Autonomic effects of refractory epilepsy on heart rate variability in children: influence of intermittent vagus nerve stimulation

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ABBREVIATIONS

HFnu	High-frequency normalized units
HRV	Heart rate variability
LFnu	Low-frequency normalized units
SWS	Slow-wave sleep
VNS	Vagus nerve stimulation

AIM Vagus nerve stimulation (VNS) is a therapeutic option for individuals with refractory epilepsy. Individuals with refractory epilepsy are prone to dysfunction of the autonomic nervous system. Reduced heart rate variability is a marker of dysfunction of the autonomic nervous system. Our goal was to study heart rate variability in children with refractory epilepsy and the influence of VNS on this parameter.

METHODS In 17 children (13 male; four female; mean age 7y 6mo; age range 3–16y) with refractory epilepsy, electroencephalographic and electrocardiographic data were obtained before and after implantation of VNS during stage 2 and slow-wave sleep. Time and frequency domain parameters were calculated and the results were compared with an age- and sex-matched group of individuals without refractory epilepsy.

RESULTS Our results show that autonomic cardiac control is affected in individuals with refractory epilepsy. There is a striking reduction in vagal tone during slow-wave sleep and modulation capacity is smaller than in individuals without refractory epilepsy. Implantation of VNS induces a shift in sympathovagal balance towards sympathetic predominance and an improvement in autonomic modulation.

INTERPRETATION Heart rate variability is affected in children with refractory epilepsy, and changes after implantation of VNS. The observed changes could be of importance in the cardiac complications of individuals with epilepsy and should be explored in more detail.

In individuals with refractory epilepsy, vagus nerve stimulation (VNS) is an alternative therapeutic option. The working mechanism is still incompletely understood. In VNS therapy, the left vagal nerve is stimulated at the level of the neck by an electrode connected to a subcutaneous device. The left nerve is chosen to minimize the effect on heart rhythm because most of the cardiovagal fibers course through the right vagus nerve.

The vagus nerve consists of 20% of efferent and 80% of afferent fibers. The efferent fibers originate from two separate nuclei in the brainstem, the dorsal motor nucleus and the nucleus ambiguus. They supply parasympathetic fibers to all the internal organs except the suprarenal glands. The afferent fibers originate in the end organs and project to the nucleus tractus solitarius. From the nucleus tractus solitarius, axons project throughout the brain. These afferent axons and synapses are thought to be responsible for the therapeutic effect of VNS.

Heart rate variability (HRV) is defined as the fluctuation in length in consecutive RR intervals. This variability is mediated by sympathetic and parasympathetic efferent activity to the heart and can provide information on the functional state of the autonomic nervous system. The vagal influences on the heart are most pronounced during sleep. In early sleep stages there is still a relatively large influence of the sympathetic branch on HRV. In typically developing individuals there is a relative vagal predominance during sleep compared with when awake, and this vagal component of heart rate modulation reaches a maximum in synchronized or slow-wave sleep (SWS).[1] Reduced HRV is a marker of dysfunction of the autonomic nervous system and can be considered a risk factor in chronic disease, for example after myocardial infarction.[2] Various diseases including epilepsy are now known to be accompanied by a loss of autonomic functionality and reduced HRV.[3] Only recently diminished HRV has been associated with high-risk arrhythmias and sudden unexpected death in individuals with epilepsy.[4]

In this study, the first goal was to evaluate the autonomic nervous system in children with refractory epilepsy. HRV was used as a parameter of cardiac autonomic outflow. The sympathovagal balance is reflected by the fractional distribution of power across the frequency axis. This balance can be assessed by the relation between low- and high-frequency components in normalized units or by the low-frequency/high-frequency

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ratio. The ability to change between sympathetic and vagal influences is referred to as modulation capacity.

The second goal was to monitor the influence of vagus nerve stimulation on the autonomic nervous system in individuals with refractory epilepsy.

