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Generator replacement in epilepsy patients treated with vagus nerve stimulation

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End of battery life (EOBL)

Summary

Purpose: In epilepsy patients treated with vagus nerve stimulation (VNS), the occurrence of end of battery life (EOBL), when the generator will no longer deliver any stimulation, was investigated with regard to seizure control. EOBL is preceeded by end of effective stimulation (EOES) when irregular stimulation may occur.
Methods: In 14/78 patients, treated with VNS at Ghent University Hospital, generators were replaced at different times following EOES or EOBL. We retrospectively analysed the time of occurrence of EOES and EOBL and seizure control before and after generator replacement.
Results: EOES or EOBL was indicated by loss of seizure control, decreased perception of stimulation and recurrence of depression in 3, 3 and 1/14 patient(s), respectively. In 2 and 1/14 patient(s), EOBL and premature generator failure, respectively, were detected during routine check-up at the epilepsy clinic. In 4/14 patients, generator replacement was performed before estimated EOES.

Pre-replacement seizure control could not be regained in 2/14 patients in whom replacement had been postponed for several months. Estimation of EOES and EOBL occurrence proved difficult in individual patients.
Conclusion: EOES or EOBL may be indicated by loss of seizure control, decreased or irregular perception of stimulation by the patient and loss of other VNS-induced effects. Postponing generator replacement may result into permanent loss of seizure control. In responders we suggest generator replacement before EOBL. Our results call for performance of prospective studies in larger patient groups that may eventually lead to general guidelines on the indication and timing of generator replacement.

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Introduction

Vagus nerve stimulation (VNS) is a symptomatic add-on treatment for patients with medically refractory epilepsy that reduces seizure frequency with more than 50% in 30% of patients and is available in epilepsy centers worldwide since 1997.[1–3] Patients with a more than 50% reduction in seizure frequency are designated as responders. More than 20,000 patients are currently being treated with VNS for epilepsy. Recent pilot studies have also shown promising results in medication resistant depression and Alzheimer's disease.[4,5]

VNS is performed by implanting a pulse generator (VNS Therapy System, Cyberonics, Houston, Texas, USA) in a subcutaneous pouch in the left chest area. The pulse generator is connected to a helical electrode that is wound around the left vagus nerve in the upper neck. In general, intermittent stimulation is used with standard stimulation parameters (pulse width: 500 μs; frequency: 30 Hz; duty cycle: on-time: 30 s, off-time: 300–600 s). Patients or caregivers are also supplied with a magnet to administer additional stimulations by applying it over the implanted generator, which in a substantial number of patients interrupts an ongoing seizure, or upcoming seizure in case of an aura.[6] VNS has mild stimulation-related side effects such as hoarseness and voice change that most often occur during the ramping-up period of the output current and during the stimulation on-time.[1–3]

The battery life of the generator depends on the generator model, the programmed stimulation parameters and the lead impedance values of the stimulation electrode (normal values: <1–8 kΩ). The generator model 100 was the first model developed for human use with an expected battery life of 4–8 years. It has been replaced by the smaller model 101 available since 2001 with an expected battery life of 8–12 years. Model 102 is the most recently marketed even smaller device and has an expected battery life between 6 and 11 years. When a new battery is required, the whole generator is replaced to prevent opening the hermetically sealed titanium case and to avoid contact between body fluids and generator components with the risk of inducing a rejection reaction. The electrode is usually left in place.

Patients who underwent generator replacement have been mentioned in efficacy and safety reports.[7] In the randomized controlled trials, the high number of patients who underwent replacement and stayed on the treatment was considered a reflection of the excellent tolerability as well as efficacy of the treatment.[3] The issue of generator replacement and battery life has been addressed in only a few reports. There is relatively little information on prediction of battery life in individual patients and there is no consensus on the indication for replacement, e.g. in patients with a seizure reduction of <50% or in non-responders who may benefit from VNS in a different way such as an increase in the seizure-free interval, a decrease in seizure severity or duration or improved mood. As VNS is considered to be a symptomatic treatment, seizure recurrence or loss of beneficial effects can be expected when the battery of the generator expires. In a group of 12 patients, seizure recurrence after end of service due to battery expiration was reported.[8] Following 18 months of stimulation, there was a 2-week interval after end of service before seizure rate returned to pre-VNS numbers. Tatum et al. described a group of 18 patients who underwent generator replacement and found that seizure increase or changes in seizure pattern often indicated battery failure.[9]

Currently, there are only limited reports or guidelines in the literature with regard to the indications and optimal timing for generator replacement.

