Palliative Surgical Techniques (VNS, Callosotomy)

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Introduction

While most patients with epilepsy can be managed medically, up to 30% of epilepsy patients have medically refractory epilepsy (MRE) (Kwan and Brodie 2002), defined as resistance to two or more antiepileptic drugs, appropriate for epilepsy type and adequate dosing, either in monotherapy or combination, without significant seizure

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improvement (Jadhav 2012). Most MRE patients are candidates for curative or palliative surgical treatment. When an epileptic onset zone can be identified, resection can result in a cure (seizure freedom). If resective surgery is not an option, then palliative (to make less harmful or harsh) (Palliative 2016) surgery may prove beneficial in reducing seizure burden and seizure-related injuries. In this chapter, we will discuss epilepsy surgery techniques with palliative intent: Corpus Callosotomy and Vagus Nerve Stimulation.

Corpus Callosotomy

Brief History

After observing a reduction in generalized seizure activity in two patients with callosal tumors, and two cases of callosal vascular insult, van Wagenen and Herren introduced corpus callosotomy in 1940 as a treatment for reducing generalized convulsive seizures (van Wagenen and Herren 1940). Simultaneously, Erickson (1940) demonstrated the role of the corpus callosum as a major pathway for generalization of experimentally induced focal epilepsy. Interest in corpus callosotomy reemerged in the 1960s when Bogen and Vogel published data on the clinical and neuropsychological outcomes after callosotomy. Since then, numerous studies regarding the indication and outcomes of corpus callosotomies have been published.

Patient Selection

Prior to considering a corpus callosotomy as palliative intervention, patients should undergo a tailored comprehensive epilepsy evaluation. This entails prolonged video electroencephalogram monitoring and various neuroimaging modalities, including: 3-Tesla magnetic resonance imaging (3 T MRI) of brain, F18-positron emission tomography (FDG-PET), ictal and interictal single photon emissions computed tomography (SPECT), and magnetic encephalogram (MEG). The subtracted ictal SPECT coregistered to MRI (SISCOM) was applied to further visualize hyperperfusion for seizure localization. In addition, it is desirable to perform neuropsychological testing prior to surgical intervention. Antiepileptic medications are optimized by an epileptologist, and surgery is considered after failure of two or more antiepileptic drugs, suitable for epilepsy type, and completion of epilepsy evaluation.

Improved surgical outcomes over the years have been attributed to advances in noninvasive presurgical evaluation to identify epileptogenic lesions. For instance, the use of stronger MRI magnets, more intricate FDG-PET scans and incorporation of magnetic source imaging, fMRI, MEG into the presurgical evaluation improves identification of epileptogenic focus and important functional cortex (Hemb et al. 2010; Lin et al. 2011; Wu et al. 2006; Chandra et al. 2006).

Once identified as candidates for this procedure, patients should be counseled about the potential risks and benefits of corpus callosotomy, as well as the risks and benefits of other therapeutic options, including further resective surgeries post CC, other surgical intervention, further medication trials, and ketogenic diet if applicable. In addition, surgical candidates should also be informed of the long-term outcome data on seizure control that are available, including the possibility that some patients may initially have seizures and become seizure free after a few months, while other patients who are initially seizure free may experience late seizure recurrence. This approach will ensure transparent communication and realistic expectations.

Indications

Corpus callosotomy (CC) is traditionally used as a palliative treatment for medically refractory generalized epilepsy. With improved understanding of epilepsy and surgical intervention, the indications for corpus callosotomy have expanded to include individuals with simple and complex partial seizures of multifocal origin, generalized

intractable seizures with no epileptogenic focus and/or not amenable to focused resection (Graham et al. 2016; Maehara and Shimizu 2001; Spencer et al. 1988; Tanriverdi et al. 2009; van Wagenen and Herren 1940; Andermann 1992; Andermann et al. 1987; Rayport et al. 1983). CC is a well-established treatment for patients with drop attacks, where 88.2% had a desirable reduction in seizure burden observed post CC (Wilson et al. 1978). Additionally, a general reduction in generalized tonic-clonic seizures of 50% has been observed in a third of patients (Maehara and Shimizu 2001), while patients with partial seizures who underwent CC demonstrated minimal to no improvement (Palliative 2016; Maehara and Shimizu 2001; Iwasaki et al. 2016).

Genetic Epilepsy: Over the past 10 years there has been an explosion in the understanding of the genetic causes of medically refractory epilepsy (MRE). Most of the genetic MREs are generalized and progressive. With the exception of tuberous sclerosis complex, resective surgery has not been effective for genetic MRE patients. CC is increasingly recognized as a palliative surgical intervention for these patients and can decrease seizure burden, which reduces cognitive decline associated with progressive neuronal loss seen in recurrent seizures (Pitkänen and Sutula 2002).

Refractory Status Epilepticus: Status epilepticus (SE) is a life-threatening emergency. Typically aggressive medical management can control SE. Rarely, SE persists in spite of aggressive medical management. If the epileptiform discharges are generalized, then emergent CC can be used to abort seizure activity (Greiner et al. 2012). Locally, a 20-year-old female with developmental delay and medically refractory epilepsy presented in refractory status epilepticus (RSE). EEG demonstrated bilateral generalized epileptiform discharges, warranting an emergency anterior 2/3 CC. She continued to have subclinical and clinical seizures, with intracranial EEG revealing isolated and rhythmic spikes in the right frontal region. Complete CC and bilateral multiple supbial transections were performed, with resolution of seizures. This demonstrates the emerging role of CC in management of RSE.