METHODS

Seventeen eligible individuals (13 male; four female; mean age 7y 6mo; age range 3–16y) were selected from the epilepsy clinic of UZ Leuven and the Epilepsy Center Pulderbos in Belgium. All individuals suffered from refractory epilepsy and were treated with VNS (Neuro-Cybernetic Prosthesis System; Cyberonics, Pulse Generator, Houston, TX, USA). Individual characteristics and background medication are shown in Table I. A comparison group with staring episodes or learning problems was referred to the epilepsy clinic for electroencephalography (EEG) to exclude absence seizures and had normal EEG findings. This comparison group comprised 17 age- and sex-matched individuals to take into account age-dependent differences. EEG recordings were obtained using the 10 to 20 International System of Electrode Placement. Sampling rate was 250Hz. Twenty-four-hour EEG and electrocardiography (ECG) data were obtained before and after implantation of the VNS. Sleep data were used to evaluate the typical shifts in autonomic balance during sleep and to exclude differences due to mental state during daytime. Fifty-minute epochs of ECG were extracted from stage 2 sleep and SWS in the first sleep cycle to exclude circadian and endocrine influences. The individuals had no seizures during the data extraction periods or in the hour before. All individuals had ongoing seizures after implantation of the VNS. Sleep stage was determined by the investigator by visual analysis of the EEG and spectral analysis by BrainRT (OSG, Rumst, Belgium). The RR interval was calculated by the BrainRT software after automatic QRS complex detection. Extraventricular beats were replaced by a 20% filter, meaning that every RR interval that differs by more than 20% of the previous one is replaced by an interpolated value, defined via spline interpolation over the five previous and

What this paper adds

- This paper describes features of heart rate variability in children with refractory epilepsy.
- Vagus nerve stimulation results in an increase in heart rate.
- Individuals with refractory epilepsy have reduced vagal tone during slow-wave sleep.
- Implantation of vagus nerve stimulation causes an increase in sympathetic activity.

Table I: Individual characteristics

No.	Age (y)	Sex	Type of epilepsy	AED at time of implantation	AED after implantation	Imaging	Output current (mA)
1	16.5	M	Lennox–Gastaut	Lamotrigine, levetiracetam, sodium valproate	Lamotrigine, sodium valproate, clobazam	Normal	2.25
2	6.6	M	ESES	Topiramate	Topiramate, clobazam, sodium valproate	Thalamic bleeding	0.75
3	8.7	M	ESES	Sodium valproate, lamotrigine	Sodium valproate, lamotrigine	Thalamic bleeding	1.5
4	5.7	M	Lennox–Gastaut	Sodium valproate, lamotrigine, levetiracetam	Sodium valproate, lamotrigine, clobazam	Insular pachygyria	1.25
5	7.5	M	Lennox–Gastaut	Topiramate, lamotrigine, clonazepam	Topiramate, lamotrigine, clonazepam	Normal	1.5
6	4.8	M	Frontal lobe epilepsy	Levetiracetam, carbamazepine	Carbamazepine	Normal	1.25
7	4.3	F	Lennox–Gastaut	Sodium valproate, lamotrigine, clonazepam	Sodium valproate, lamotrigine, clonazepam	Normal	1.5
8	4	M	Myoclonic astatic	Sodium valproate, lamotrigine, nitrazepam	Sodium valproate, levetiracetam, clonazepam	Normal	1.5
9	4	M	Lennox–Gastaut	Sodium valproate, gabapentin	Sodium valproate, gabapentin	Normal	1.5
10	6.6	M	Frontal lobe epilepsy	Sodium valproate, lamotrigine	Sodium valproate, lamotrigine	Normal	1
11	3	M	Myoclonic epilepsy	Sodium valproate, levetiracetam, clonazepam	Sodium valproate, levetiracetam, clonazepam	Normal	0.75
12	6.8	F	Myoclonic epilepsy	Sodium valproate, levetiracetam, clonazepam, ethosuximide	Topiramate, clobazam, sodium valproate	Normal	2.25
13	8.7	F	Lennox–Gastaut	Levetiracetam, clobazam, sodium valproate	Levetiracetam, clobazam, sodium valproate	Normal	1
14	13.2	M	Lennox–Gastaut	Phenytoin, carbamazepine, sodium valproate	Phenytoin, carbamazepine, clobazam, phenobarbital	Normal	1
15	12.5	F	Absence epilepsy	Sodium valproate, lamotrigine, clobazam	Lamotrigine, ethosuximide	Normal	0.75
16	11.9	M	Temporal lobe epilepsy	Sodium valproate, lamotrigine	Sodium valproate, clonazepam	Postischaemic white matter lesions	1.25
17	4.3	M	Lennox–Gastaut	Sodium valproate, clonazepam	Sodium valproate, topiramate, clobazam	Normal	1.5

AED, antiepileptic drug; ESES, electrical status epilepticus in sleep; M, male; F, female.

five subsequent intervals. Finally, all RR interval time series were checked manually. The protocol was approved by the ethics committee of the University Hospitals of the University of Leuven, Belgium.

