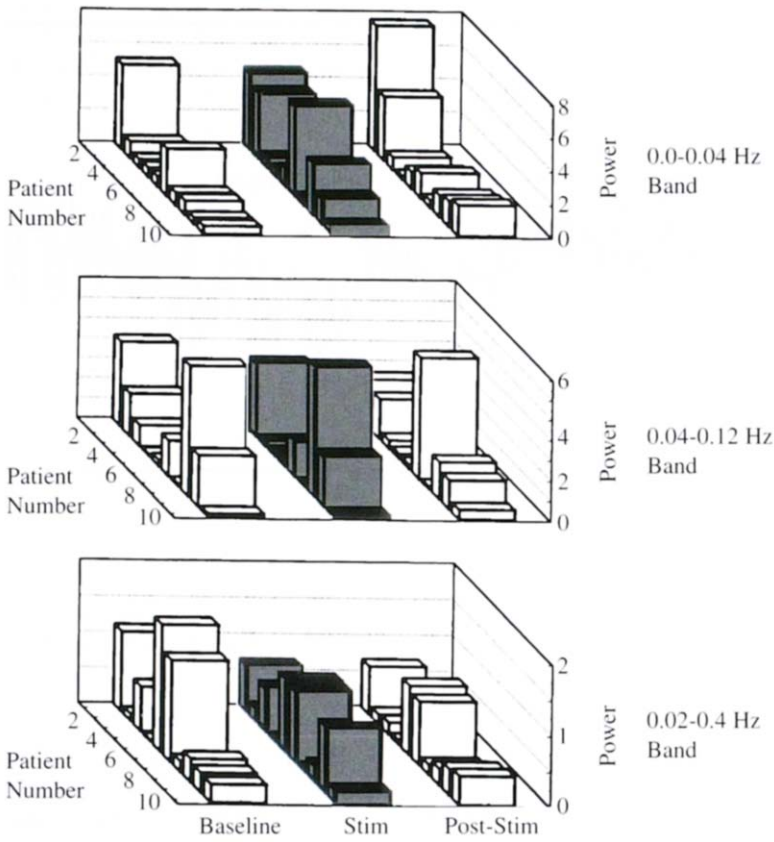

Fig. 2: Total power in each frequency band for each of the 10 patients separated into baseline, stimulation and post-stimulation data sets on the *x*-axis. The *y*-axis is power (s^2/s^2/Hz), the *z*-axis is the patient number. The power values for patient number one post stimulation in the low-frequency band (0.0–0.04 Hz) is actually 18.3 s^2/s^2/Hz but is reduced to demonstrate the relationships between the other power values.

This study shows that direct stimulation of the left vagus nerve has no significant effect on the HPV. We found no significant change in the HF band after HF left VNS. This finding is consistent with current knowledge of anatomic pathways for the left vagus nerve as well as the clinical findings of other researchers[2,5]. This is, however, in contrast to the findings of increased power in the HF band by Kamath *et al*[4]. All of our patients were stimulated for at least 1 month at the tested settings, and therefore some accommodation to the stimulation not observed in the Kamath study may have occurred. Additionally, the difference may be related to differences in stimulation settings (pulse width 750 μs in our study versus 500 μs in the Kamath study) which may selectively activate different efferent fibre types. Due to mixed reports in the literature, the precise cardiodepressor vagal fibre type is not clearly known. The evidence indicates that a mixture of B and C fibre types innervate the heart[22–24]. Results from Woodbury and Woodbury[25] suggest the settings used in this study may activate a larger number of vagal C fibre types than stimulated in the Kamath study.

Kamath found an increase in HF power after VNS without a change in heart rate and speculated the existence of a feedback loop through vagoafferent pathways which would stimulate the heart without causing bradycardia[4]. Although four of our subjects had an increase in power in the HF band with stimulation, we found no statistically significant change in heart rate or the power of any frequency bands during stimulation for the group of 10 subjects. While the feedback

loop may exist, our results suggest that there are no significant changes in HPV to demonstrate that this loop influences the cardiac cycle through other frequency bands.

Anticonvulsants may alter autonomic responses. All patients in the study remained on their anticonvulsant therapy. Two patients were treated with carbamazepine, which is known to have an anticholinergic effect, and may have masked any cholinergic changes due to VNS. These two patients had mixed changes of HPV. The other eight patients in the study were not using any medication with a known significant anticholinergic effect. Finally, we did not find any relationship between clinical effectiveness and stimulation intensity in terms of VNS and HPV changes. Future studies with more patients will be needed to address these issues.

CONCLUSIONS

Given the potential for VNS as a therapy for intractable epilepsy this study suggests that left VNS has little acute effect on the cardiac rhythm or HPV.

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