Anatomic Considerations

The corpus callosum is crucial in providing interhemispheric communication between the hemispheres of the brain. It is a large bundle of myelinated, with some nonmyelinated, fibers and is composed of the splenium (posterior), isthmus, body, rostrum, and genu (anterior). The body of the corpus callosum is arched with the genu continuing anteroventrally as the rostrum and the splenium overlying the midbrain (Waxman 2003). The corpus callosum is somatotopically organized so that the anterior fibers connect the frontal regions of the hemispheres and the posterior fibers connect the posterior regions. This results in specific regions of the corpus callosum correlating to modality-specific functions: the rostrum transfers higher cognitive information; the anterior midbody transfers motor information; the posterior midbody transfers somatosensory information; the isthmus transfers auditory information; and the splenium transfers visual information (Wong et al. 2006; Funnell et al. 2000). It is stipulated that the fiber tracts of the anterior half of the corpus callosum are responsible for generalization of seizure activity.

The corpus callosum is one of six midline commissural structures connecting the cerebral hemispheres. These include the anterior commissure, posterior commissure, hippocampal commissure, massa intermedia of thalamus, and fornix. The corpus callosum is the most significant in interhemispheric seizure generalization.

Surgical Technique

The patient is placed supine on the operating table with the neck slightly flexed. Mayfield fixation is utilized for patients greater than 5 years of age. Neuronavigation is preferred. A sinusoidal incision centered over the junction of the sagittal and coronal sutures is created (Fig. 1a), and the soft tissues elevated in a subperiosteal plane to expose the confluence of the sutures (Fig. 1b). Burr holes are created just behind and four centimeters anterior to the sutural confluence (Fig. 1c), and the

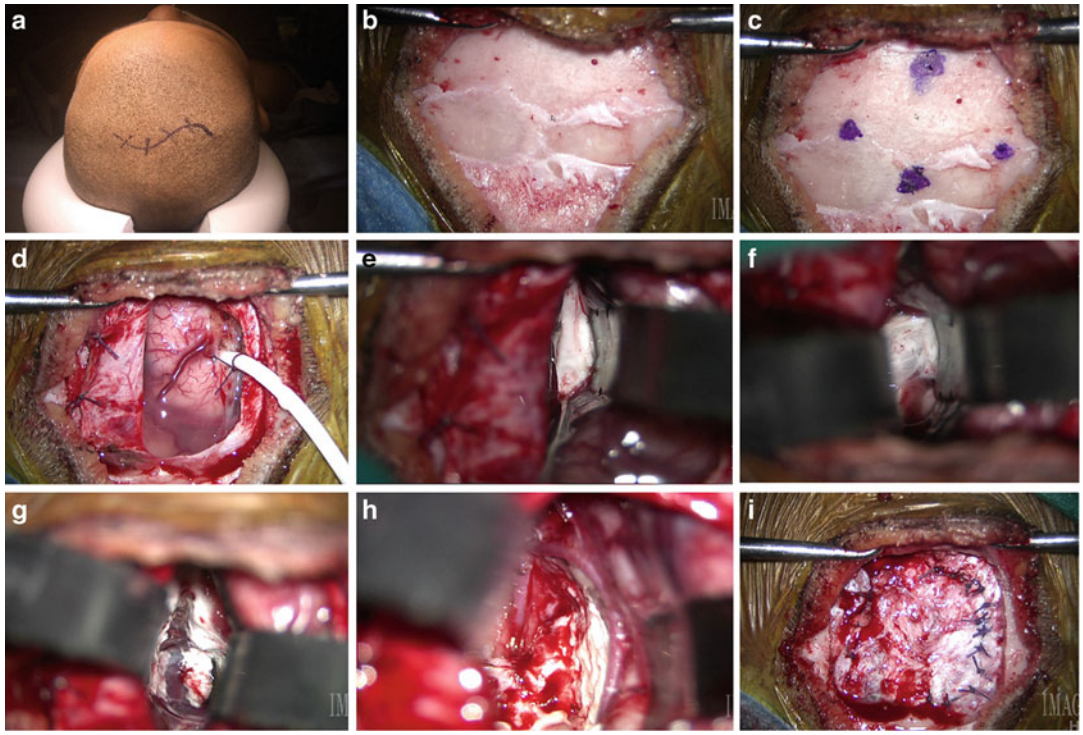

Fig. 1 Surgical technique for complete corpus callosotomy. (**a**) sinusoidal incision; (**b**) coronal suture (superior), sagittal suture (inferior); (**c**) sterile ink marking site for burr holes; (**d**) C-shaped opening, with dura reflected to the left; (**e**) glistening white corpus callosum; (**f**) dissection through corpus callosum with choroid plexus exposed superiorly; (**g**) dissection of the splenium, with exposure of the pia arachnoid mater; (**h**) distal anterior cerebral artery with branching pericallosal vessels at level of genu; (**i**) closed suturing of dura

dura is dissected free of the inner table of skull along the coronal sutures bilaterally. A bifrontal craniotomy is created, using a craniotome to connect the burr holes crossing the coronal sutures two to three centimeters to the left and right of midline. The bone flap is elevated to expose the dura overlying the superior sagittal sinus. A ventriculostomy is placed through a durotomy, and the catheter allowed to drain at the level of the dural opening throughout the procedure. Depending upon the venous anatomy, a dural opening is created either to the left or right of midline, extending from just lateral to the superior sinus anteriorly to a point just lateral to the superior sagittal sinus posteriorly. The dural flap is reflected away from midline to expose the superior falx (Fig. 1d). If possible, the cortical and bridging veins are preserved.

