HHS Public Access

Author manuscript

Epilepsia. Author manuscript; available in PMC 2022 May 17.

Published in final edited form as:

Epilepsia. 2021 September ; 62(9): e140–e146. doi:10.1111/epi.16997.

Hypercapnic ventilatory response in epilepsy patients treated with VNS: a case-control study

Rup K. Sainju[1], **Deidre N. Dragon**[1], **Harold B. Winnike**[2], **Patrick Ten Eyck**[2], **Mark A. Granner**[1], **Brian K. Gehlbach**[3,*], **George B. Richerson**[1,4,5,6,*]

[1]Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City, IA

[2]Institute for Clinical and Translational Science, University of Iowa, Iowa City, IA

[3]Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, IA

[4]Department of Molecular Physiology and Biophysics, Carver College of Medicine, University of Iowa, Iowa City, IA

[5]Iowa Neuroscience Institute, Carver College of Medicine, University of Iowa, Iowa City, IA

[6]Veterans Affairs Medical Center, Iowa City, IA

Abstract

Objective—Central CO_2 chemoreception (CCR), a major chemical drive for breathing, can be quantified with a CO_2 re-breathing test to measure the hypercapnic ventilatory response (HCVR). An attenuated HCVR correlates with the severity of respiratory dysfunction after generalized convulsive seizures and is a potential biomarker for sudden unexpected death in epilepsy (SUDEP) risk. Vagus nerve stimulation (VNS) may reduce SUDEP risk, but for unclear reasons the risk remains higher during the first 2 years after implantation. The vagus nerve has widespread connections in the brainstem, including key areas related to CCR. Here we examined whether chronic electrical stimulation of the vagus nerve induces changes in CCR.

Methods—We compared the HCVR in epilepsy patients with or without an active VNS in a sex- and age-matched case-control study. Eligible subjects were selected from a cohort of patients who previously underwent HCVR testing. The HCVR slope, change in minute ventilation (VE) with respect to change in end-tidal (ET) CO_2 (Δ VE/ Δ $ETCO_2$) during the test was calculated for each subject. Key variables were compared between the two groups. Univariate and multivariate analyses were carried out for HCVR slope as dependent variable.

Corresponding author: Rup Sainju, MBBS, Department of Neurology, University of Iowa Carver College of Medicine, 200 Hawkins Drive, 8820 JPP, Neurology, Iowa City, Iowa 52242, USA, rup-sainju@uiowa.edu, Telephone: 319-384-9666.

*Drs. Richerson and Gehlbach contributed equally to this work.

Author contribution

Dr. Sainju: Study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript. Ms. Dragon: Acquisition and interpretation of data, critical revision of manuscript. Mr. Winnike: Acquisition and interpretation of data, critical revision of manuscript. Dr. Ten Eyck: Statistical analyses and interpretation of data, critical revision of manuscript. Dr. Granner: Interpretation of data, critical revision of manuscript. Dr. Gehlbach: Study concept and design, interpretation of data, critical revision of the manuscript Dr. Richerson: Study concept and design, interpretation of data, critical revision of the manuscript.

Disclosure/Ethical Publication:

None of the authors has any conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Results—A total of 86 subjects were in the study. HCVR slope was significantly lower in the cases compared to the controls. Cases had longer duration of epilepsy and higher number of anti-epileptic drugs (AEDs) tried during lifetime. Having active VNS and $ETCO_2$ were associated with a low HCVR slope while high BMI was associated with high HCVR slope in both univariate and multivariate analyses.

Discussion—We found having an active VNS was associated with relatively attenuated HCVR slope. Although duration of epilepsy and number of AEDs tried during lifetime was significantly different between the groups, they were not predictors of HCVR slope in subsequent analysis.

Conclusion—Chronic electrical stimulation of the vagus nerve by VNS may be associated with an attenuated CCR. A larger prospective study may help to establish the time course of this effect in relation to the time of VNS implantation, whether there is a causal relationship, and determine how it affects SUDEP risk.

