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Cardiac responses of vagus nerve stimulation: Intraoperative bradycardia and subsequent chronic stimulation

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Abstract

Objectives: Few adverse events on heart rate have been reported with vagus nerve stimulation (VNS) for refractory epilepsy. We describe three cases with intraoperative bradycardia during device testing.
Patients and methods: At our hospital 111 patients have received a VNS system. Intraoperative device testing is performed under ECG-monitoring. We reviewed the patients and their VNS-therapy follow-up outcome who experienced a change in heart rate, during device testing (Lead Test).
Results: Three patients with medically refractory epilepsy showed a bradycardia during intraoperative Lead Test. Postoperative the VNS-therapy started under ECG-monitoring. No change in cardiac rhythm occurred. Subsequent chronic stimulation is uneventful. All three have reduced seizure frequency. Two already have had their second implant, without the occurrence of bradycardia.
Conclusion: In case of intraoperative bradycardia VNS-therapy onset should be done under ECG-monitoring. Subsequent chronic stimulation is safe in respect to heart rate. Bradycardia during intraoperative device testing is no reason to abort the operation.

Keywords: Vagus nerve stimulation; Cardiac responses; Epilepsy; Seizure; Chronic electrical stimulation

1. Introduction

Bradycardia or even asystole have been reported in association with vagus nerve stimulation (VNS). Most of these events have occurred during intraoperative device testing (Lead Test) of the VNS pulse generator [1–3], and have often lead to the decision of the neurosurgeon to discontinue the VNS-system implant procedure. Implantation of a VNS-system for medically refractory epilepsy is a relatively routine operation for the neurosurgeon. But what should the neurosurgeon do when a bradycardia occurs during intraoperative device testing? Should he continue the operation or not?

Normally, the left vagus nerve is used for stimulation, because it contains mainly afferent cardiac fibers and therefore should have less effect on cardiac rhythm, in contrast to the right vagus nerve which has mainly efferent cardiac fibers. Vagus nerve stimulation experiments on animals and humans have shown profound effects on the sinoatrial and atrioventricular node and therefore on cardiac rhythm [4,5]. Others reported slight changes in cardiac autonomic regulation [6–8]. There are few reports on the effect of chronic vagus nerve stimulation in patients who experienced intraoperative bradycardia [1,9]. In our hospital, out of 111 patients, three experienced an intraopertive bradycardia during Lead Test. At this time it was up to the neurosurgeon to decide whether or not to continue with the operation. We would like to present these three patients with intraoperative bradycardia during VNS device testing, evaluate the VNS follow-up outcome and discuss possible mechanisms.

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Table 1
Patients' characteristics

	Mean	Standard deviation
Age at onset epilepsy	13 years	11
Years of epilepsy	25 years	14
Seizure frequency per month prior to VNS	56	105
Number AEDs prior to VNS	3	1
Age at vagus nerve stimulation	39 years	14

VNS, vagus nerve stimulation; AED, antiepileptic drug.

2. Patients and methods

Between July 1999 and July 2006, 119 VNS-systems were implanted in 111 patients, at our hospital, Medisch Spectrum Twente, Enschede. Patients' characteristics are shown in Table 1. MRI and EEG findings are listed in Table 2. Implantations were carried out according to protocol under full anaesthesia. All patients received lorazepam, thiopental, fentanyl and rocuronium during surgery. During the time of operation an ECG is being recorded to monitor cardiac rhythm. An intraoperative Lead Test with 1.0 mA current output, 500 μs pulse width and 20 Hz frequency, for approximately 20 s, is always performed for testing the pulse generator. Of these 111 patients, 3 patients experienced a clearly noticeable change in heart rate on ECG recording during this test. These intraoperative ECGs were seen by a consulted cardiologist. Initiation of VNS was done under ECG-monitoring. Initial stimulator parameters are: current output 0.25 mA, 250 μs pulse width and 20 Hz frequency. These three patients are described here in more detail, including their long-term follow-up of VNS (we have not published other papers based on these cases, some years ago).

Table 2
MRI and EEG findings

MRI findings	Number of patients
Normal	64
Temporal sclerosis	9
Multiple lesions/gliosis	8
Cortical malformation	8
Tumor	3
Vascular malformation	1
Loss of white matter	5
Not otherwise specified	13
Location of epileptic activity on EEG	
Generalized	10
Left temporal	19
Left frontal	2
Left parieto-occipital	1
Right temporal	10
Right frontal	4
Right parieto-occipital	2
Bilateral frontal	27
Bilateral temporal	6
Central	2
Left central	2
Right central	1
Unknown	25

3. Results

Patient 1 is a 32-year-old female, with medically refractory complex-partial seizures since age 14. Various EEG's showed epileptic activity in the right temporal region, but MRI did not show any structural lesions. She had no medical history of cardiac disease. Physical examination at first consultation was normal, blood pressure was 130/85 mm Hg and heart rate was 84 beats/min. At the time of implantation her current antiepileptic drugs (AED) were oxcarbazepine 1200 mg and felbamate 2100 mg.