Using the operative microscope, retractors, and navigation, an interhemispheric approach is pursued to the body of the corpus callosum (Fig. 1e). The pericallosal vessels are identified, separated, and retracted gently. The mid-body of the callosum is divided to the ependyma of the ventricle. Working within the callosum, dissection is carried posteriorly through the splenium, to expose the arachnoidal planes overlying the great veins (Fig. 1f). Dissection is then redirected through the residual anterior body and splenium. The pericallosal vessels are followed as they curve inferiorly and posteriorly around the splenium (Fig. 1g, h). The superior rostrum is divided, and the dissection is then completed.

The retractors are removed, and the ventricles gently expanded with irrigation introduced through the ventriculostomy catheter. Once the dura has been closed (Fig. 1i), the ventriculostomy is withdrawn, the bone flap replaced, and the scalp closed.

The operative microscope should have a long focal length to allow visualization of the splenium

and surrounding structures. Long bipolar and long suction instruments are sometimes necessary for complete callosal division. The surgery can usually be completed in under 90 min.

Completion Callosotomy

If following a partial callosotomy, a second surgery to covert the incomplete disconnection to a complete one is deemed necessary, two approaches can be considered. The first is an extension of the division of the posterior callosal fibers using the same bifrontal approach outlined above. At re-operation, neuronavigation is particularly useful in defining the interhemispheric approach to the residual callosal structures. If the length of the patient's callosum is long and if difficulty was encountered completing the callosotomy using a frontal entry point, a posterior interhemispheric approach can be used. While division of bridging veins is usually well tolerated anterior to the coronal suture, it is poorly tolerated behind that structure. Preoperative planning with MRI sequences that allow veins to be well visualized is mandatory. Using navigation, an entry point can usually be chosen which allows exposure of the interhemispheric structures without disrupting bridging veins. The approach to the splenium is aided by navigation. Because completion of the callosotomy is critical in these cases, intraoperative imaging with DTI sequences is used to confirm adequate disconnection.

Figure 2 demonstrates diffusion tensor imaging (DTI) in a patient who underwent CC, with the intent of complete CC, where postoperative MRI and DTI demonstrated 90% completed transection. Due to ongoing seizures, the patient underwent a second surgery for completion of CC and became seizure free postoperatively.

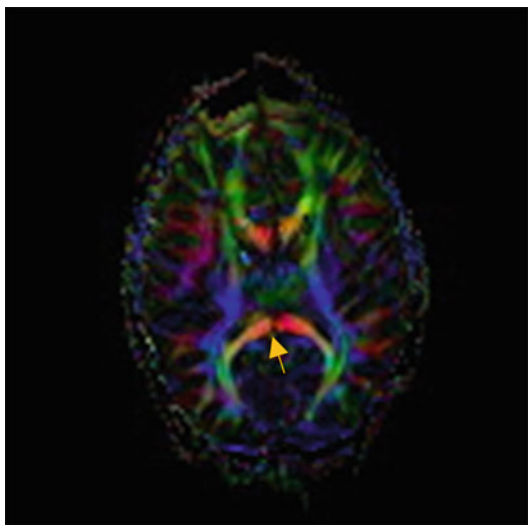

Fig. 2 Diffusion tensor imaging after incomplete corpus callosotomy. *Arrow (yellow)* show residual bridging fibers along the anteroinferior margin of splenium of corpus callosum and the hippocampal commissure

Postoperative Care

It is our practice to place all callosotomy patients on a 30-day course of Diamox. Steroids are tapered over 10–14 days.

Outcomes

The rationale behind corpus callosotomy is that by sectioning the corpus callosum, bilateral synchrony of epileptic discharges may be prevented, minimizing the frequency and severity of primary and secondary generalized seizures. Studies have demonstrated a dissociation between interictal EEG changes and post CC and surgical outcome, where, to a variable degree, there was a disruption of bisynchronus interictal discharges. Observed persisting bisynchrony rarely manifested in clinical seizures post CC. Additionally, ictal EEG changes of lateralization were observed in patients with clinical seizures post CC, which notably have been observed with better prognostic value than bilateral independent spike waves (Rayport et al. 1983; Iwasaki et al. 2016; Greiner et al. 2012; Spencer et al. 1993; Matsuzaka et al. 1999). In addition, because CC prevents rapid secondary bisynchrony and generalization of seizure activity, more recent studies have demonstrated that after complete CC a high proportion of patients demonstrate lateralization and/or localization (Oguni et al. 1994; Chen et al. 2015). In a

study of nine patients who underwent multi-stage surgical procedure using bilateral intracranial electroencephalogram (iEEG) monitoring before and after complete CC, patients demonstrated diffuse bisynchronous activity prior to complete CC. After complete CC, seizure onset zone was lateralized to one hemisphere in four patients, with further localization of a focal area being identified in four patients (Fig. 3). This facilitated second surgery in three patients who underwent functional hemispherectomy and four patients who underwent regional resection.

Figure 4 illustrates the change of bilateral iEEG findings between the two stages, where Panel a shows diffuse bisynchronous inter-ictal epileptiform discharges in stage 1, which lateralize and become independent from the right after complete CC (stage 2). Panel b shows a second patient with bilateral inter-ictal discharges with higher amplitude spikes in the right hemisphere (Stage 1), transforming to epileptiform discharges isolated to the right hemisphere arising from temporal lobe after complete CC.

The significance is paramount as complete CC can play a role in revealing a resectable epileptogenic focus.

The effect of this on overall daily function, as assessed by families, was reported in a study, where improvement was observed in 62% of patients after CC; improvements were noted in hyperactivity (93%), emotional well-being (42%), social function (36%), speech (21%), and memory (17%) (Maehara and Shimizu 2001). While corpus callosotomy has the potential to be curative for a select group of patients, the significant reduction in seizure frequency in patients with intractable epilepsy is paramount in improving both physical, psychological, and social wellbeing. In addition, the advancing role of CC in unveiling seizure localization for a second, potentially curative surgery is of expanding significance.