Methods

Since March 1995, 78 patients have been treated with VNS in the Reference Center for Refractory Epilepsy at Ghent University Hospital in Belgium. All patients had refractory complex partial or generalized epilepsy and were included in the presurgical evaluation program that has been described previously.[10] All patients were shown to be ineligible for resective surgery and subsequently underwent implantation with the VNS Therapy™ System (model 100 or model 101). The surgical procedure was performed under general anaesthesia during a 48-h admission in the neurosurgery department. During the implantation procedure the generator circuitry as well as the lead impedance was tested. The stimulator was activated 2 weeks postoperatively at the epilepsy clinic using standard stimulation parameters (pulse width: 500 μs, frequency: 30 Hz, time on/off: 30 s/600 s) and an initial output current of 0.25 mA.[11] The output current was gradually increased every 2–3 weeks up to patient's tolerance or until seizure control was reached. Patients were provided with a magnet to allow additional stimulations in case of an aura or in case of a seizure being observed by a caregiver. When stable regimens of stimulation were achieved patients were followed-up at the epilepsy clinic every 3–4 months.

When *end of battery life* (EOBL) of the generator is reached, the pulse generator will no longer deli-

ver any output, the patient will not feel stimulation and telemetric communication with the pulse generator using the programming wand is no longer possible. However, before EOBL is reached, there is a time span when the battery nears depletion. For the purpose of this study we defined this period as *end of effective stimulation* (EOES). In the variable time period of days to months between EOES and EOBL, the pulse generator can still be interrogated but may provide 'unscheduled' stimulation as stated in the manufacturer's manual.[12] The generator replacement procedure consists of disconnecting the generator from the electrode, removing it in its whole and replacing it by a new device that is reconnected to the electrode. The electrode usually stays in place. The replacement procedure is generally performed under local anaesthesia in the operating theatre and lasts for approximately 1 h.

The generator is accessed through a 4—5 cm incision subclavicularly in the scar tissue of the first generator implantation. A subcutaneous area of a few square centimeters exposing the proximal insertion of the electrode into the generator is carefully dissected. The generators are generally found to be surrounded by strong connective tissue. In this way, a pouch is formed around the stimulator that allows the device to be explanted easily. The electrodes are disconnected from the generator using the provided screwdriver and reconnected to a new device. Following replacement, according to the manufacturer, output current should be increased again gradually during a ramping-up period starting from 0.25 mA.[13]

The first generator models (model 100) with serial number under 10.000 have no specific features that allow physicians to anticipate EOES or EOBL when interrogating the device with the available programming wand. It is recommended by the manufacturer that patients should be instructed to activate the pulse generator manually with the magnet on a daily basis to test for the presence of perceptible stimulation. Patients should contact a physician when the stimulation is no longer felt.[12,13] The physician can then confirm EOBL using the programming wand.

In generator model 100 with serial numbers above 10.000 as well as in model 101 and model 102, a built-in feature called the 'elective replacement indicator' (ERI) is available. It provides a warning period prior to EOBL of the device. The time period between the ERI warning and the actual EOBL is very variable depending on the programmed stimulation parameters and lead impedance and may be very short, e.g. 1 week. The manufacturer does recommend prompt replacement when the ERI is shown by the laptop software.[13]

It is unclear however, how soon EOES follows the ERI warning, or whether the two are synonymous. Generally, in our patients, at 4 years of follow-up after the initial implantation date, when EOES or EOBL could be expected, the frequency of the clinic visits was intensified to once every 2 months.