Keywords

VNS; SUDEP; Epilepsy; Hypercapnic ventilatory response

1. BACKGROUND

Sudden unexpected death in epilepsy (SUDEP) is a major cause of mortality in patients with epilepsy.[1] The incidence of SUDEP is highest among patients with drug resistant epilepsy (DRE).[1] Generalized convulsive seizures (GCS) are strongly associated with occurrence of SUDEP. An increasing body of literature supports the notion that severe peri-ictal respiratory dysfunction associated with GCS is a biomarker of SUDEP risk.[2, 3]

An attenuated interictal ventilatory response to CO_2 (hypercapnic ventilatory response, HCVR), a measure of central CO_2 chemoreception (CCR), correlates with the severity of respiratory dysfunction after GCS and may be a surrogate for SUDEP risk.[4] Serotonergic neurons in the medullary raphe play an important role in CCR as cellular sensors of changes in CO_2 and pH.[5, 6]

Vagus nerve stimulation (VNS) is a neurostimulation device used to treat DRE. There is a lack of conclusive evidence if VNS changes SUDEP risk. Studies suggest SUDEP risk remains high for the first 2 years for unclear reasons before possibly decreasing.[7, 8]

The sensory afferent cell bodies of the vagus nerve are located in the nodose ganglion.[9] Afferent fibers from this ganglion relay incoming sensory information to the nucleus tractus solitarius (NTS). The NTS further relays sensory information widely to brainstem networks including key areas involved in CCR, control of breathing, and arousal, including the parabrachial nucleus (PB), nucleus ambiguus, preBötzinger complex, retrotrapezoid nucleus, and amygdala.[10] Therefore, it is possible that chronic electrical stimulation of the vagus nerve may influence CCR and control of breathing. Attenuation of CCR may be particularly harmful when cortical drive for breathing is compromised, such as during coma following a GCS.

We hypothesized that chronic electrical stimulation by VNS induces changes in CCR and it may alter SUDEP risk. In this study, we conducted a case-control design to compare the HCVR in patients with an active VNS and those without VNS.

2. METHODS AND MATERIALS

2.1 Study design

This is a retrospective case-control study matched (1:1) for age (+/− 5 years) and sex.

The study was approved by the University of Iowa Institutional Review Board. The peri-ictal physiology and HCVR of some subjects have been reported previously.[3, 4]

2.2 Subjects

Eligible subjects were selected from a cohort of patients with epilepsy aged ≥ 18 years who underwent interictal HCVR testing using a previously described modified hyperoxic CO_2 rebreathing technique at the University of Iowa Hospitals and Clinics from June 2015 to April 2019.[4] The HCVR slope, defined as the change in minute ventilation (VE) with respect to change in end-tidal (ET) CO_2 (Δ VE/ Δ $ETCO_2$), during the test was calculated for each subject as previously reported.[4] Cases had a functional VNS device for at least 6 months or longer, while controls were without a VNS device.

2.3 Clinical variables

Electronic medical records were reviewed to collect key variables including age, gender, presence of VNS, VNS stimulation parameters during the most recent interrogation, duration of epilepsy, type of epilepsy, putative epileptogenic zone, duration of VNS implant, body mass index (BMI), active selective serotonin reuptake inhibitors (SSRI)/ serotonin and norepinephrine reuptake inhibitor (SNRI) use, number of anti-epileptic drugs (AEDs) tried in lifetime and used at the time of HCVR testing, history of obstructive sleep apnea (OSA), and history of depression.

VNS current stimulation per day: The following formula was used to quantify current stimulation from VNS:

$$\text{Daily current stimulation} = \text{output current} \times \text{pulse width} \times \text{frequency} \times \text{duty cycle (on time} \div \text{on time} + \text{off time)} \times 24\ \text{hrs}$$

2.4 Statistical analysis

Continuous variables are presented as medians (including inter-quartile range or IQR) or mean and standard deviations stratified by cases and controls and were compared using the T-test or Wilcoxon rank-sum test as appropriate. Poisson regression was also used on count variables (number of AEDs used lifetime and at the time of HCVR testing). Categorical variables were compared using Pearson's Chi-square test and Fisher's exact test. Spearman's correlation was calculated to determine if there was any relationship between HCVR slope and duration of VNS. Univariate and multivariate linear models were fitted to assess the unadjusted and adjusted differences in HCVR slope between cases and controls.

Comparisons between different predictor sets were made using the Akaike information criterion (AIC), where a smaller value indicates a more appropriate model fit. The optimal model revealed which predictors were significantly related to HCVR slope or modified the relationship between HCVR for cases and controls. Estimates and confidence intervals of the mean differences in HCVR slope were provided for each predictor.