At present, debate on complete versus anterior 2/3 CC and the role is seizure control, postoperative neurological complication rate, and long-term outcome exists. The senior author has performed over 80 complete corpus callosotomies since July 2011. Complete CC might facilitate seizure lateralization better than anterior 2/3 CC (Tanriverdi et al. 2009; Chen et al. 2015), and more recent data has supported that anterior 2/3 CC is inferior to complete CC in seizure outcome for both generalized and focal epilepsy (Hemb et al. 2010; Maehara and Shimizu 2001; Spencer et al. 1988; Iwasaki et al. 2016; Jalilian et al. 2010; Pinard et al. 1999). In a systematic review of literature on CC outcomes in pediatric patients, complete CC was statistically more effective in reducing

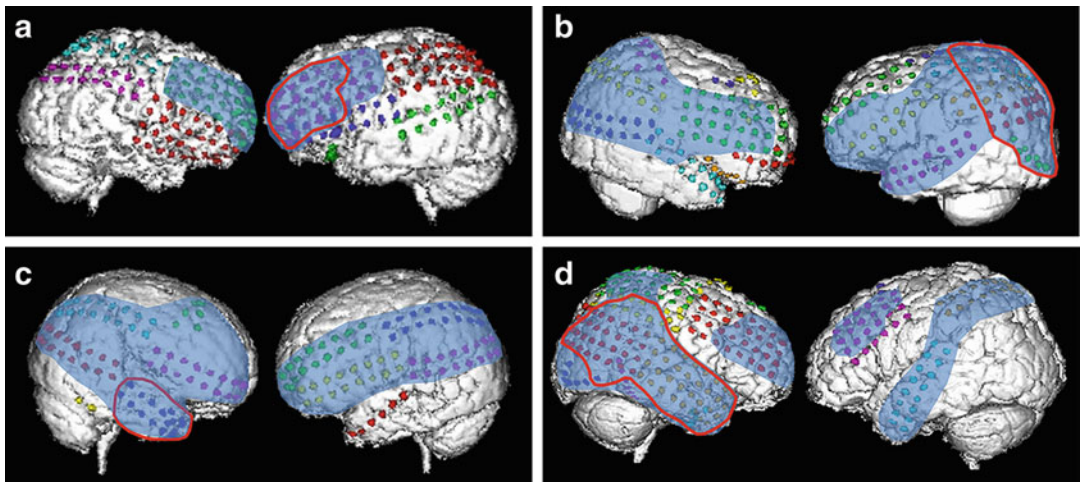

Fig. 3 Bilateral iEEG coverage and ictal onset zones before and after complete CC. (**a**) is Patient 1, (**b**) is Patient 2, (**c**) is Patient 7, (**d**) is Patient 8. The electrodes in *shaded area* indicate the ictal onset zone identified by bilateral iEGG in stage 1 and within *red* demarcation indicate the ictal onset zone in stage 2