In responders (>50% seizure frequency reduction) replacement was planned immediately following EOES or EOBL. In non-responders (<50% reduction in seizure frequency), individual cases were considered and benefits were discussed with the patients or caregivers. In some cases seizure frequency was closely observed during the months following EOBL without changing AED regimens. In case of a significant increase in seizure frequency generator replacement was planned.

Since October 1999, generator replacements have been performed in 14/78 patients. We compared the different approaches in these patients and correlated them with seizure control before and after generator replacement.

Results

In 14/78 patients treated at Ghent University Hospital generators were replaced. In 13 patients, replacement followed EOES or EOBL. In one patient, the generator was replaced prematurely due to generator failure after 16 months of treatment. Table 1 shows the individual patient characteristics.

A number of 5/14 patients were reimplanted with the VNS Therapy™ model 100 with serial numbers above 10.000 and 9/14 received the VNS Therapy™ model 101. In two cases, the replacement procedure was performed under general anaesthesia on the patients' request. Peri-operative testing of generator circuitry and lead impedance was performed. In none of the patients was there an indication for electrode replacement at the time of the procedure of the generator replacement as intraoperative testing of the lead showed acceptable impedance values below 8 kΩ. There were no peri-operative complications. All patients were discharged from the hospital within 24 h. In 6/14 patients, the output current was programmed at similar pre-replacement values 1 day postoperatively. In one patient, an output current of 0.5 mA (versus 2.5 mA pre-replacement) was programmed 1 day postoperatively. In 7/14 patients, output current was gradually ramped-up during the weeks following the generator replacement procedure.

Table 1 shows the pre- and post-replacement efficacy and output currents in each patient.

In three patients (UP, BIV, VA) EOES or EOBL was indicated by loss of seizure control. Two of these

Table 1 Patient characteristics, VNS efficacy and stimulation parameters before and after generator replacement.

pt	Gender	Age (years)	Seizure duration (years)	Follow-up (months)	History	Seizure type	CPS/month before VNS	CPS/month after VNS before generator replacement	CPS/month after generator replacement	Output current before generator replacement (mA)	Output current after generator replacement (mA)
UP	M	33	22	101	Febrile seizures, head trauma	CPS + SG	8	0	4	2.75	2.25
VD	F	30	4	101	Head trauma	CPS ± SG/SPS	3	0	0	2.25	1.25
BIV	M	35	12	95	Head trauma	CPS ± SG	4	0	0	1.75	1.75
VDC	F	29	18	94	Encephalitis	CPS ± SG	40	25	25	2.5	2.5
SP	M	30	18	88	Premature birth, callosotomy	CPS ± SG/SPS	4	2	2	2.5	2.75
HF	M	19	18	88	Febrile seizures	CPS + SG	4	<1	0	2.5	0.5[a]
BI	F	21	18	81	Febrile seizures, head trauma	CPS ± SG/SPS	4	0	0	1.5	1.5[a]
JA	F	31	9	78	Febrile seizures	CPS ± SG	16	3	3	2	2[a]
BJ	F	24	23	76	Febrile seizures, encephalitis	CPS ± SG	35	25	45	3	3
VJC	F	43	35	69	Meningitis with right frontal brain abcess	CPS + SG	2	0	0	1.5	1.25[a]
VC	M	20	6	65	Meningitis, head trauma	CPS	4	2	2	2.75	2.5[a]
DKE	F	12	5	60	None	CPS ± SG	12	6	6	2.25	2.25[a]
DK	F	28	26	48	Lennox–Gastaut syndrome	CPS ± SG	150	60	60	1.75	1.75[a]
VA	F	22	16	43	Surgery for left temp lesion	CPS	10	4	4	2	2

pt: patient; CPS: complex partial seizures; VNS: vagus nerve stimulation; mA: milliamperes; SG: secondary generalisation; SPS: simple partial seizures.

[a] Stimulation reinitiated 1 day postoperatively.

patients had experienced long-term seizure freedom.