Time and frequency domain analysis of HRV was done according to the standards of the Task Force of the European Society of Cardiology:[5] in the time domain, mean RR interval, SD of all normal to normal intervals, the square root of the mean of the sum of the squares of differences between adjacent NN intervals, and numbers of pairs of adjacent NN intervals differing by more than 50ms in the entire recording divided by the total number of all NN intervals were calculated. Spectral analysis of heart rate can provide more information on the sympathetic and parasympathetic contribution to autonomic outflow to the heart. Looking at the power spectral density, the high-frequency components are related to parasympathetic activity, whereas low frequency provides a marker of sympathetic activity. However, low frequency is not restricted to a particular neural circuit. Spectral components below 0.04Hz were defined as very low frequency, between 0.04Hz and 0.15Hz as low frequency, and those between 0.15Hz and 0.40Hz were defined as high frequency. Low- and high-frequency normalized units (LFnu and HFnu respectively) were used to compare spectra with different total power. LFnu=LF/(total power−VLF)×100, HFnu=HF/(total power−VLF)×100. The low-frequency/high-frequency ratio was used to quantify the sympathovagal balance as an indicator of autonomic modulation.

Statistical analysis was executed in Matlab R2008a (The Mathworks Inc., Natick, MA, USA). Statistical significance of the VNS effect on heart rate modulation was tested pairwise by the Wilcoxon signed-rank test. Differences between individuals with epilepsy and the comparison group were also obtained via the Mann–Whitney *U* test, also called the Wilcoxon rank-sum test. $p<0.05$ was considered statistically significant.

RESULTS

Of the 17 individuals included in the study, eight were diagnosed with Lennox–Gastaut epilepsy, three with myoclonic epilepsy, two with electrical status epilepticus during sleep, two with frontal lobe epilepsy, one with absence epilepsy, and one with temporal lobe epilepsy. The output current was between 0.75mA and 2.25mA, the stimulation frequency was 30Hz, the pulse width was 500ms, the on time was 30 seconds, and the off time was 5 minutes. The mean time between the baseline registration and implantation of VNS was 7 months and 2 weeks (range 1–48mo), the mean time between registration after implantation was 11 months (range 1–39mo). The mean duration of epilepsy was 6 years 4 months (range 1–14y). The median time interval between pre- and post-VNS measurements was 11.5 months (range 3–36mo). Individuals continued to have refractory epilepsy during the period of follow-up.

Time domain analysis showed a significantly higher heart rate in individuals with epilepsy than in the comparison group, both in stage 2 sleep ($p=0.009$; $z=-2.618$; rank sum=221) and during SWS ($p=0.042$; $z=-2.032$; rank sum=238). VNS therapy did not alter the higher heart rate in individuals with refractory epilepsy. Other time domain analyses showed no significant findings (Tables II and III).

In the frequency domain analysis, HRV characteristics in individuals with refractory epilepsy were different from those in individuals without (Tables IV and V). During stage 2 sleep, LFnu in individuals with refractory epilepsy was lower than the control level before VNS therapy. The contribution of low-frequency power increased after implantation of VNS, but was still reduced compared with the control level. HFnu was increased in individuals with refractory epilepsy before VNS compared with that in individuals without epilepsy, decreased after VNS, but still remained higher than the control level. During SWS, there was an increase in LFnu and a decrease in HFnu in individuals with refractory epilepsy before VNS therapy when compared with individuals without epilepsy. After implementation of VNS, the changes observed in individuals with epilepsy become more prominent and statistically significant (LFnu in individuals with epilepsy after VNS treatment vs comparison group: $p=0.007$; $z=2.686$; rank sum=376; HFnu in individuals with epilepsy after VNS treatment vs comparison group: $p=0.009$; $z=-2.618$; rank sum=221; Figs 1 and 2).

