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Baseline elevation and reduction in cardiac electrical instability assessed by quantitative T-wave alternans in patients with drug-resistant epilepsy treated with vagus nerve stimulation in the AspireSR E-36 trial

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ABSTRACT

Objective: Reports of cardiac arrhythmias and cardiac pathology at postmortem examination of patients with epilepsy suggest a possible cardiac component of risk for sudden unexpected death in epilepsy (SUDEP). T-wave alternans (TWA) is an established marker of cardiac electrical instability and risk for sudden death in patients with cardiovascular disease. We determined the TWA level before vagus nerve stimulation (VNS) system implantation and subsequently the effect of VNS on TWA in patients with drug-resistant epilepsy.
Methods: Patients (n = 28) from the Seizure Detection and Automatic Magnet Mode Performance Study (E-36), a clinical trial of the AspireSR® VNS Therapy System® (NCT01325623), were monitored with ambulatory electrocardiograms (ECGs) ~2 weeks before *de novo* VNS system implantation and following 2- to 4-week VNS titration during a protocol-specified 3- to 5-day epilepsy monitoring unit stay with concurrent EEG/ECG recordings. The TWA level was assessed interictally by the Modified Moving Average (MMA) method.
Results: At preimplantation baseline, TWA was elevated above the 47-μV abnormality cutpoint in 23 (82%) patients with drug-resistant epilepsy. In 16 (70%) patients, TWA level was reduced during VNS treatment to <47 μV, thereby converting positive TWA test results to negative. Peak TWA level in all 28 patients improved (group mean, 43%, from 72 ± 4.3 to 41 ± 2.3 μV; $p < 0.0001$). Vagus nerve stimulation was not associated with reduced heart rate (77 ± 1.4 to 75 ± 1.4 beats/min; $p = 0.18$). Heart rate variability was unchanged.
Significance: These findings suggest significant interictal cardiac electrical instability in this population of patients with drug-resistant epilepsy and suggest that VNS may be a novel approach to reducing risk.

1. Introduction

Approximately 40% of patients with epilepsy have seizures that do not respond adequately to antiepileptic drug therapy [1], a condition that is an established risk factor for sudden unexpected death in epilepsy (SUDEP). Biomarkers other than recurrent seizures for determining and monitoring SUDEP risk are currently unavailable.

Microvolt T-wave alternans (TWA), a subtle, beat-to-beat fluctuation in the morphology and amplitude of the ST segment or T-wave in the electrocardiogram, is a biomarker for cardiac electrical instability that correlates with risk for sudden cardiac death (SCD) in patients with cardiovascular disease [2]. During the postictal period in a group of patients with focal epilepsy, Strzelczyk et al. [3] reported markedly elevated levels of TWA. In a pilot study, we found interictal TWA levels in excess of the 47-μV cutpoint of abnormality in 100% (9 of 9) of patients with drug-resistant epilepsy and, furthermore, that interictal TWA was significantly reduced in association with vagus nerve stimulation (VNS) [4], suggesting an effect through alterations in autonomic tone and/or direct effects on myocardial substrate. Peak TWA level was converted from positive to negative in 67% (4 of 6) of patients.

The objective of the present study was to confirm and further extend these published pilot results by examining the impact of a combination of routine intermittent (open-loop) VNS and automatic (closed-loop) VNS on TWA in a larger subset of patients with drug-resistant epilepsy

Abbreviations: ARREST, Amsterdam Resuscitation Studies; AspireSR, Seizure Detection and Automatic Magnet Mode Performance Study; EMU, epilepsy monitoring unit; HF HRV, high-frequency heart rate variability; HRV, heart rate variability; LF HRV, low-frequency heart rate variability; MMA, Modified Moving Average; SCD, sudden cardiac death; SUDEP, sudden unexpected death in epilepsy; TWA, T-wave alternans; VNS, vagus nerve stimulation.

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enrolled at multiple sites in the Seizure Detection and Automatic Magnet Mode Performance Study (E-36). Effects of VNS on autonomic nervous system tone and heart rate were also assessed. Our hypotheses were that interictal TWA would be elevated preimplantation and reduced in association with VNS.

2. Methods

2.1. Patient selection

The Seizure Detection and Automatic Magnet Mode Performance Study (E-36) (NCT01325623) was a prospective, multicenter study of VNS with the AspireSR Model 106 VNS Therapy® System implantable pulse generator (Fig. 1) in patients with drug-resistant epilepsy and a history of ictal tachycardia (defined either as 55% or a 35-beats/min increase in heart rate to ≥100 beats/min near seizure onset) (N = 30) [5]. The study conformed to the Declaration of Helsinki and was approved by the Competent Authorities and Ethics Committees at the participating centers. All patients signed informed consent. Patients were implanted between April 2011 and June 2013 at 13 European sites. To be eligible, patients also had to be at least 18 years old, be clinically diagnosed with drug-resistant epilepsy dominated by focal seizures, have an average of 3 or more seizures per month in the 3 months prior to the screening visit, and otherwise be in general good health and ambulatory. Patients were excluded if they had contraindications for the existing labeling for VNS, significant psychiatric or addictive disorders, a history of status epilepticus within 3 months of enrollment, were prescribed drugs specifically for a cardiac or autonomic nervous system disorder that potentially affected heart rate, had known clinically meaningful cardiovascular arrhythmias (including bradycardia), or had clinically meaningful cardiovascular arrhythmias determined by a 24-hour Holter recording obtained at the baseline visit.