Exactly 4 years following initial implantation, patient UP reported the occasional recurrence of epigastric auras and the feeling that a stimulation train was initiated but abruptly stopped after a few seconds. At that time, the pulse generator could still be interrogated for three more days before EOBL occurred. Replacement of the generator was postponed for 6 months after EOBL due to financial problems at a time when VNS was not yet reimbursed in Belgium. Two months after EOBL, the patient had a generalized tonic clonic seizure (GTCS) and seizure frequency increased up to 2 GTCS per month over a time period of 6 months. Eventually, a public charity provided a grant and the generator was replaced. Output current was gradually increased until 2.75 mA but seizure control could not be regained. Moreover, the patient could not tolerate this original output current due to neck muscle pain especially during night time. Output current was reduced to 2.25 mA which resulted in relief of the side effects. Seizure frequency further increased to 4 GTCS per month and in the meantime the patient was admitted for an episode of convulsive status epilepticus. Topiramate and levetiracetam were added to his drug regimen without achieving any improvement in seizure frequency or severity at the time of this analysis.

In patient BIV, family members had noticed short-lasting and infrequent break-through episodes of loss of awareness and asked whether this could be due to EOES. This was exactly 5 years following initial implantation. The generator could still be interrogated. Two months later, EOBL was reached. When reimbursement was granted 3 weeks later, replacement was performed. Postoperatively one more CPS was reported. Output current was reinitiated at 1.75 mA over a time period of several weeks without any CPS or VNS-related side effects occurring.

Patient VA noticed an increase in CPS from 4/month to 7/month after 2 years and 10 months of treatment with VNS on rapid cycling for 2 years. MRI was planned to investigate the status of the intracranial astrocytoma. Before this procedure was performed, the generator was interrogated at the epilepsy clinic and indicated EOBL. Two months earlier, the generator had been interrogated normally. MRI showed no changes in the intracranial lesion. The generator was replaced 1 month later. After ramping-up to previous output current, seizure control was regained.

In two patients (VDC, BJ) with a $<$50% reduction in seizure frequency, generator replacement was postponed following EOBL detection at the epilepsy clinic. During further follow-up seizure frequency and severity increased and both patients underwent replacement of the generator. In patient VDC seizure frequency increased to prestimulation frequency over 4—6 months. Levetiracetam was tried without success. After 12 months, generator replacement was performed and a reduction of seizure frequency was reached after several weeks to 25 CPS/month on a stimulation parameter scheme similar to the one before replacement. In patient BJ, seizure frequency and severity (recurrence of secondary generalized convulsions) significantly increased up to 45 seizures per month over 2 months time compared to 25 seizures before replacement of the generator. Following reimplantation 1 month later, output current was increased over several weeks up to 3 mA without improvement in clinical efficacy at follow-up 17 months later.

In one patient, recurrence of a depressive episode indicated EOBL. Patient VD was free of complex partial seizures (CPS) but still had simple partial motor seizures (SPS) of the left hand. The patient had last visited the epilepsy clinic 5 years following initial implantation when pulse generator communication was still possible. She was then lost in follow-up for a period of 10 months. Due to the recurrence of a major depressive episode she was admitted to a psychiatric hospital and treated with antidepressant medication. CPS had not reoccurred nor had the frequency of SPS increased. Pulse generator interrogation at this time revealed EOBL. Generator replacement was performed 4 weeks later and output current gradually increased. The patient was much more sensitive than before (throat ache and hoarseness) to the stimulation side effects, and it took 3 months before an output of 1.25 mA could be reached. In the meantime, she had recovered from her depression and antidepressant medication was tapered. The patient remains free of CPS.

In the remaining eight patients, the generator replacement period was covered without changes in seizure frequency. In three patients, a decrease of stimulation perception indicated EOES. In patient BI, this occurred 5 years after initial implantation. Telemetric communication with the generator was still possible indicating EOES. The generator was replaced after a few days. No change in seizure control occurred and output current could be reinitiated at 1.5 mA during the postoperative day. In two patients (SP, HF), the generators could no longer be interrogated indicating EOBL. In both patients, the generators had been interrogated normally 2 months before.