3. RESULTS

Baseline characteristics of the cohorts are shown in Table 1. The study was comprised of 86 subjects (43 cases with active VNS and 43 controls without VNS implant) matched for age (+/− 5 years) and sex. Twenty-six (30.2%) of eighty-six participants were women. All the subjects in the control group had a prior video-EEG (vEEG) study in the epilepsy monitoring unit (EMU), with recording of 11 GCS, of which 6 yielded valid transcutaneous CO_2 data during and after the seizure. In contrast, only 10 subjects in the VNS group had a prior vEEG study in the EMU in the time frame of the study, with recording of 4 GCS but only one GCS with CO_2 data.

HCVR slope was significantly lower in the cases compared to the controls (mean ± SD: 1.41 ± 1.15 vs 1.91 ± 1.21 L/min/mm Hg, mean difference −0.5147 [95% CI of −1.01 to −0.02], p = 0.0411). Cases had longer duration of epilepsy (25.3 ± 13.5 vs 13.9 ± 13.4 years; p = <0.0001) compared to controls and had higher number of AEDs tried during lifetime (7.7± 3.2 vs 3.33 ± 2.18; p = <0.001) as well as at the time of HCVR testing (2.0 ± 0.85 vs 1.81 ± 0.96; p = 0.0010) but no other variables analyzed were significantly different between the groups. Mean duration of VNS implant was 6.2 years (range 0.5 to 12 years) in the cases.

In univariate analyses, several clinical variables were evaluated as predictors for HCVR slope. We found that having an active VNS device was associated with a low HCVR slope (mean estimate −0.60 [95% CI: −1.05 to −0.15] L/min/mm Hg; p = 0.0086), and end-tidal (ET) CO_2 during HCVR testing, with every 1 mm Hg increase in $ETCO_2$ increase associated with a mean decrease in HCVR slope of 0.1007 ([95% CI: −0.15 to −0.05]; p =< 0.0001). On the other hand, every 5-unit increase in BMI was associated with a mean increase in HCVR slope of 0.36 L/min/mm Hg [95% CI: 0.20 to 0.53]; p = <0.0001). All three variables remained statistically significant in multivariate analysis using AIC, with smaller values indicating a more appropriate model fit, Table 2.

Variables that were significantly different between the cases and controls (duration of epilepsy, number of AEDs tried over their lifetime and at the time of HCVR testing) were not predictors of HCVR slope. Variables that were not significantly different between the two groups, including type of epilepsy (focal, multifocal, generalized or unclear; p = 0.426) and putative epileptogenic zone (temporal, extratemporal, both or unclear; p =0.638) were also not predictive of HCVR slope Likewise, duration of VNS implant (both as a continuous variable and when dichotomized as <2 years vs ≥ 2 years), as well as stimulation parameters also did not predict HCVR slope.

4. DISCUSSION

In this age and sex matched retrospective case-control study, we found that having an active VNS implant, an elevated baseline $ETCO_2$ and a lower BMI were independently associated with attenuated CCR as reflected by a decrease in slope of the HCVR (Table 2). A previous study has shown that there is a strong correlation between an attenuated HCVR slope and severe postictal respiratory dysfunction following GCS, a potential SUDEP risk.[4] Hence, our findings may be relevant in regard to SUDEP risk.

There is a paucity of studies assessing CCR in patients with epilepsy, and there have been relatively few direct measurements of HCVR slopes in this population. The average estimate of HCVR slope for controls in our study lies within the 95% CI of values that we previously reported, whereas that of cases is below the 95% CI,[4] indicating that epilepsy patients with VNS have a decrease in CCR compared to those without VNS. It is not clear how the difference in HCVR slope between the groups translates to severity in respiratory dysfunction following GCS due to lack of peri-ictal respiratory data in this study, but previous data indicate that those with an attenuated HCVR slope have greater postictal respiratory dysfunction.[4]

It is possible that the lower HCVR observed in patients with VNS reflects alterations in control of breathing induced by uncontrolled epilepsy over time. Indeed, when compared with controls, patients with VNS had significantly longer duration of epilepsy and higher number of lifetime AEDs use. This is not surprising as VNS is often offered for patients with DRE, particularly if surgical treatment is not possible or desirable. In our optimal model, however, neither duration of epilepsy nor number of AEDs tried were associated with HCVR slope. This suggests that the VNS implant itself might modulate the HCVR. Alternatively, patients who receive VNS implants might be different from patients who do not in ways that are not captured by our covariates.