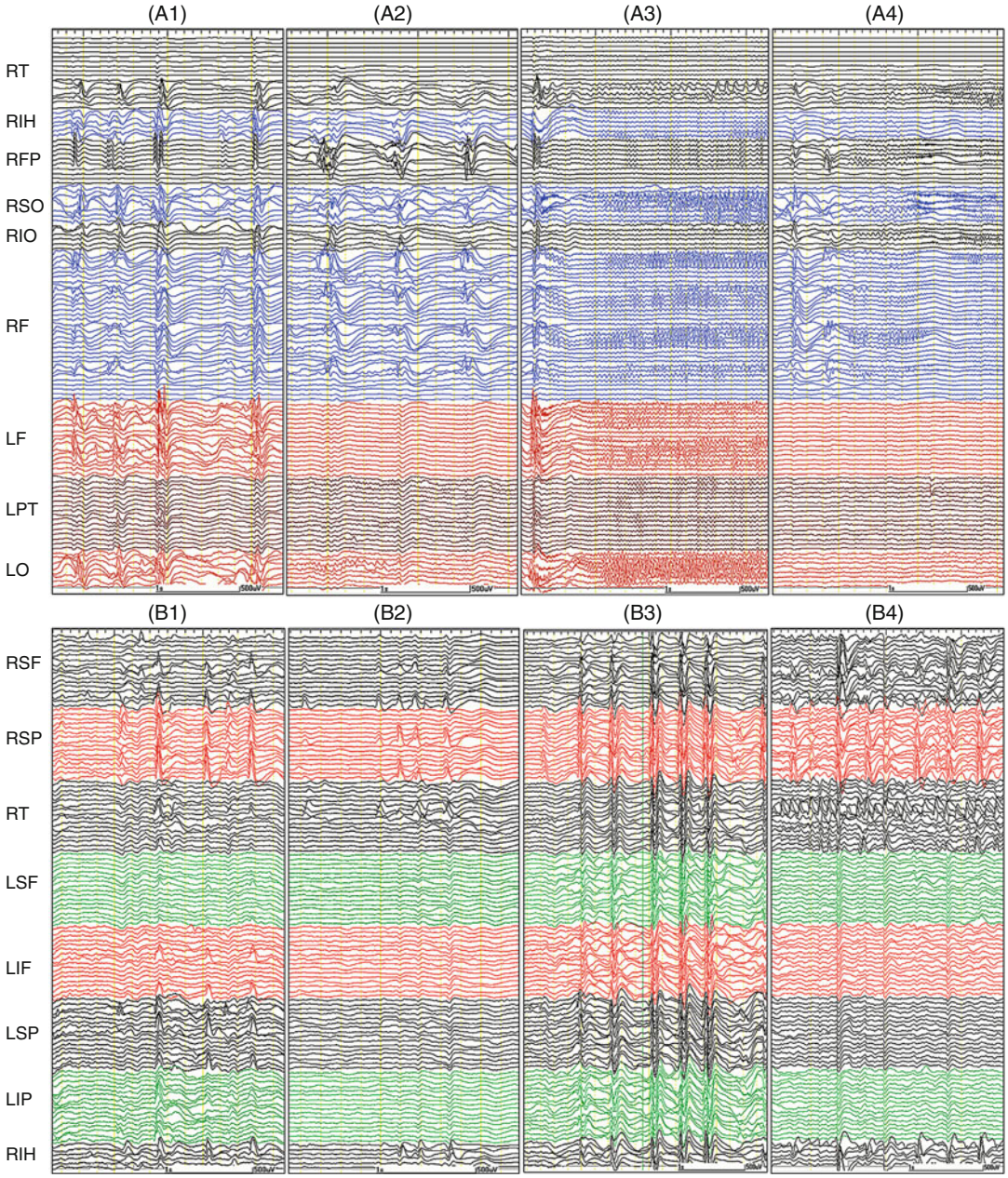

Fig. 4 Bilateral iEEG recordings before and after CC. Panel (**a**) is Patient 9 where (A1) shows inter-ictal recordings in stage 1, (A2) shows inter-ictal recordings in stage 2, (A3) shows ictal recordings in stage 1. (A4) shows ictal recordings in stage 2. Panel (**b**) is Patient 2 where (B1) shows inter-ictal recordings in stage 1, (B2) shows inter-ictal recordings in stage 2, (B3) shows ictal recordings in stage 1, (B4) shows ictal recordings in stage 2. L = left, R = right, S = superior, I = inferior, F = frontal, P = parietal, T = temporal, IH = inter-hemispheric

seizures (88.2%) compared to anterior 2/3 CC (58.6%) ($p = 0.049$) (Hemb et al. 2010). Studies have demonstrated that subjects who underwent anterior 2/3 alone or 2-stage complete CC had a less favorable outcome is seizure control compared to those who had a 1-stage complete CC

($p = 0.02$) (Rathore et al. 2007; Sorenson et al. 1997; Kasasbeh et al. 2014; Bower et al. 2013). Local data reviewed also demonstrated that five of seven patients who underwent anterior 2/3 CC required further surgical intervention to complete the CC due to no seizure reduction after anterior 2/3 CC. In all studies that compared complete CC to anterior 2/3 CC, improved outcomes in seizure reduction, especially drop attacks, behavior, attentiveness, and quality of life were reported. In addition, pediatric patients had a better seizure outcome after CC, compared to adult patients (Graham et al. 2016). Early intervention reduces the progression of epileptic encephalopathy, improving quality of life and lifespan of patients with MRE (Fernándes et al. 2015).

Debate still exists over the extent of callosal resection, side effect profile, and neuropsychological outcome post CC. However, improvements in quality of life, intelligence/development quotient, and parental quotient positively correlate with seizure outcome after CC (Graham et al. 2016).

Avoidance and Management of Complications

While previously neurological deficits after CC have attributed to hesitance in surgical resection, an increasing number of studies have demonstrated the effects to be temporary or treatable, with minimal risk of long-term surgical complications (Jadhav 2012; van Wagenen and Herren 1940; Hemb et al. 2010; Tanriverdi et al. 2009; Iwasaki et al. 2016; Jalilian et al. 2010).

Acute Complications

These include epidural hematoma, hydrocephalus, and infections including meningitis, osteomyelitis, and wound infection. In our series of >500 callosotomies, we have experienced two infections requiring bone flap removal and cranioplasty. To prevent infections, a broad spectrum antibiotic is administered prior to the incision being made. Intravenous dexamethasone may also be administered to reduce edema and prevent iatrogenic chemical meningitis.

One of our patients required a ventriculoperitoneal shunt following callosotomy.

Disconnection Syndrome

There are still discordant reports regarding the incidence of transient disconnection syndrome. A transient disconnection syndrome is found in up to one third of patients following surgery. This consists of a hemi-neglect which can take 12 h to become fully evident. While some studies have reported it to be more likely in complete CC than in anterior two thirds CC (12.5% vs. 0%; $p < 0.0001$) (Graham et al. 2016), other studies have reported that the incidence of disconnection syndrome is the same in patients who undergo anterior two thirds CC compared to those who undergo complete CC (Sorenson et al. 1997; Shim et al. 2008). Local experience supports the latter finding. In addition, it is widely accepted that the incidence of disconnection syndrome is less in the pediatric age group, supporting earlier surgical intervention, when applicable. Objects presented to only the nondominant hemisphere for language may not be reported verbally by the patient; for example, visual stimuli presented to the nondominant visual field is not reported by the patient, as the language-dominant hemisphere does not have access to that information. The nondominant hand does not respond reliably to verbal command, because the dominant hemisphere is less readily able to transfer information to the nondominant motor cortex (Asadi-Pooya 2008). However, most patients are unaware of the deficit. Transient apathy may be observed and is likely due to medial and convexity frontal lobe disconnections. Hemineglect may be observed and attributed to posterior corpus callosal interruption (Asadi-Pooya 2008; Cuckiert et al. 2006). The symptoms usually last weeks to months and recovery is supported by speech, physical, and occupational therapy. A speech therapy swallowing evaluation is required before oral feeding can resume. Younger patients tend to recover more rapidly than older patients, and those with a shorter seizure history recover more quickly than those with a longer duration of refractory epilepsy. Depending upon the physical

therapy assessment patients with a disconnection syndrome are discharged to in- or out-patient physical therapy. All of our affected patients have recovered.