In June 1999, a VNS-system was implanted. There were no side-branches noticed at inspection of the vagus nerve. During the intraoperative Lead Test of VNS her heart rate changed from 65 beats/min to a bradycardia of ∼43 beats/min during the period of stimulation. A second test resulted in a similar response, with 25 beats/min. Heart rate returned to normal, rapidly after stimulation and the implantation procedure was carried out as planned.

Postoperatively there were no complications. After 10 days VNS was initiated under ECG-monitoring. No cardiac effects were noted. She was evaluated by a cardiologist with a 24-h ECG monitoring and echocardiogram. There were no cardiac dysfunctions. Once, the patient reported a rebounce tachycardia when she interrupted stimulation for 10 min with the use of the magnet. This could not be reproduced under ECG monitoring at the hospital.

After 2 years, she had a seizure reduction of 50%. Stimulation parameters were: current output of 1.50 mA, pulse width 250 μs and was on the rapid cycle (7 s on/0.3 min off). After 6 years of VNS she still has a 50% seizure reduction compared to baseline. The patient reported that her seizures are less severe and that postictal duration is shorter. Furthermore, she is now able to live independently. Side effects are mild, and consist of hoarseness, coughing and paraesthesia during stimulation.

In 2006 she received a new stimulator, when the battery was depleted. This time, during the intraoperative Lead Test there were no changes on ECG.

Patient 2 is a 52-year-old male, with medically refractory partial seizures since age 6. No abnormalities were found on MRI. He had a medical history of depression and no cardiac history. Physical examination at first consultation was normal, with a blood pressure of 140/80 and heart rate of 60 beats/min. His current medication was phenytoin 375 mg and topiramate 500 mg daily.

In September 1999, a VNS-system was implanted. There were no anatomic variations of the vagus nerve. During intraoperative lead testing of the VNS ECG changes were noted, his heart rate changed from 52 to 40 beats/min for the period of stimulation. A second measurement showed a similar result. After the test the heart rate rapidly returned to normal.

The VNS-system implantation proceeded as planned. ECG was reviewed by a cardiologist, who noted a PR interval of 0.20 s. Further evaluation with 24 h ECG recording showed a first degree AV block (PR interval 0.23 s) during night time period with an episode of sinusbradycardia with a frequency of 54 beats/min, considered as normal variation.

Strong voice alterations were reported within 3 days following implantation. Laryngoscopy confirmed a left vocal cord paralysis. At the patient's request the initiation of VNS was postponed until his voice improved. Three month after implantation the voice regained its strength and the hoarseness diminished. VNS was initiated. Under ECG registration no cardiac effects were recorded. During current ramp-up the patient did not report any cardiac side effect. Repeated ECG's and evaluation by a cardiologist with echocardiogram, and 24-h ECG recording, revealed no cardiac dysfunction. There were no signs left of a first degree AV-node block.

Currently, after 6 years, the patient has the following stimulation parameters; 2.00 mA, 250 μs, 30 Hz, on/off period 30 s/3 min. After 6 years of VNS seizure frequency has decreased by 35%. The patient claims to have less severe seizures and also his postictal period diminished, especially with the magnet activation of the stimulator. Patients or caregivers can activate an extra, on-demand stimulation by passing a magnet over the pulse generator. This can be used in order to abort or prevent a seizure.

In 2005 he received a new pulse generator due to battery depletion. During the Lead Test no cardiac changes were noticed on ECG.

Patient 3 is a 59-year-old female, with tonic clonic seizures from age 2, probably as a result of meningitis. EEG showed frontotemporal epileptic activity. MRI showed bilateral temporal sclerosis. From age 30, seizures became more frequent and severe. Antiepileptic drugs were not well tolerated. There was no cardiac history and physical examination at first consultation was normal.

In January 2002, a VNS-therapy system was implanted. At the time of implantation she used carbamazepine 1000 mg, valproate 900 mg and clobazam 20 mg for her epilepsy. No anatomical variation of the vagus nerve was described by the surgeon. Heart rate prior to stimulation was 63 beats/min. On intraoperative testing of the VNS-system (Lead Test) a "bradycardia" of 54 beats/min was recorded. A second test showed the same effect on heart rate. After the test the heart rate returned to normal. The VNS-system implantation was preceded as planned.

Eleven days after surgery VNS was initiated, under ECG monitoring. No changes in cardiac rhythm were detected upon initiation of therapy. During current ramp-up the patient did not report any cardiac side effects. After 3 years of VNS she had a seizure frequency reduction of 80%, with the following parameters; 1.25 mA, 500 μs, 30 Hz, on/off period 30 s/3 min.

We found no difference in patient's characteristics, MRI, EEG and ECG of the three cases compared to the other 108 patients receiving VNS, which could explain the bradycardia.