In the comparison group, the sympathovagal balance (low frequency/high frequency) shifted more towards sympathetic predominance in stage 2 sleep than in SWS. In contrast, in individuals with epilepsy, low and high frequency was higher during SWS than during stage 2 sleep, and this was even more pronounced after VNS. Low frequency/high frequency was therefore statistically significantly higher during SWS in individuals with epilepsy after VNS treatment than in the comparison group ($p=0.007$; $z=2.687$; rank sum=376; Fig. 3). The normal reduction in low-frequency/high-frequency ratio observed in the comparison group during SWS was abolished in individuals with refractory epilepsy, before and after VNS therapy.

Table II: Results of time domain analysis in individuals with refractory epilepsy before implantation of vagus nerve stimulation (VNS), after implantation of VNS, and the comparison group during stage 2 sleep

	Individuals before VNS, mean (SD)	Individuals after VNS, mean (SD)	Comparison group, mean (SD)
Mean RR interval	716.99 (89.45)	715.08 (95.43)	837.32 (136.53)
SDNN	90.46 (46.63)	78.88 (35.69)	98.05 (28.31)
SDANN	28.31 (20.13)	23.92 (18.20)	29.86 (14.61)
RMSSD	98.76 (62.99)	77.13 (39.86)	92.19 (43.82)
pNN50	33.36 (21.98)	27.42 (22.54)	38.31 (22.45)

SDNN, standard deviation of all normal to normal intervals; SDANN, standard deviation of the averages of NN (normal sinus to normal sinus) intervals; RMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN50, numbers of pairs of adjacent NN intervals differing by more than 50ms in the entire recording divided by the total number of all NN intervals.

Table III: Results of time domain analysis in individuals with refractory epilepsy before implantation of vagus nerve stimulation (VNS), after implantation of VNS, and the comparison group during slow-wave sleep

	Individuals before VNS, mean (SD)	Individuals after VNS, mean (SD)	Comparison group, mean (SD)
Mean RR interval	719.66 (107.41)	723.78 (84.20)	814.64 (129.57)
SDNN	83.76 (35.55)	84.55 (49.40)	75.38 (27.87)
SDANN	26.46 (15.76)	25.51 (18.05)	19.00 (11.69)
RMSSD	90.07 (47.66)	82.15 (59.86)	84.87 (50.44)
pNN50	33.22 (24.18)	28.04 (23.52)	39.90 (24.02)

SDNN, standard deviation of all normal to normal intervals; SDANN, standard deviation of the averages of NN (normal sinus to normal sinus) intervals; RMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN50, numbers of pairs of adjacent NN intervals differing by more than 50ms in the entire recording divided by the total number of all NN intervals.

DISCUSSION

The higher heart rate in individuals with refractory epilepsy before and after implantation of VNS compared with individuals without epilepsy suggests already a change in autonomic balance in individuals with long-lasting epilepsy. The increase in heart rate is one of the first signs of sympathetic predominance or vagal withdrawal on the autonomic outflow to the heart. The peripheral autonomic nervous system is regulated by the control centres of the autonomic nervous system in the brain.[6–8]

In healthy persons, vagal influences become more important during sleep, with a maximum in synchronized sleep. These findings were confirmed in our comparison group.

In individuals with refractory epilepsy, our results showed a lower contribution of sympathetic activity and more prominent vagal activity in stage 2 sleep compared with individuals without epilepsy, marked by lower low-frequency and higher high-frequency power. After implementation of VNS, sympathetic activity became more prominent, and low-frequency power increased but did not reach the normal level observed in our controls. The same was observed in the low-frequency/high-frequency ratio. Individuals with refractory epilepsy had a lower ratio compared with healthy individuals, and although this ratio increased after VNS therapy, it still remained below the value of normal individuals.

