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Case Report

New onset syncopal events following vagus nerve stimulator implantation might be key to preventing vagus nerve stimulation-induced symptomatic bradycardia — A case report and review

Hiroko Kato [b], Ayataka Fujimoto [a,*], Tohru Okanishi [a], Ryo Sugiura [b], Kentaro Ijima [a], Hideo Enoki [a]

[a] Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital, Japan
[b] Department of Cardiology, Seirei Hamamatsu General Hospital, Japan

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ABSTRACT

Purpose: To identify risk factors for VNS-associated arrhythmia.
Methods: A literature review identified 14 papers with 21 patients. We compared patients with VNS associated arrhythmia (arrhythmia group, n = 22) and patients without VNS associated arrhythmia (control group of our VNS implanted patients, n = 29).
Results: New onset syncopal events following VNS placement were seen in the arrhythmia group ($p < 0.001$).
Conclusion: Even though arrhythmia could be symptomatic, most cases associated with syncope were treated as new-onset epileptic seizures with adjustment of anti-seizure drugs. To detect cardiac asystole during VNS treatment, clinicians should be alert to the possibility of new onset syncopal events that differ from habitual seizures.

1. Introduction

Vagus nerve stimulation (VNS) therapy has been widely used. The most common stimulation-associated side effects are voice alteration, hoarseness, throat and neck pain, headache, cough, and dyspnea [1]. The most severe side effects of VNS therapy are bradycardia and cardiac asystole [2]. We encountered a patient with symptomatic bradycardia due to VNS who underwent cardiac pacemaker (PM) implantation and resolved symptomatic bradycardia. We hypothesized that risk factors for such bradycardia may exist, identification of which would help prevent VNS-induced critical arrhythmia.

2. Methods

A search for medical papers on PubMed and Google Scholar using the key words “vagus nerve stimulation”, “arrhythmia”, and “bradycardia” revealed 14 papers with 21 patients, not including our case.

We compared patients with VNS-induced arrhythmia (arrhythmia group, n = 22) and patients without such arrhythmia (control group, n = 29). The control group comprised all other patients who underwent VNS implantation in our facility between 2011 and 2014 and had not developed any VNS-induced arrhythmia for more than four years. Inclusion criteria for the control group were: 1) >4 years follow-up; and 2) surgery performed by the same surgeon (AF).

We statistically compared each factor between groups, using the Mann–Whitney rank-sum test and Fisher's exact test as appropriate. Statistical significance was set at $p < 0.05$. All analyses were performed using Sigma Plot 14 software (Systat Software, San Jose, CA).

3. Case report

A 43-year-old, right-handed man was admitted to our hospital due to loss of consciousness (LOC). At 17-years-old, he experienced a right temporal lobe contusion in a motor cycle accident. The patient started to exhibit focal impaired awareness seizures and focal to bilateral tonic-clonic seizures at 27 years old, followed by psychiatric symptoms and accompanying delusions and hallucinations from his early thirties. Temporal lobe epilepsy and epileptic psychosis were diagnosed in his early thirties and he was followed by a local psychiatrist. As his epilepsy had been drug-resistant, he was referred to our hospital. He was on topiramate 200 mg/day, carbamazepine (CBZ) 400 mg/day and risperidone 4 mg/day when he visited our hospital. He underwent long-term video-electroencephalography (VEEG), brain magnetic resonance imaging (MRI), ^{123}I-iomazenil single-photon emission computed tomography (IMZ-SPECT), 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), and neuropsychiatric tests. Interictal VEEG showed frequent epileptiform discharges in the right frontotemporal

* Corresponding author at: Seirei Hamamatsu General Hospital, 2-12-12 Sumiyoshi, Nakaku, Hamamatsu, Shizuoka 430-8558, Japan.
E-mail address: ataka_fuji@sis.seirei.or.jp (A. Fujimoto).