In patient SP, initial implantation was performed 3 years and 11 months earlier; in patient HF 6 years

earlier. Both patients were reimplanted 1 month following EOBL. In SP seizure control was maintained and output current reinitiated over several weeks. Patient HF had a 90% reduction in seizure frequency with the first generator and was put on 0.5 mA the day following the replacement operation. Since that day and for about 15 months, he has remained seizure-free. So far, output current has not been further increased.

In four responders (JA, VJC, VC, DKE), generator replacement was performed before any signs of EOES were present. Factors taken into account were the time of service after initial implantation, lead impedance values, programmed stimulation parameters, use of magnet and estimated battery life based on the tables in the Physician's Manual.[12] Generator replacement was performed after 72, 63, 61 and 59 months of follow-up, respectively.

Table 2 gives an overview of the time periods and seizure frequency evolution during treatment with the initial generator and following replacement of the generator. It also shows the estimated duration without stimulation before generator replacement and the time to recurrence of seizures during this interval.

Discussion

Over the past decade, it has become clear that VNS is an efficacious treatment in a substantial number of patients with refractory epilepsy who are left with few therapeutic alternatives if surgery is not an option or has not been successful. VNS is an add-on treatment in patients treated with one or more antiepileptic drugs. The precise mechanism of action of VNS in suppressing seizures remains to be elucidated.[14] Some hypotheses such as VNS-related changes in neurotransmitter release and thalamic cerebral blood flow have been postulated.[15,16] VNS is generally regarded as a symptomatic treatment. Increase in clinical efficacy with longer follow-up has been demonstrated.[2,3] This may be due to VNS-related long-term changes in the central nervous system as shown by PET and SPECT studies and may reflect a central modulatory effect of VNS rather than a purely seizure suppressing effect.[17,18]

There are indications that seizure frequency may suddenly increase even during a short period of interruption of stimulation for the purpose of performing magnetic resonance imaging.[19] One report in the literature describes increased seizure frequency 2 weeks following EOBL.[8]

All these facts imply that when EOES or EOBL is reached, the decision as to whether and when the generator needs replacement has to be considered in light of the achieved clinical efficacy with the initial device. Until now, no specific guidelines are available for this crucial decision in the ongoing and strongly individualized treatment that has sometimes taken the treating physicians years to establish.

In the first patients treated with VNS and included in the EO1 and EO2 open trials, two interesting facts occurred that may help to document unanswered questions with regards to this issue.[20] First, the design of the study consisted of alternating 4–8 weeks stimulation periods with 4 weeks control periods during which stimulation was interrupted. Secondly, in 9 of the first 10 patients, breakage of the wires of the electrode occurred resulting in unexpected interruption of stimulation. Uthman et al. describe five patients who had electrode breaks after 10–20 weeks of implantation.[21] In three responders, seizure rate had gradually recurred to baseline. In two patients, seizure control was regained within 8 weeks after repair of the electrode. In one patient, a seizure reduction of 32% had been achieved 4 weeks following the repair but no further follow-up was not reported. In one non-responder, who did report decreased seizure severity and duration, this effect was reported to be regained after electrode repair and an additional 30% seizure reduction occurred 8 weeks later. It is not described in detail but the statement suggests that the effect on seizure severity and duration had also been lost following electrode break. In 1993, in a follow-up report, Uthman et al. describes a case report that illustrates the time relationship between stimulation periods, control periods without stimulation, electrode breaks, battery depletion and seizure outcome.[20] In a patient with >50% seizure frequency reduction, control periods were characterised by a doubling of seizure frequency. Following the lead break, seizure frequency returned to baseline after 4–8 weeks. Following repair, seizure control was regained although it is not clear over what time period this happened. After this, the battery depleted after 1 year of service. Erroneous continuous stimulation at 10 Hz occurred during 2 weeks. The patient restarted having SPS and 3 weeks later there was a dramatic increase in CPS. After the generator was replaced, seizure control was regained.