During SWS, our results demonstrated a clear shift towards sympathetic dominance in individuals with refractory epilepsy already before VNS. After implantation of VNS, the reduction in vagal tone, marked by a decrease in high-frequency power

Table IV: Results in frequency domain of individuals with refractory epilepsy before vagus nerve stimulation (VNS), individuals with refractory epilepsy after VNS, and the comparison group during stage 2 sleep

	Individuals before VNS, mean (SD)	Individuals after VNS, mean (SD)	Comparison group, mean (SD)	p_1 before VNS vs after	p_2 before VNS vs comparisons	p_3 after VNS vs comparisons
TP	10929.1 (15432.94)	7347.04 (6949.94)	9209.69 (5146.71)	0.266	0.449	0.202
VLF	2776.6 (2734.68)	2901.27 (3339.16)	3002.89 (1691.55)	0.943	0.469	0.335
LF	2503.07 (4443.86)	1501.29 (1705.62)	2125.53 (1326.51)	0.163	0.130	0.058
HF	5456.12 (8276.02)	2794.78 (2257.14)	3896.67 (3395.45)	0.124	0.810	0.371
LFnu	32.35 (8.54)	35.43 (11.12)	37.25 (11.21)	0.227	0.255	0.679
HFnu	64.89 (9.29)	61.31 (12.46)	59.29 (12.92)	0.210	0.228	0.679
LF/HF	0.525 (0.199)	0.644 (0.357)	0.716 (0.452)	0.177	0.242	0.679

p_1 was obtained via the Wilcoxon signed-rank test. p_2 and p_3 were obtained via the Mann–Whitney *U* test. TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency; nu, normalized units.

Table V: Results in frequency domain of individuals with refractory epilepsy before vagus nerve stimulation (VNS), individuals with refractory epilepsy after VNS, and the comparison group during slow-wave sleep

	Individuals before VNS, mean (SD)	Individuals after VNS, mean (SD)	Comparison group, mean (SD)	p_1 before VNS vs after	p_2 before VNS vs comparisons	p_3 after VNS vs comparisons
TP	7934.9 (7027.31)	8620.55 (1037.63)	5493.97 (4823.95)	0.906	0.469	0.809
VLF	2029.08 (2056.22)	2795.76 (3034.60)	1117.27 (684.57)	0.266	0.091	0.073
LF	1765.43 (1714.25)	1984.67 (2590.870)	1032.47 (893.15)	0.844	0.301	0.930
HF	3986.57 (3622.27)	3681.99 (5070.690)	3258.57 (3661.12)	0.945	0.757	0.153
LFnu	34.77 (12.59)	40.09 (12.99)	29.64 (11.840	0.109	0.168	0.007
HFnu	62.27 (13.85)	56.41 (14.21)	68.82 (13.18)	0.039	0.158	0.009
LF/HF	0.640 (0.39)	0.822 (0.488)	0.497 (0.473)	0.035	0.148	0.007

p_1 was obtained via the Wilcoxon signed-rank test. p_2 and p_3 were obtained via the Mann–Whitney *U* test. TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency; nu, normalized units.

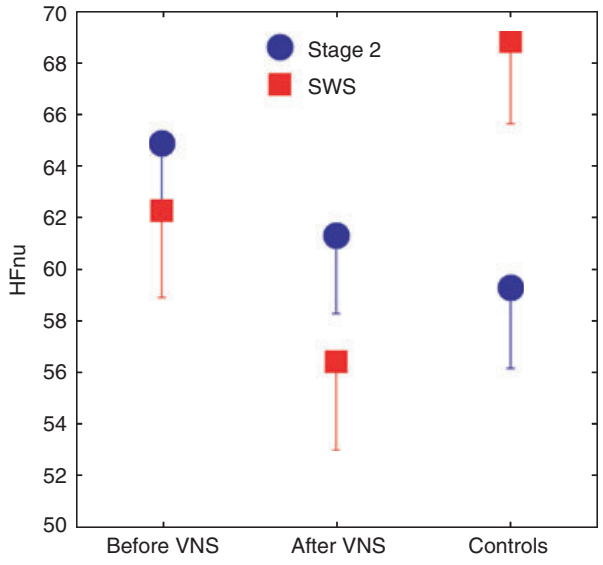

Figure 1: High frequency (HF) content before and after vagus nerve stimulation (VNS), and in control population. SWS, slow-wave sleep; nu, normalized units.