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area, while ictal VEEG right frontotemporal rhythmic activities with short periods of loss of awareness and mouthing movements followed by postictal confusion. MRI, FDG-PET and IMZ-SPECT were all concordant, showing a right mesial temporal seizure onset zone. We diagnosed right temporal lobe epilepsy. At 36 years old, he underwent right frontotemporal invasive monitoring. The invasive monitoring showed a seizure onset area arising from the mesial temporal lobe, quickly spreading to the right frontal area. We therefore performed right temporal lobectomy. Weekly seizures reduced to monthly. VNS treatment was then started at 37-years-old for residual seizures. Intraoperative VNS stimulation did not induce any electrocardiographic (ECG) changes. Generalized seizures disappeared, but from 40 years old he sometimes exhibited sudden LOC, differing in character from the habitual seizures. At first, we regarded these sudden LOC as epileptic seizures and continued to adjust the regimen of anti-seizure drugs (ASDs). As he exhibited sudden LOC and fell weekly at this point, he was placed under VEEG monitoring, which revealed bradycardia for several seconds during sleep. As VNS reproducibly caused arrhythmia including bradycardia, atrioventricular (AV) block, and a short period of cardiac arrest (Fig. 1), symptomatic bradyarrhythmia with third-degree AV block induced by VNS was diagnosed and a PM was implanted. When implanting the PM, we conducted an electrophysiological study while changing the output for VNS and decided to position the pacemaker where it would not over-sense stimulation from VNS.

At this time, the patient was on levetiracetam (LEV) 3000 mg/day, CBZ 400 mg/day and risperidone 4 mg/day. Since implantation of the PM, the patient has remained free of sudden LOC.

3.1. Ethics approval

Written informed consent for publication of case details was obtained from our patient. This study was approved by the ethics committee at Seirei Hamamatsu General Hospital.

4. Results

All clinical data are shown in Table 1. The 22 patients [1–14] in the arrhythmia group comprised of 8 females and 16 males (mean age, 39 years; range, 8–59 years), while the 29 patients in the control group comprised of 11 females and 18 males (mean age, 31 years; range, 9–52 years). The arrhythmia group was significantly older than the control group ($p = 0.038$). Epilepsy onset occurred at an older age in the arrhythmia group (mean age, 35.8 years; range, 2–59 years) than in the control group (mean age, 8.6 years; range 0.3–43 years; $p < 0.001$). The output current of VNS was significantly lower in the arrhythmia group (median, 1.0 mA) than in the control group (median, 2.0 mA; $p < 0.001$). The duty cycle of VNS was lower in the arrhythmia group (median, 10%) than in the control group (median, 15%; $P = 0.028$). No significant difference in the number of times an ASD was used ($p = 0.097$) was apparent between groups. However, concomitant psychiatric disorder ($p = 0.034$) and usage of psychotropic drugs ($p < 0.001$) were both significantly more frequent in the arrhythmia group than in the control group. New onset syncopal events differing in character from the habitual seizures were seen only in the arrhythmia group ($p < 0.001$).