Other neurological complications were equally likely, regardless of the extent of CC (15.3% in complete CC vs. 6.9% in anterior 2/3 CC, $p = 0.23$) (Graham et al. 2016).

Language Impairment and Transient Aphasia

Language disturbances are extremely rare but may occur following CC. A speech difficulty with sparing of writing (alexia without agraphia) may present and is attributable to buccofacial apraxia. A second language disturbance involves both speech and writing difficulties, and more commonly occurs in patients with language dominance in the right hemisphere. A final language disturbance that can occur post CC involves agraphia with intact speech, occurring in patients with language dominance in the left hemisphere or left-handed patients. These impairments are more commonly seen in patients with crossed cerebral dominance; communication and integration is interrupted after CC. This can occur secondary to traction on the supplementary motor area and/or diaschisis from disconnection (Shim et al. 2008; Cuckiert et al. 2006). Patients usually recover within 4 weeks, and symptoms diminish over time with rehabilitation. However, some cases with prolonged mutism have been observed. A rare subgroup of patients with bilateral-dependent speech can develop a permanent aphasia after corpus callosotomy. This has been demonstrated in patients following an infarction in the corpus callosum (Sass et al. 1990; Ishizaki et al. 2012; Saba and Blum 2014).

Conclusion

Corpus callosotomy is a safe and effective palliative surgical procedure for eligible patients with medically refractory epilepsy not amenable to focal resection. Recent reports suggest the earlier in the course of refractory epilepsy that the CC is performed, the better the outcome and the lower the risk of postoperative complications. The indication and acceptance of CC in its role of significantly reducing seizure burden is expanding, with CC being included as a feasible intervention in patients with refractory seizures.

Vagus Nerve Stimulation (VNS)

Brief History

In 1997 the Food and Drug Administration (FDA) approved vagus nerve stimulation (VNS) as a treatment modality for patients with medically refractory seizures. The concept of VNS dates back to the 1880s, where electrical vagal nerve and cervical sympathetic stimulation and carotid artery compression were used in the treatment of seizures (Lanska 2002). In 1938, Bailey and Bremer demonstrated desynchronization of orbital cortex activity with VNS therapy in a cat model (Bailey and Bremer 1938). A second study demonstrating the effects of VNS was conducted by Zanchetti et al. in 1952; using an isolated cat encephalon preparation, he observed that synchronous cortical activity, arising spontaneously in 5 of 15 animals, was reduced or eliminated by stimulation of the vagus nerve (Zanchetti et al. 1952). In the following decades, numerous experiments confirmed the potential of VNS to decrease epileptic activity in animal models. Based on these experiments, in 1985 Zabara proposed that if VNS is able to desynchronize electroencephalographic (EEG) activity, it might be effective in diminishing epileptic seizures. It was postulated that afferent vagal synapses reduce seizure activity through neurotransmitter modulation (Zabara 1985a, b). Subsequent animal studies supported Zabara's hypothesis and facilitated clinical trials to be performed in humans (Zabara 1992; Penry and Dean 1990).

Cyberonics, Inc. (Houston, TX), was founded in 1987 to develop VNS therapy in humans. In 1988, the first epileptic patient to undergo VNS therapy from the device became seizure free (Penry and Dean 1990). Five acute-phase clinical

trials analyzing the safety and efficacy of VNS therapy followed (Penry and Dean 1990; Utham et al. 1993; The Vagus Nerve Stimulation Study Group 1995; Handforth et al. 1998; DeGiorgio et al. 2000), which resulted in FDA approval of VNS therapy "for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures that are refractory to antiepileptic medications" (Cyberonics Inc 2016).

Cyberonics, Inc., compiled a registry recording long-term outcome of VNS therapy in patients. The registry included data from November 7, 1997, to April 1, 2003; patient enrollment was voluntary and data entry was provided by physicians. Data obtained demonstrated a median reduction in seizure activity of 46% ($n = 4448$) at 3 months, 57% ($n = 2696$) at 1 year, and 63% ($n = 1114$) at 2 years, in patients who received VNS therapy (Baumgartner and Von Allmen 2011). Favorable outcome in quality of life parameters have been reported in refractory childhood epilepsies, where verbal performance, alertness, motor and cognitive function, and behavior have significantly improved with VNS therapy (Hornig et al. 1997; Wilfong and Schultz 2006; Parker et al. 1999; Park 2003). Numerous studies have followed supporting the finding of VNS therapy as an effective tool to reduce seizure frequency in patients with intractable epilepsy and improve quality of life measures (Baumgartner and Von Allmen 2011; Helmers et al. 2002; MacLachlan 1993; Morris and Mueller 1999; Elliot et al. 2011; Uthman et al. 2004; Englot et al. 2011; Amar et al. 2008; Rvylin et al. 2014; Vale et al. 2011; Helmers et al. 2011; Saneto et al. 2006; Orosz et al. 2014; Renfro and Wheless 2002).

Patient Selection

Prior to considering VNS therapy in patients with medically refractory epilepsy, all patients should undergo a tailored comprehensive epilepsy evaluation at an epilepsy center. This entails a history, examination, video EEG, anatomic and/or functional imaging if applicable, and optimization of antiepileptic medication for epilepsy type by an epileptologist. Neuropsychological testing prior to surgical intervention is desirable. Surgery is considered after failure of two or more antiepileptic drugs, suitable for epilepsy type, and completion of epilepsy evaluation. VNS therapy is considered in patients with medically refractory epilepsy, and in patients with underlying genetic epilepsy, who are not resective surgery candidates and may benefit from this intervention. VNS therapy is rarely curative and therefore considered a palliative intervention. Seizure outcome in response to VNS therapy is variable and cannot be predicted; however, when effective it has significantly reduced seizure burden and the number of antiepileptic drugs, and improved patient quality of life.