The effect of VNS implantation on SUDEP risk remains unclear and controversial given the lack of prospective studies. Earlier retrospective studies were often limited by a small number of SUDEP cases. One study suggested SUDEP risk was reduced after 2 years of VNS therapy while the other study did not find any benefit on SUDEP risk reduction.[8, 11] The most recent study included 632 SUDEP cases; however only ~16% were definite or probable SUDEP. This study suggests VNS therapy may be associated with reduction of SUDEP risk but the risk remains higher during the first two years after implantation.[7] If there was a direct effect of VNS therapy on the slope of the HCVR, it would be expected that the HCVR slope would be lowest during the first two years after VNS implantation, and yet we found that the duration of VNS implant and stimulation intensity were not significantly associated with HCVR slope. It is possible that other factors play a dominant role, and VNS parameters are typically adjusted to clinical response after implantation, so duration of VNS may not be a good predictor of HCVR slope. Alternatively, an effect of stimulation parameters and duration of VNS on the HCVR might be detected in a larger, prospective study. One can also speculate that because VNS therapy reduces frequency of seizures including GCS[12], which is a strong clinical risk factor for SUDEP[1], VNS may lower risk of SUDEP despite its association with a low HCVR slope. Therefore, it points to

a possibility that HCVR slope may not be a reliable biomarker for SUDEP risk for epilepsy patients when considered alone but may still be a factor that contributes to risk. Since patients were not randomly assigned to VNS and control groups, it is possible that the VNS group in our study had different baseline characteristics than the control group. For example, the decision to place a VNS may have been made in patients that had more severe epilepsy, and the severity of their epilepsy may have put them at greater risk of SUDEP. Therefore, our results may not reflect any direct causative or protective effect of VNS on the risk of SUDEP.

Biological factors, particularly age and gender, are known to influence the HCVR.[13, 14] We controlled both covariates in our study. We found that an elevated baseline $ETCO_2$ is a strong independent predictor of a low HCVR slope, which is consistent with our prior study. A similar association has also been reported in prior studies. [15, 16] This relationship is biologically plausible given patients with highly sensitive CCR (high HCVR slope) will likely increase ventilation in response to a slight increase in systemic PCO_2, thus driving their baseline CO_2 to a low level. The opposite is true for patients with insensitive CCR (low HCVR slope). The relationship between HCVR and obesity is complex, with some studies reporting attenuated but others reporting increased HCVR.[17-19] Obesity increases the risk of alveolar hypoventilation and CO_2 retention as well as OSA which may be asymptomatic and undiagnosed. These factors may at least partly explain the variability of association with HCVR. A study of eucapnic patients found obesity was associated with higher HCVR. [17] Hence, the positive association between BMI and HCVR in our study is not surprising.

Our study has certain limitations. First, we identified cohorts based on retrospective review of medical records. Data are often incomplete when retrospectively reviewed and there is a chance of introduction of certain biases that may affect the results. Second, although we found a strong association of having a VNS implant with low HCVR slope, due to the design of the study, specifically due to lack of pre-implant and post-implant HCVR tests, we cannot prove causation, and our results should be viewed as hypothesis-generating. A prospective study measuring HCVR slopes before and after VNS implant would strengthen the evidence for such a relationship. If such causal relationship exists, then testing HCVR with VNS on and off could further clarify if the effect is due to acute or chronic stimulation, which the current study fails to examine. Third, we were not able to analyze important clinical variables related to epilepsy severity, such as frequency of GCSs and overall seizure control after VNS implantation, which are also likely determinants for SUDEP risk, and which may affect HCVR slope. For example, patients with VNS may have more severe epilepsy, and that may cause a decrease in HCVR slope. Similarly, VNS may reduce HCVR, but can also decrease GCS frequency. The former may increase SUDEP risk, whereas the latter would decrease it. Future work will be needed to examine the effects of each of these variables on HCVR and SUDEP risk and can be reliably studied in a standardized way in future prospective studies.

5. CONCLUSION

Our findings suggest that chronic electrical stimulation of the vagus nerve by VNS may be associated with an attenuated CCR, although causality is not established, and the clinical

significance of our finding is unclear. A larger prospective study may be helpful to confirm our findings while also examining the effect of VNS on CCR and SUDEP risk.