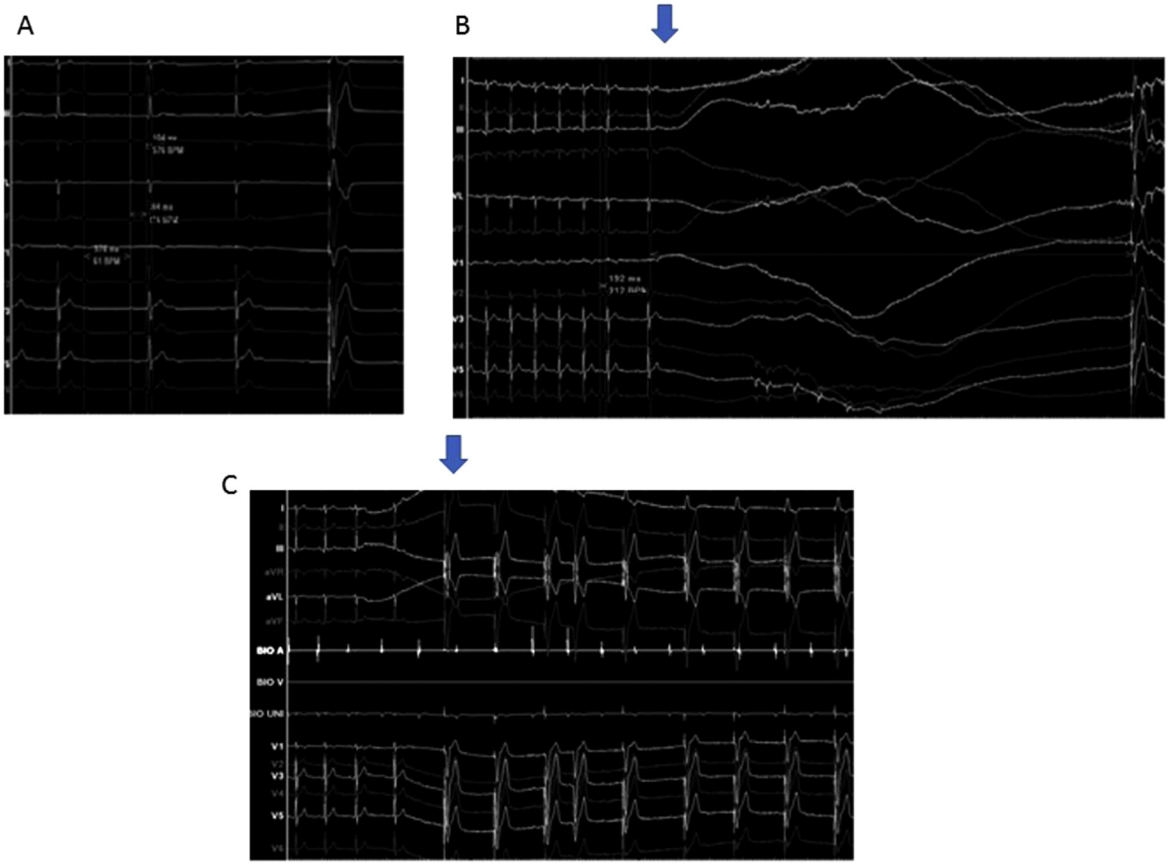

Fig. 1. A) Critical atrioventricular (AV) block did not occur when vagus nerve stimulation (VNS) was turned off, according to pressure in bilateral carotid arteries. B) With the 1.75-mA output current of VNS, cardiac arrest (arrow) lasted 15 s. C) Complete AV block (arrow) was also detected.

Table 1
Reviewed patients and our case. Onset, epileptic seizure onset; VNS, vagus nerve stimulation; CPS, complex partial seizure; GTC, generalized tonic–clonic seizure; sGTC, secondary GTC; LOC, loss of consciousness; n.a, not available; ASD, anti-epilepsy drug; LEV, levetiracetam; PER, perampanel; CBZ, carbamazepine; OXC, oxcarbazepine; LTG, lamotrigine; CLB, clobazam; CLZ, clonazepam; PB, phenobarbital; PRM, primidone; VPA, valproate; TPM, topiramate; PHT, phenytoin; FMB, felbamate; BZP, benzodiazepine; GBP, gabapentin; ZNS, zonisamide; DM, diabetes mellitus; AV block, atrioventricular block.

Author	Age [years]	Sex	Onset [years]	Age at VNS [years]	Main seizure	VNS induced symptoms	VNS output	Duty cycle	AED	Other medication	Concomitant symptoms	VNS
Tatum 1999	38	F	n.a	38	CPS	n.a	1 mA	n.a	PHT/lorazepam/tiagabine	n.a	Anxiety	Deactivation
	57	M	n.a	57	Partial seizure	n.a	1 mA	n.a	LTG/PRM	Olanzapine/sertraline	Encephalopathy/depression/ alcohol abuse/	Deactivation
	38	M	n.a	38	Partial seizure	n.a	1 mA	n.a	CBZ/VPA/vigabatrin	n.a	Left encephalomalacia	Deactivation
	42	M	n.a	42	Partial seizure	n.a	>1 mA	n.a	TPM/FMB/PHT/PB	Trifluoperazine	Encephalopathy/multiple handicaps/autism	Dose decreased
Asconape 1999	56	M	n.a	56	CPS	n.a	1 mA	n.a	LTG/PRM	Olanzapine/sertraline	Encephalopathy/pulmonary disease/hypertension	Deactivation
Ali 2004	53	M	4	53	GTC/atypical absence	n.a	1 mA	n.a	CBZ/VPA	n.a	Encephalopathy	Deactivation
	40	M	n.a	40	GTC/CPS/myoclonus	n.a	1 mA	n.a	CBZ/VPA	n.a	Encephalopathy	Deactivation
	42	F	n.a	42	CPS	n.a	1.25 mA	n.a	GBP/CZP	DM/vasodilator	Diabetes/hypertension/1st degree AV block	Dose decreased
Srinivasan 2004	40	F	n.a	40	Partial seizure	Nausea/vomiting/ lightheadedness/palpitation	n.a	n.a	n.a	n.a	n.a	Continued
Adresh 2007	32	F	14	32	CPS	n.a	1 mA	n.a	OXC/FMB	n.a	n.a	Continued
	52	M	n.a	52	Partial seizure	n.a	1 mA	n.a	PHT/TPM	n.a	Depression/1st-degree AV block	Continued
	59	F	2	59	GTC	n.a	1 mA	n.a	CBZ/VPA/CLB	n.a	Bitemporal sclerosis	Continued
Koeing 2008	8	F	3 m	8	Multiple types	Improved	n.a	n.a	VPA/FMB/BZP	n.a	Respiratory sinus arrhythmia	Continued
Amark 2008	17	M	5 m	15	CPS	Sudden LOC uncontrollable fall	1.75 mA	10%	VPA/GBP/acetazolamide	n.a	n.a	Deactivation
Borusiak 2009	13	M	5	7	CPS without sGTC	Significant increase in seizure frequency	2.25 mA	10%	PB/FMB/ZNS	Calcium/vitamin D	n.a	Deactivation
Irarte 2009	47	F	12	38	CPS/status epilepticus	New events of dizziness, unsteadiness	1.75 mA	10%	PGB/CZP/LEV	n.a	Psychogenic non-epileptic spell	Deactivation
Clark 2012	13	M	2	2	GTC	Syncope/obtundation	1.25 mA	8%	CZP/ZNS/RFM	n.a	Septo-optic dysplasia	Revision/continued
Shanker 2013	55	M	n.a	47	Partial seizure/sGTC/drop attack	Sudden increase in frequency of atonic spells	2.25 mA	16%	LEV/PGB	n.a	Encephalopathy/cerebral anoxic brain	Deactivation
Schevchuck 2014	40	M	n.a	39	CPS without sGTC	New type of seizure	n.a	10%	LCM/LTG/LEV/PGB		Encephalopathy	Continued
Cantarin 2016	13	F	2	3	Drop attack/myoclonus	New attack with sudden fall/LOC	1.25 mA	10%	VPA	n.a	n.a	Dose decreased
Pascual 2015	56	M	9	42	CPS	Syncope/lightheadedness/LOC	2.75 mA	12%	LEV/TPM	Alprazolam	Anxiety	Deactivation
Our case	47	M	27	37	CPS	Sudden LOC with uncontrollable fall	1.75 mA	10%	LEV/CBZ	Risperidone	Epileptic psychiatric disorder	Continued with pacemaker