All potential candidates for VNS implantation should be counseled about the potential risk and benefits of VNS therapy and alternative management options including corpus callosotomy, resective surgeries, antiepileptic medication trials, and if applicable ketogenic diet. Information on the long-term outcome data on seizure control should be made available to all surgical candidates; this should include the possibility that the effectiveness of the device and the time to witness effectiveness may vary in patients. This approach will ensure transparent communication and realistic expectations.

Additional indications of VNS therapy include its role as an adjunct to chronic or recurrent depression in patients 18 years or older, experiencing major depressive symptoms with an inadequate response to four or more appropriate antidepressant medications. Furthermore, an off-label indication of VNS therapy includes its use as an adjunct, to other surgical intervention, in patients under the age of 12 years with generalized epilepsy, who have inadequate seizure control.

Anatomic Considerations

Vagal nerve fibers are composed of somatic and visceral afferents. They have diffuse CNS projection, with efferent innervation to the larynx and parasympathetic projection to the gastrointestinal tract, heart, and lungs. Activation of these pathways broadly affects neuronal excitability. The

VNS electrode is applied to the vagal nerve at the midcervical section, to avoid major branches. Branches arising off the vagal nerve carry substantial function; at the upper portion, branches supply the pharynx, carotid sinus, and superior and inferior cardiac branches, which lead to the cardiac plexus. Animal studies in dogs have demonstrated that the left vagal nerve usually innervates the atrioventricular node, while the right vagal nerve innervates the sinoatrial node. Resultantly, it is recommended to implant the VNS electrode to the left vagal nerve, to reduce the risk of bradycardia or asystole (Cyberonics Inc 2016; Agostini et al. 1957; Tatum et al. 1999; Ascapone et al. 1998). However, studies conducted on patients who had a VNS implanted over the right vagal nerve demonstrated that VNS stimulation did not alter heart rate on Holter monitoring (Navas et al. 2010; McGregor et al. 2005).

Nerves surrounding the vagal nerve include the recurrent laryngeal nerve, phrenic nerve, hypoglossal, and facial nerves. Transient voice changes can occur postoperatively during initial vagal nerve stimulation; this occurs due to the recurrent laryngeal nerve coursing with the main vagal nerve trunk and then branching at the aortic arch and ascending in the tracheoesophageal groove. In addition, during VNS therapy, unilateral paralysis of the left hemidiaphragm may occur, as phrenic nerve function may be altered. Additional reports of hypoglossal and facial nerve dysfunction have been reported with VNS therapy. A report of Horner's syndrome occurring post VNS implantation has been published and is believed to be caused by injury to the sympathetic trunk that runs deep to the common carotid artery and ascends along the internal carotid artery (Aalbers 2009) (Fig. 5).

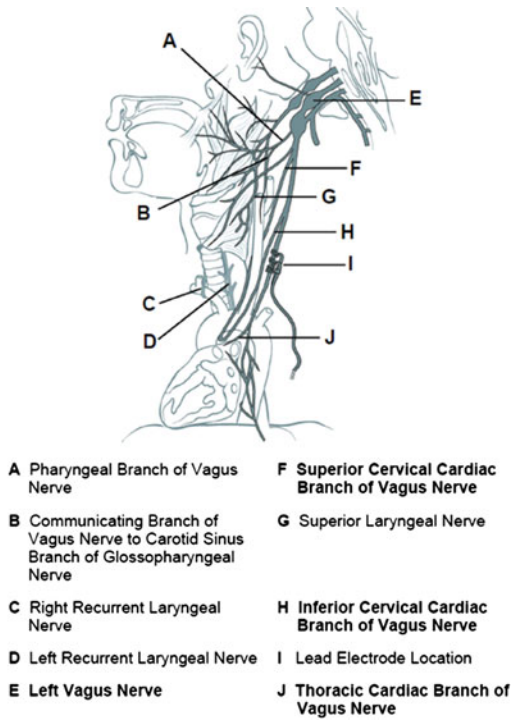

Fig. 5 Vagal nerve anatomy and anatomic considerations in lead placement

Neurocybernetic Prosthesis

The neurocybernetic prosthesis (NCP) consists of an implantable VNS therapy generator, lead, and external programming system. The generator is sealed in a titanium case and powered by a single battery; it delivers electrical stimuli to the vagus nerve via a monopolar or bipolar lead. The lead is made up of a connector pin or pins that insert directly into the generator on one end; the other end is made up of helices, containing stimulation electrodes, that are anchored around the vagal nerve. The lead models are available in two sizes based on helical inner diameter of 2.0 mm or 3.0 mm. While the proximal coil serves as an anchor to prevent excessive force from being applied to the electrodes when patients turn their neck, the middle coil is the positive electrode and the distal coil is the negative electrode. Each electrode helix contains three loops; inside the middle turn is a platinum coil welded to the lead wire. Extending from either end of the helix are suture tails, allowing manipulation of the coils without damage to the platinum contacts (Fig. 6).