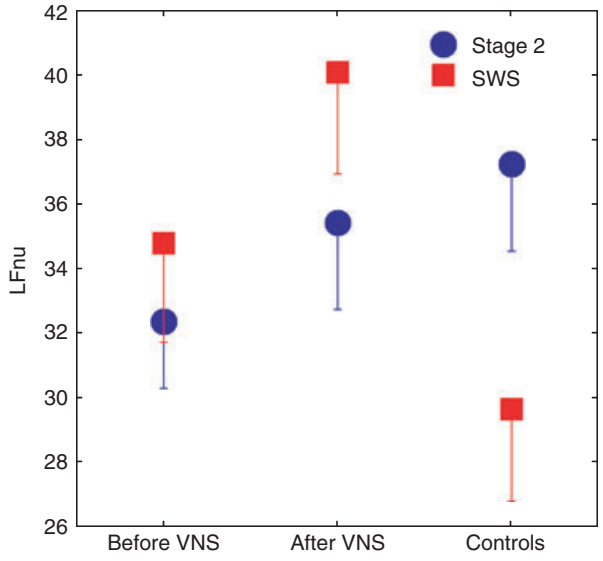

Figure 2: Low frequency (LF) content before and after vagus nerve stimulation (VNS), and in control population. SWS, slow-wave sleep; nu, normalized units.

and an increase in sympathetic activity, or low-frequency power, became even more clear and statistically significant. The low-frequency/high-frequency ratio showed an opposite trend compared with stage 2 sleep. The low-frequency/high-frequency ratio was higher in individuals with refractory epilepsy before VNS compared with individuals without refractory epilepsy and showed another increase after VNS, making the difference with healthy individuals even more striking.

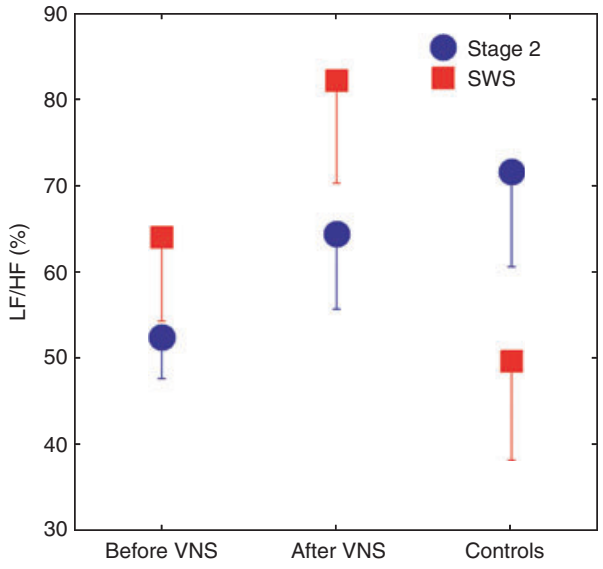

Figure 3: LF/HF (low frequency/high frequency) ratio before and after vagus nerve stimuation (VNS), and in control population. SWS, slow-wave sleep.

To summarize the most important findings, individuals with refractory epilepsy had less sympathetic activity in stage 2 sleep, reflected by a lower contribution of LFnu and a higher contribution of HFnu, where sympathetic activity was expected to be high. The typical nocturnal increase in HRV after transition to SWS was not seen.

VNS treatment seemed to increase sympathetic activity in every sleep stage. Compared with individuals without refractory epilepsy, the effect was most important during SWS, where vagal components of autonomic tone are physiologically the most prominent.[1]

Changes in high-frequency and low-frequency power bands in both sleep stages were smaller in individuals with refractory epilepsy than in the comparison group. Individuals with refractory epilepsy seemed to have lost the ability to make changes in the contribution of the sympathetic or parasympathetic system to the autonomic outflow to the heart. This could be considered a marker of impaired modulation capacity in individuals with severe epilepsy and appeared to be improved after VNS treatment.