Although our patient group is small, it is surprising that two patients, of whom one was a clear responder, have not regained seizure control following generator replacement. Our data suggest that a longer time span without stimulation may be associated with an increased risk of not regaining seizure control. Even if VNS provokes long-term changes, it

Table 2 Time periods and changes in seizure frequency with the first generator, following replacement of the generator and during the time period without VNS.

Patient	Time until initial improvement with first generator (months)	Time until stable seizure frequency with first generator (months)	Time until generator replacement (months)	Follow-up after generator replacement (months)	Estimated duration without VNS before generator replacement (months)	Change in seizure frequency during time without VNS	Estimated time until change in seizure frequency during time period without VNS (months)
UP	3	2[a]	54	41	6	Increase	2
VD	1.5	1.5	71	10	≥1	No	—
BIV	1[a]	1[a]	63	26	1	Increase	Unknown
VDC	5	7	74	14	12	Increase	4
SP	6	1	48	34	1—3	No	—
HF	1	16	73	9	1—3	No	—
BI	1[a]	1[a]	60	16	0	No	—
JA	6	6	74	4	0	No	—
BJ	3	12	59	11	3	Increase	2
VJC	<1[a]	<1[a]	63	6	0	No	—
VC	3	6	61	4	0	No	—
DKE	6	12	59	1	0	No	—
DK	3	14	16	32	Unknown	No	—
VA	10	12	35	8	2	Increase	1

[a] Seizure free.

cannot be considered a curative treatment. There seems to be a certain safety margin during which breakthrough auras and infrequent seizures occur. This is probably due to the fact that during EOES, stimulation is not stopped abruptly but rather gradually in contrast to the situation where the generator is suddenly put in the off-mode, e.g. for the purpose of performing MRI. Apart from the fact that seizure control is lost, it is currently unclear why it cannot be regained after reinitiation of VNS. Since follow-up time after generator replacement in our patients clearly exceeds the time interval to initial response to VNS with the first generator, it seems unlikely that seizure control will be regained after longer follow-up. One similar case was reported by Ben-Menachem et al.[2] In a patient with primary generalized epilepsy who had a >75% decrease in seizures with VNS, the battery expired and was replaced 2 months later. During that time and the following weeks, increased generalized tonic seizures resulted in status epilepticus and eventually death. Analogous problems arise in medical therapy. It is well known that in individual patients previously successful antiepileptic treatment does not guarantee efficacy in a second trial later during life. Only controlled studies can clarify this matter, as the major confounding factor to be considered in refractory patients is the natural history of epilepsy.

In the physician's manual, the manufacturer provides approximate battery lives for each available VNS Therapy™ model. However, the expected time of EOBL covers a wide span of several years. The manufacturer also lists different values of battery life correlated to specific stimulation parameter combinations and lead impedance values and also approximate time intervals between EOES or ERI notification and EOBL. Especially in patients with high output currents (>2 mA) and/or relatively high lead impedance values (>3 kΩ) and/or high duty cycles, the time between EOES or ERI notification and EOBL can be very short. There is some evidence in the literature that high duty cycles with off-times ≤1.1 min (rapid cycling) may result in a significant improvement in clinical efficacy in a subgroup of patients initially resistant to VNS.[22] In many patients, over the years different stimulation parameter regimens and duty cycles have been tried, so estimation of battery life in an individual patient proves difficult (Table 3). In one of our patients, 2 years of rapid cycle stimulation clearly reduced battery life to less than 3 years. Moreover, there is a wide variability in magnet use among patients. It is unclear to what extent total number of extra stimulations should be taken into account when estimating battery life in an individual patient.

Lead impedance is clearly an important factor that has also to be taken into account when battery life is being considered. Usually, lead impedance testing is performed perioperatively but it is not regularly performed during follow-up clinic visits. However, there are no reports in the literature suggesting that there is an increase in lead impedance during long-term VNS. Considering the fact that EOES may be accompanied by the delivery of unreliable output current, reliable impedance testing at this time may not be possible.