References

1. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: A nationwide population-based case-control study. Neurology 2020; 94: e419–e429. [PubMed: 31831600]
2. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013; 12: 966–977. [PubMed: 24012372]
3. Vilella L, Lacuey N, Hampson JP, Sandhya Rani MR, Sainju RK, Friedman D, et al. Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP). Neurology 2019; 92: e171–e182. . [PubMed: 30568003]
4. Sainju RK, Dragon DN, Winnike HB, Nashelsky MB, Granner MA, Gehlbach BK, et al. Ventilatory response to CO2 in patients with epilepsy. Epilepsia 2019; 60: 508–517. [PubMed: 30756391]
5. Richerson GB. Response to CO2 of neurons in the rostral ventral medulla in vitro. J Neurophysiol 1995; 73: 933–944. [PubMed: 7608778]
6. Gargaglioni LH, Hartzler LK, Putnam RW. The locus coeruleus and central chemosensitivity. Respir Physiol Neurobiol 2010; 173: 264–273. [PubMed: 20435170]
7. Ryvlin P, So EL, Gordon CM, Hasdorffer DC, Sperling MR, Devinsky O, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. Epilepsia 2018; 59: 562–572. [PubMed: 29336017]
8. Annegers JF, Coan SP, Hauser WA, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. Epilepsia 2000; 41: 549–553. [PubMed: 10802760]
9. George MS, Sackeim HA, Rush AJ, Marangell LB, Nahas Z, Husain MM, et al. Vagus nerve stimulation: a new tool for brain research and therapy. Biol Psychiatry 2000; 47: 287–295. [PubMed: 10686263]
10. Terhorst GJ, Deboer P, Luiten PGM, Vanwilligen JD. Ascending Projections from the Solitary Tract Nucleus to the Hypothalamus - a Phaseolus-Vulgaris Lectin Tracing Study in the Rat. Neuroscience 1989; 31: 785–797. [PubMed: 2594200]
11. Granbichler CA, Nashef L, Selway R, Polkey CE. Mortality and SUDEP in epilepsy patients treated with vagus nerve stimulation. Epilepsia 2015; 56: 291–296. [PubMed: 25580645]
12. Labar D, Murphy J, Tecoma E. Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 VNS Study Group. Neurology 1999; 52: 1510–1512. [PubMed: 10227649]
13. Brischetto MJ, Millman RP, Peterson DD, Sukage DA, Pack AI. Effect of aging on ventilatory response to exercise and CO2. J Appl Physiol Respir Environ Exerc Physiol 1984; 56: 1143–1150. [PubMed: 6427148]
14. Aitken ML, Franklin JL, Pierson DJ, Schoene RB. Influence of body size and gender on control of ventilation. J Appl Physiol 1986; 60: 1894–1899. [PubMed: 3087935]
15. Garay SM, Rapoport D, Sorkin B, Epstein H, Feinberg I, Goldring RM. Regulation of ventilation in the obstructive sleep apnea syndrome. Am Rev Respir Dis 1981; 124: 451–457. [PubMed: 7294507]
16. Trachiotis GD, Knight SR, Hann M, Pohl MS, Patterson GA, Cooper JD, et al. Respiratory responses to CO2 rebreathing in lung transplant recipients. Ann Thorac Surg 1994; 58: 1709–1717. [PubMed: 7979741]
17. Narkiewicz K, Kato M, Pesek CA, Somers VK. Human obesity is characterized by a selective potentiation of central chemoreflex sensitivity. Hypertension 1999; 33: 1153–1158. [PubMed: 10334803]
18. Ge RL, Stone JA, Levine BD, Babb TG. Exaggerated respiratory chemosensitivity and association with SaO2 level at 3568 m in obesity. Respir Physiol Neurobiol 2005; 146: 47–54. [PubMed: 15733778]

19. Buyse B, Markous N, Cauberghs M, Klaveren RV, Muls E, Demedts M. Effect of obesity and/or sleep apnea on chemosensitivity: differences between men and women. Respir Physiol Neurobiol 2003; 134: 13–22. [PubMed: 12573877]

Table 1.