F, female; M, male; m, months; Onset, epileptic seizure onset; VNS, vagus nerve stimulation; CPS, complex partial seizure focal impaired awareness seizure; GTC, generalized tonic–clonic seizure; sGTC, secondary GTC (focal to bilateral tonic-clonic seizure); LOC, loss of consciousness; n.a, not available; AED, anti-epilepsy drug; LEV, levetiracetam; PER, perampanel; CBZ, carbamazepine; OXC, oxcarbazepine; LTG, lamotrigine; CLB, clobazam; CLZ, clonazepam; PB, phenobarbital; PRM, primidone; VPA, valproate; TPM, topiramate; PHT, phenytoin; FMB, felbamate; BZP, benzodiazepine; GBP, gabapentin; ZNS, zonisamide; DM, diabetes mellitus; A-V block, atrioventricular block.

5. Discussion

From our data and another study assessing the relationship between VNS and sudden unexpected death in epilepsy [15], the VNS dose and duty cycle themselves did not appear directly linked to arrhythmia. This stimulation might not directly affect cardiac conduction, but indirect stimulation of the central nervous system involving the cardiac conduction system might cause bradycardia. If the bradycardia had been induced by direct stimulation, the control group (which showed both higher output current and higher duty cycle) would have been expected to show a higher prevalence of arrhythmia. Ali et al. [5] speculated that activation of the afferent pathway for the left vagal nerve has wide-ranging effects on multiple systems and pathways, and may result in activation of multiple other synaptic pathways with influences on cardiac rhythm. This might be the mechanism underlying arrhythmia.

In this study, the arrhythmia group was significantly older than the control group. Arrhythmia associated with vasovagal syncope is reportedly seen most often in the adult population [16,17]. Increased hypersensitivity of the vagus nerve induced symptomatic arrhythmia even without relatively stronger stimulation in our case. We therefore suggest patients with VNS be monitored the long term. In the case of repetitive syncopal events seen, not only an ECG but also prolonged ECG using a Holter ECG or loop recorder are recommended [18].

Future work is needed to validate these findings from a multi-center reports with a greater number of patients.

6. Conclusion

Even though arrhythmia could become symptomatic, most cases were treated as new-onset epileptic seizures with adjustment of ASDs. To interrupt prolonged cardiac asystole in VNS treatment patients, clinicians should be alert to the possibility of new-onset syncopal events when they differ from habitual seizures.

Author contributions

Pacemaker implantation: HK and RS. Neurosurgical operation: AF. Acquisition of data: KI, HK and AF. Analysis and interpretation of data: AF, TO, and HE.

Conflict of interest

No funding was received for this research.

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