EOES can be suspected when irregular stimulation is felt by the patient. However, a substantial number of patients with long follow-up do not feel stimulation on a regular basis or at all. The manufacturer suggests using the magnet feature to check daily functioning of the generator. This implies that the magnet output current be set to a value that causes a perceptible but not uncomfortable sensation in the throat. It is not always possible to fine-tune output current and control side effects in such a desirable way. Sometimes there is no intermediate output current between 'no side effects' and 'uncomfortable side effects' such as throat pain. Patients who use the magnet primarily in case of an aura are likely to prefer efficacy without side effects.

When the magnet is mainly used in case of GTCS, higher output currents are generally not a problem during the seizure. When used outside an epileptic episode, however, this may cause clear side effects. Moreover, standard on-time for the magnet is usually 60 s versus 30 s on-time in the automatically programmed duty cycle. This longer on-time may prolong discomfort in some patients.

VNS is often used in patients who have both epilepsy and mental retardation, e.g. Lennox–Gastaut syndrome. These patients often cannot report side effects or they produce little spontaneous speech so that voice changes cannot be appreciated when the magnet is applied. In order to be able to evaluate EOBL, high output currents would have to be administered causing more serious and obvious adverse effects such as choking or coughing.

With regards to generator replacement in responders (>50% reduction in seizure frequency) and non-responders (<50% reduction in seizure frequency), no guidelines are available. From our own experience, we are of the opinion that it might be beneficial to responders, especially in seizure free patients, to anticipate EOBL and perform generator replacement before any signs of EOES have been reached. The benefit of continued seizure control in these patients is balanced by the cost of losing several months of battery life.

Table 3 Comparison of observed end of effective stimulation and end of battery life and predicted battery life.

Patient	Output current before generator replacement (mA)[a]	Magnet output current (mA)	Use of magnet	EOES (years)	EOBL (years)	Lead impedance[b] (kΩ)	Predicted battery life[c] (years)
UP	2.25	0	—	4	4	3—5	4.9—4.3 (output current of 2 mA)
VD	2.25	0	—	Unknown	5.8[d]	3—5	4.9—4.3 (output current of 2 mA)
BIV	1.75	1.75	Frequently, mean: 1/day	5	5.1	3—5	4.9—4.3 (output current of 2 mA)
VDC	2.5[a]	0	—	Unknown	5.1	5—8	4.3—3.8 (output current of 2 mA)
SP	2.5[a]	2.75	Frequently, mean: 1/day	Unknown	3.9	3—5	4.9—4.3 (output current of 2 mA)
HF	2.5	0	—	Unknown	6	<1	4.9 (output current of 2 mA, lead impedance of 3 kΩ)
BI	1.5	0	—	5	Unknown	3—5	4.3—3.8 (output current of 2 mA)
JA	2.5[a]	2.5	Frequently, mean: 1/day	Unknown	Unknown	<1	4.9 (output current of 2 mA, lead impedance of 3 kΩ)
BJ	3[a]	2.25	<1/month	Unknown	4.6	<1	4.9 (output current of 2 mA, lead impedance of 3 kΩ)
VJC	1.5	0	—	Unknown	Unknown	<1	5.5 (output current of 1 mA, lead impedance of 3 kΩ)
VC	2.75	2.75	Seldom	Unknown	Unknown	3—5	4.9—4.3 (output current of 2 mA)
DKE	2.25	2.5	1/week	Unknown	Unknown	3—5	4.9—4.3 (output current of 2 mA)
DK	1.75	1.75	Frequently, mean: 1/day	Unknown	Unknown	<1	4.9 (output current of 2 mA, lead impedance of 3 kΩ)
VA	2[e]	2.25	Seldom	Unknown	34	3—5	4.9—1.9

mA: milliamperes; EOES: end of effective stimulation; EOBL: end of battery life; kΩ: kiloOhms.

[a] Other parameters standard with 5% duty cycle (on/off, 30/600 s) except for patients in whom rapid cycle was tried for several months without additional improvement.

[b] Lead impedance testing performed at 1.0 mA, 500 μs and deducted from physician's manual model 100—101, Table 10, p. 55.