Refractory epilepsy

The vagal reduction observed in our individuals with refractory epilepsy has been previously reported in adults with refractory epilepsy and children with complex partial seizures.[3,4,9] The explanation for this phenomenon is still not known. In lesional epilepsy, it is possible that parts of the central autonomic regulation centres are disrupted. In individuals with long-lasting epilepsy taking multiple drugs, the effect of chronic administration of medication remains a possibility.

Another hypothesis is that the chronic epilepsy itself causing the almost continuous epileptic discharges and an epileptic encephalopathy disturbs the typical function of the autonomic

nervous system in the long term. This is supported by the findings that individuals with newly diagnosed and untreated epilepsy show no difference in HRV.[10] The same applies to individuals with well-controlled seizures in partial epilepsy.[11] In contrast, individuals with refractory seizures are prone to autonomic dysfunction. All our included individuals suffered from chronic epilepsy with refractory seizures and continued to have seizures after implantation of VNS.

VNS

Previous reports on VNS in refractory epilepsy have had different results concerning heart rate variability. Setty et al.[12] found no difference in cardiac parameters in individuals with epilepsy after implantation of VNS, but only short fragments were used for analysis. Stemper et al.[13] found an increase in both low-frequency and high-frequency power of the RR intervals during a 60-second on phase. Galli et al.[14] did not find important cardiac effects of VNS stimulation, although HRV analysis revealed subtle changes in cardiac sympathovagal balance: a reduction in vagal tone, marked by a reduction in high-frequency power, was noted after long-term vagal nerve stimulation, mainly during sleep. Ronkainen et al.[15] found a clear impairment of HRV in individuals with chronic refractory epilepsy but no change after treatment with VNS.

As previously mentioned, the mechanism of action in VNS is still not completely understood. The vagal afferents project to the solitary tract, which in turn has widespread connections to the brainstem and forebrain with an inhibitory effect. Ben-Menachem et al.[16] demonstrated an increase in gamma-aminobutyric acid and decrease in aspartate in the cerebrospinal fluid of individuals with VNS, supporting this hypothesis. More recently, the function of the locus coeruleus in epilepsy and VNS therapy has gained importance. Animal data show increased activity in the locus coeruleus, marked by increased c-fos expression, a marker of neuronal activity.[17] Long-term stimulation of the vagus nerve in rats shows enhancement of the activity of serotonin and noradrenaline neurons in the dorsal raphe nucleus and the locus coeruleus. Neurons of the locus coeruleus project to the hippocampus and the prefrontal cortex and are the source of hippocampal and cortical noradrenaline.[18] This increase in the activity of noradrenaline neurons could be the explanation for the additional increase in sympathetic activity in HRV characteristics in individuals with VNS compared with individuals without VNS, as observed in our study, but this should be explored in more detail.

As we conducted a retrospective study, there are some important limitations to mention. The timing of assessment of HRV before and after implantation of the VNS varied from individual to individual. Therefore, we were unable to consider the influence of the duration of VNS stimulation on HRV. Antiepileptic drugs can have an important influence on HRV, as demonstrated by Hallioglu et al.[19] for carbamazepine. However, for most of the antiepileptic drugs, this effect has not been thoroughly investigated. In our population, background medication was kept the same in some but not in all individuals, as shown in Table I. The population of individuals itself was very heterogeneous, and we were unable to investigate whether the type of epilepsy is important when looking at cardiac changes owing to sample size constraints.

In conclusion, our results show that autonomic cardiac outflow is affected in individuals with refractory epilepsy. There is a lower sympathetic activity in stage 2 sleep, but most striking is the reduction in vagal tone during SWS. Modulation capacity was smaller than in comparison individuals. Implantation of a vagus nerve stimulator induces an overall sympathetic effect and emphasizes the observed loss of HRV in SWS. Autonomic modulation slightly improves after VNS. The observed changes could be of importance in cardiac complications in individuals with epilepsy and should be explored in more detail.

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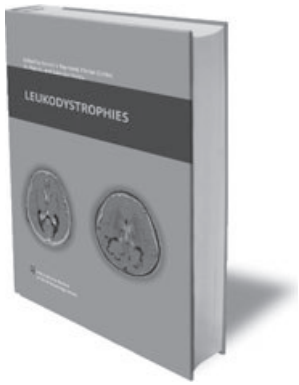

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