4. Discussion

Out of 111 patients who received a VNS-therapy system at our hospital, only three patients experienced a clearly noticeable slowing of their heart rate, during intraoperative device testing (Lead Test). The bradycardia only occurred during device testing, and heart rate returned to normal when stimulation stopped. In all three patients it was decided not to abort the operation and to implant the VNS-system. The stimulator was switched on, under ECG-monitoring 2 weeks later. No bradycardia or other changes in heart rate were noted. At long-term VNS follow-up, all three had a significant seizure frequency reduction, and experienced other benefits with the aid of VNS. Two patients received a new pulse generator without any complications concerning cardiac response.

The mechanism of intraoperative bradycardia with VNS is still unclear. Few studies described changes in heart rate with VNS-therapy [6,7] or showed profound effects on the sinoatrial and atrioventricular node cardiac rhythms [4,5]. Most studies showed no cardiac effects of VNS [8,10,11]. However, the patients in these studies were already implanted with the VNS-system at time of ECG-monitoring, this in contrast to our patients who experienced intraoperative bradycardia. Both animal and human studies have demonstrated that there may be a role for the immune system in the modulating effect of VNS (which might subsequently alter cardiac rhythm). VNS is associated with a marked increase in the plasma levels of pro- and anti-inflammatory circulating cytokines like Il-6, TNF-alpha and TGF-beta [12,13]. These changes are unlikely to be non-specific inflammatory reactions and may be therapeutically relevant. Although this is very interesting to investigate, retrospectively there is no method to evaluate in what way this might have been an influence on our cases.

One explanation for the observed bradycardia concerns electrical stimulation of the small myelinated 'B-fibers'. These fibers carry parasympathetic motor information responsible for cardiovascular changes, such as bradycardia or prolongation of P-R and S-T intervals [10,14]. These studies showed that increasing stimulation current output and duration, recruits vagal fibers in the order A, B and then C. They concluded that stimulation of the human vagus with the VNS-system is not strong enough to activate B or C-fibers. In their attempt to induce respiratory responses of C-fiber activation, they found no changes in ECG, heart rate or arterial pressure, which are typical for B-fiber activation [10,14]. However, because the patient population already received VNS for 2–12 months, they suggested a habituation to persistent vagus nerve stimulation and central adaptation to brief vagus nerve stimulation [14]. The effects found in our three patients can be explained by B-fibers activation during intraoperative Lead Test. Central adaptation can explain why bradycardia did not re-occur during the Lead Test after surgical replacement of the pulse generator several years later.

In literature a number of other possibilities have been considered to explain VNS induced bradycardia. Asconapé et al. hypothesized that the electrodes could have been placed

on the cervical cardiac branches of the vagus nerve. They reported one case of bradycardia and eventually an asystole intraoperatively during device testing. In that patient the stimulator was not implanted [2]. This explanation does not seem to relate to our patients, since bradycardia did not occur postoperatively, nor at the second implantation. However, in patients both the superior and inferior cervical branches may be stimulated. Activation of all cardiac efferent fibers could then possibly result in asystole. Although cranial parasympathetic nerves are located proximal to the electrode, stimulation of these fibers can anatomically also be explained by stimulating the recurrent laryngeal nerve which give rise to cranial cardiac nerves [15]. The finding that one of the three patients reported a cardiac rebounce tachycardia during post surgical follow-up, when chronic intermittent stimulation was temporarily halted using the magnet, supports the idea that a large number of cardiac fibers is being stimulated in this patient.

Asconapé et al. also suggested impairment of the conduction mechanism by saline solution used during surgery and pooling of blood. During intraoperative stimulation of the vagus nerve, current may spread and could possibly stimulate the cardiac nerves located next to the vagus [2]. This temporarily altered conduction mechanism can also explain the intraoperative occurrence of bradycardia in our patients and those cases reported by others [1,3,9]. However, the rebounce tachycardia during VNS follow-up in one of our patients contradicts this.

Effects of vagus nerve stimulation on the sympathovagal balance during full anaesthesia are still unclear. One patient with an asystole during Lead Test was reported to be associated with anaesthesia. However, no explanation is given for this association [16]. Dardis et al. describe one episode of asystole followed by bradycardia during Lead Test and recommend deactivating the device during any subsequent anaesthesia of VNS patients [17]. One study describes the exact anaesthesia (propofol, remifentanil and vecuronium bromide) used in eleven patients. Bradycardia occurred in one patient. They reported no association with anaesthesia [18]. In our three patients we did not find an association with anaesthesia and bradycardia, because all patients received the same anaesthesia.

Intraoperative VNS Lead Test may rarely result in a bradycardia. Our data might suggest that intraoperative bradycardia does not have to be a reason to abort implantation. We do however, suggest starting VNS under ECG monitoring when intraoperative bradycardia has occurred. Furthermore, long-term VNS in these patients does seem safe in respect to heart rate.

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