Patient demographics and baseline characteristics

Characteristics	Cases (N=43)	Controls (N=43)	p value
Age, year			
Median (IQR)	38 (30-45)	39 (28-43)	0.7623
Sex, n (%)			
Female	13 (30.23)	13 (30.23)	> 0.99
Duration of epilepsy, y			
Median (IQR)	25 (12-37)	9 (4-23)	< 0.0001
Type of epilepsy, n (%)			0.757
Focal	32 (74.41)	34 (79.06)	
Multifocal	6 (13.95)	3 (6.97)	
Generalized	3 (6.97)	4 (9.30)	
Focal + generalized	1 (2.32)	0 (0)	
Unclear	1 (2.32)	2 (4.65)	
Putative epileptogenic zone, n (%)			0.055
Temporal	15 (34.88)	22 (51.16)	
Extratemporal	20 (46.51)	7 (16.27)	
Generalized	3 (6.97)	4 (9.30)	
Temporal + extratemporal	3 (6.97)	4 (9.30)	
Unclear	3 (6.97)	6 (13.95)	
History of generalized convulsive seizure, n (%)	42 (97.67)	38 (88.37)	0.20
HCVR slope, L/min/mm Hg			
Median (IQR)	1.17 (0.57-1.99)	1.65 (1.26-2.24)	0.0402
BMI, kg/m^2			
Median (IQR)	27.4 (24.2-35.2)	26.9 (23.5-32.6)	0.4268
Duration of VNS implant, y			
Median (IQR)	6.0 (1.5-10.0)	NA	NA
Stimulation current per day, mA seconds			
Median (IQR)	203 (49-354)	NA	NA
No. of AEDs at HCVR testing, n			
Median (IQR)	2 (2-3)	2 (1-2)	0.0132
No. of AEDs tried lifetime, n			
Median (IQR)	8 (5-10)	3 (2-5)	< 0.0001
Use of SSRI/SNRI			
Number (%)	11 (25.6)	11 (25.6)	> 0.99
History of OSA			
Number (%)	6 (14.3)	8 (19.1)	0.5582
History of depression, Number (%)	20 (46.5)	20 (47.6)	0.9185

Abbreviations: BMI (Body mass index); AED (anti-epileptic drug); SSRI/SNRI (selective serotonergic reuptake inhibitor and serotonin-norepinephrine reuptake inhibitors); OSA (obstructive sleep apnea); IQR (Interquartile range)

Continuous variables were compared using the Wilcoxon rank-sum test. Categorical variables were compared using Pearson’s chi-square test and Fisher’s exact test as appropriate.

Count outcome variables used Poisson regression.

Table 2.

HCVR slope as dependent variable

	Univariate model		
Variable	**Mean estimate**	**95% CI**	**p**
VNS vs control	−0.5147	−1.0086 to −0.0208	0.0411
Age (+10 years) *	0.0870	−0.1380 to 0.3130	0.4471
Gender (women)	−0.1526	−0.7022 to 0.3971	0.5864
Duration of epilepsy	0.0007	−0.0169 to 0.0183	0.9401
BMI (+5) **	0.3475	0.1800 to 0.5150	< 0.0001
Duration of VNS implant ≥ 2 yrs vs < 2 yrs	−0.0044	−0.0804 to 0.0716	0.9105
	0.3811	−0.3906 to 1.1528	0.331
Stimulation current per day	−0.0005	−0.0021 to 0.0010	0.5111
No. of AEDs during HCVR testing	−0.1629	−0.3906 to 0.0647	0.1607
No. of AEDs tried lifetime	−0.0451	−0.1194 to 0.0292	0.2344
Use of SSRI/SNRI	−0.1872	−0.7654 to 0.3910	0.5258
History of OSA	0.4871	−0.1986 to 1.1728	0.1639
History of depression	0.0579	−0.4454 to 0.5613	0.8215
Baseline $ETCO_2$ (+1) ***	−0.1007	−0.1510 to −0.0504	<0.0001
	Multivariate model		
Case vs control	−0.5998	−1.0470 to −0.1526	0.0058
BMI (+5)	0.3657	0.2040 to 0.5274	< 0.0024
Baseline $ETCO_2$ (+1)	−0.0749	−0.1232 to −0.0265	<0.0024

* association between every change in age of 10 years and the HCVR slope

** association between every 5-unit change in BMI and the HCVR slope

*** association between every 1-unit change in $ETCO_2$ and the HCVR slope