Implantation techniques, postoperative care, and ramp-up and maintenance stimulation protocols were according to standard-of-care practices. All patients were naïve with respect to implantation of the leads and the generator. Vagus nerve stimulation settings were as follows: intensity, 0.75 mA and pulse width, 250 μs (medians). Pulse frequency was 20 Hz, and duty cycle was 30 s on followed by 5 min off. The individual settings were established by clinical personnel without knowledge of TWA status. Medications were not altered during the study period.

2.2. Ambulatory ECG recording and analysis

The patients' 24-hour electrocardiograms (ECGs) were recorded on a single day at baseline 2 weeks prior to VNS implantation and, following 2- to 4-week VNS titration, during the final seizure-free 24 h of the protocol-specified 3- to 5-day hospitalization in an epilepsy monitoring unit (EMU). The ECGs of 2 patients were not interpretable, leaving 28 subjects for our report. The baseline ECG and the ECG recorded on the final seizure-free day of the EMU stay were analyzed.

The TWA level was quantified with the Modified Moving Average (MMA) method [6] in standard precordial leads V_1, V_5, and aVF by an investigator (BDN) blinded to treatment status using the MARS Ambulatory ECG Analysis System (GE Healthcare, Milwaukee, WI). The conventional AECG configurations of V_1, V_5, and aVF provide satisfactory reliability from one recording to another from the same individual. The maximum interictal TWA level throughout the recording is reported as the TWA value for that patient. As established in patients with heart disease [2], a TWA cutpoint of ≥47 μV was defined in this study as an abnormal TWA test and ≥60 μV as markedly abnormal while TWA <20 μV was taken to indicate relative cardiac electrical stability.

Heart rate and HRV data were automatically generated by the GE Healthcare MARS version 8.0 software for the interictal period during the first hour of the recording. Heart rate variability (HRV) was analyzed in the frequency domain using the Fast Fourier spectral transform. Accordingly, the beat stream of the RR interval series was transformed to compute high-frequency (HF) power within the frequency band 0.150 to 0.400 Hz and low-frequency (LF) power within the frequency band 0.040 to 0.150 Hz, reported in milliseconds squared. The LF/HF ratio was calculated as LF frequency divided by HF frequency and is unitless. High-frequency heart rate variability (HF HRV) is a general indicator of parasympathetic tone, while LF HRV and the LF/HF HRV ratio are indicators of autonomic tone and balance [7]. Normative values of HF and LF HRV are 975 ± 203 and 1170 ± 416 ms^2, respectively, while an LF/HF HRV ratio of 1.5 to 2.0 is considered normal [7].

2.3. Statistical methods

The TWA level, HRV, and heart rate associated with VNS in AspireSR were analyzed by Student's t-test using SAS statistical package (SAS Institute, Cary, NC, USA). Fisher's exact test (two-tailed) was used to assess the significance of the change in percentage of patients with abnormal (≤47 μV) and severely abnormal (≤60 μV) TWA comparing levels before implant with levels at 2- to 4-weeks postimplant. Data are reported as means ± S.E.M., with $p < 0.05$ considered statistically significant.

3. Results

3.1. Patient characteristics

Patient characteristics are as described in detail by Boon et al. [5]. Briefly, all of the patients were Caucasian, and 19 (68%) were female. Mean age at onset of epilepsy was 16 years (range: 2–43) and at study enrollment was 40 years (range: 19–66).

3.2. Baseline interictal TWA levels

At baseline (preimplantation), interictal TWA was elevated to the ≥60-μV cutpoint of severe abnormality in 19 (68%) of the 28 patients and ≥47-μV abnormality cutpoint in 23 patients (82%). None of the patients had TWA <20 μV.

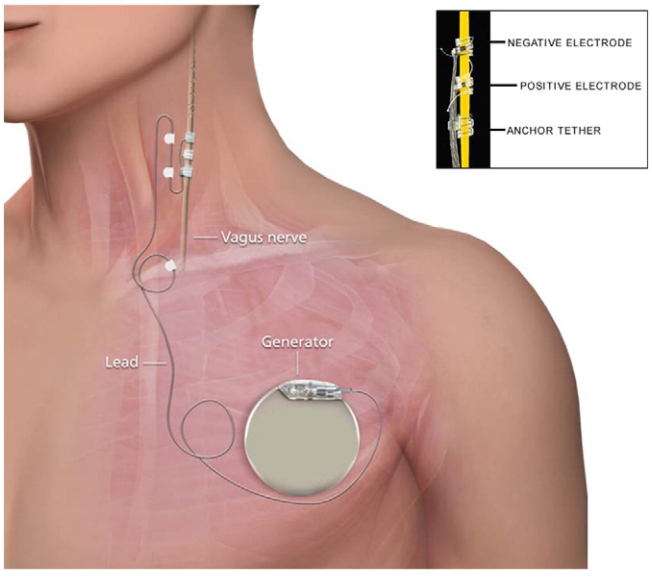

Fig. 1. Placement of vagus nerve stimulation device. As illustrated in the insert (upper right box), the distal end of the lead is wrapped around the nerve. The most proximal electrode is helical and helps to anchor the lead to the vagus nerve. The ECG sensing vector is from the generator can to the negative electrode.