[c] Closest possible deduction from listed tables in the physician's manual model 100—101, Table 14, pp. 64—65 (for model 100 with serial numbers <10.000, values only available for output currents of 1, 2 mA for lead impedances ≥3 kΩ, duty cycles of 10, 30, 50%).

[d] Approximate value as patient had been lost in follow-up for 10 months.

[e] Other parameters standard with 5% duty cycle (on/off, 30/600 s) except for patient on rapid cycle for 2 years (duty cycle > 50%).

VNS also provides beneficial side effects such as an antidepressant activity, mood improvement, enhancement of recognition memory and reduced daytime sleepiness in epilepsy patients.[5,23,24] These effects should also be taken into account when generator replacement becomes an issue. Even in patients in whom VNS does not have a clear anti-epileptic effect but a positive influence on mood and behaviour, generator replacement should be seriously considered.

In non-responders, it seems acceptable to assess changes in seizure frequency during the months following EOES. It should be taken into account however that if seizure frequency increases, it may not always be possible to easily regain control using the same stimulation parameters. Currently, the number of patients we have described is too small to identify any predicting factors for not regaining previous seizure control.

Ramping-up of the output current seems to become more difficult with an increasing time delay between EOBL and generator replacement. Two of our patients did not tolerate previously well-tolerated output current values. This finding was recently reported by Ponticello et al.[25] especially in patients with higher pre-reimplant current settings and also by Tatum et al.[9] It has been hypothesized that stimulator output current diminishes during the time between EOES and EOBL, resulting in stimulation with lower output currents during a variable period of time.[25] When generator replacement is performed before any signs of battery depletion appear, output current can usually be reinstalled immediately. Also the effect of a greater stimulus strength provided by the newer generator models has been proposed.[9]

On the basis of the detailed evaluation of our initial patients, we try to follow a clinically and economically plausible strategy for future generator replacement in a larger patient group. The magnet provides a useful feature to predict EOES in some patients, but cannot be relied on exclusively. The follow-up frequency of patients is increased a few months before the time of earliest expected battery failure has been reached. Specifically, seizure-free patients or patients that respond well to VNS are encouraged to increase the frequency of their follow-up visits. Generator replacement in these patients is planned before any signs of EOES are present, to avoid the risk of recurrent seizures or losing other beneficial side effects such as mood improvement. Especially in patients who carry a model 100 without the ERI feature this might be done weeks to months before the earliest expected EOES.

In non-responders, generator replacement is a more controversial issue. The preferred strategy could be to postpone replacement in order to evaluate possible changes in seizure frequency during several weeks following EOBL. Based on this assessment the decision to replace or remove the device can be made. The decision should take into account that regaining pre-replacement seizure reduction, even when that reduction was modest, is not always possible.

Conclusion

In patients treated with VNS, seizure control can be lost acutely or gradually following EOES or EOBL. From this report, it appears that once seizure control is lost, it cannot always be regained after generator replacement. In order to prevent this avoidable risk, an effort should be made to estimate battery life in individual patients. Defining and predicting the exact time of occurrence of EOES proves difficult. From our initial experience in this small group of patients, we suggest to perform generator replacement in responders at the time corresponding to the shortest predicted battery life before EOES or EOBL is reached. In patients with high output currents ($>$2 mA) and/or relatively high lead impedance values ($>$3 kΩ) and/or high duty cycles the time period between EOES or ERI notification and EOBL is expected to be short. In non-responders, delaying the decision to replace the generator might be a reasonable option. Frequent follow-up of these patients to monitor changes in seizure frequency and severity, and to determine whether any other beneficial effects of VNS have been lost, may help to establish the need for generator replacement. Also, in these patients, the time interval between EOES and/or ERI notification and EOBL should be monitored to guide the timing of future generator replacements in these and other patients. From these initial observations, we hope to encourage prospective collection of data on generator replacement in larger patient groups including children. This may allow meaningful statistical analysis and formulation of specific guidelines on this issue.

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