The electrode is secured to the connector pin with a set screw or screws tightened with a hexagonal torque wrench included in the generator pack. The electrode is insulated with a silicone elastomer. To anchor the electrode to soft tissue of the neck, a silicone electrode collar is included

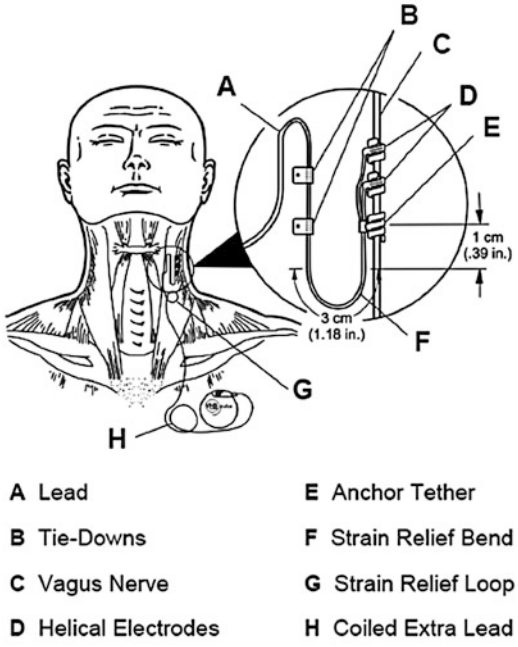

Fig. 6 Electrode placement

Fig. 7 VNS therapy generator

proximal to the helical coils. In addition, to prevent damage to the vagal nerve, the section between the electrode collar and inferior helix is secured as a "strain release loop."

The programming telemetry wand delivers radiofrequency signals to the generator through an antenna; a microprocessor regulates the electrical output of the pulse generator. The generator is able to deliver a charge-balanced signal through five programmable parameters including: output current, signal frequency, pulse width, signal-on time, and signal-off time. If signal-on time and stimulation frequencies are increased, battery life is reduced.

In addition to the programming software and programming wand, an external magnet can be used for one-way communication to the pulse generator. It can be used to initiate stimulation in patients experiencing aura or seizure onset, to temporarily inhibit stimulation, perform diagnostic tests, and reset the pulse generator in patients experiencing unwanted effects.

Since its introduction, the NCP has undergone a number of revisions. The original model 100 and second-generation model 101 used bipolar helical leads and are no longer distributed. Models 102 and 103 incorporate a monopolar lead. Generators 102R and 104 have bipolar lead acceptors facilitating revision of models 100 and 101 without replacing electrodes. Newer generators include 105 and 106 both incorporate monopolar leads. Generator 106 (Fig. 7) was introduced to incorporate an Auto-Stim Mode, which monitors and detects rapid, relative heart rate increases ($\geq$20%) that may occur with seizures. Once detected, on-demand stimulation is delivered. Customizable parameters can be set to increase sensitivity of detection of heart rate increases from 20% to 70%. However, a trade-off between sensitivity and specificity (potential false positive rate per hour) exists; as sensitivity increases, specificity decreases.

A personal digital assistant (PDA) and programming wand assist in setting the parameters of the generator. Typically, the generator is switched on at low stimulation in the operating room after implantation of the device. The generator is progressively turned up over several weeks, until the desired stimulation parameters are reached. Adjustments to the parameters can be made as required, dependent on seizure frequency and burden.

Operative Procedure

Hospitalization for implantation of the device should be preceeded by comprehensive epilepsy evaluation at an epilepsy center, as previously described. Candidates for VNS are patients with medically refractory epilepsy, who are not candidates for resective surgery. The implantation of the VNS device should be performed by a surgeon with experience in the anatomy of the carotid sheath.

Patients receive prophylactic intravenous antibiotics preoperatively and 24 h postoperatively. Patient admission is for 23 h, where they are observed for vocal cord dysfunction, dysphagia, respiratory compromise or anesthesia-induced seizures. Our practice is to turn the generator on in the operative room and increase the device parameters on the day after surgery.

Operative Technique

With the patient typically under general anesthesia, the operating table is rotated 90 degrees clockwise, from the anesthetic table, facilitating exposure of the left neck and chest to the surgeon. The patient's head is secured on a horseshoe headrest, with the neck slightly extended, and a small roll placed between the patient's shoulder blades. Surgical preparation of the site is conducted, and a horizontal incision measuring 2–3 cm in length is created at the midbody of the sternocleidomastoid (SCM). The incision is extended to the platysma and then bluntly along the medial border of the SCM to access the carotid sheath. Vein retractors are used to retract soft tissues. The carotid sheath is opened bluntly at the level of the thyroid cartilage, and the vagal nerve is identified lateral to the common carotid artery and deep to the internal jugular vein. After exposing the vagal nerve by blunt dissection, and exposing its length by approximately 4 cm, the nerve is gently retracted superiorly using a vessel loop. The inferior two electrode helices are placed around the nerve and then the nerve is gently retracted inferiorly using the vessel loop, allowing the superior helix to be placed around the nerve. The vessel loop is then gently withdrawn at the level of the skin, while gentle digital pressure is applied to the vagal nerve and helical electrodes. This prevents displacement of the applied electrode. Following this, the strain release electrode loop is created by using an electrode collar to stabilize the electrode to the medial SCM border, with approximately 6 cm of electrode exposed between the inferior helix and electrode collar.

Next, a parallel incision, measuring 1.5–6 cm (dependent on model type), is made to the chest wall overlying the lateral border of the pectoralis major. The incision is extended through the soft tissue lateral to the pectoralis major, developing a plane between the muscle and pectoralis minor. This should create an opening large enough for the generator being implanted. A NCP tunneling device is used to create a track from the chest wall to the neck incision (or from neck incision to chest wall incision). Caution should be taken to avoid injury to the surrounding neck tissues with the tunneling device. Once the track is created by the tuneling device, the bullet tip that inserts onto the end of the tunneling device is removed and the shaft is withdrawn from the clear hollow sheath. The free end of the electrode is inserted in the sheath, and drawn, with the sheath, from the neck incision to the chest wall incision. The electrode is removed from the sheath and attached to the generator with the set screw or screws and torque wrench. The generator is then placed in the chest wall incision, with the electrode inserted deep to the generator, and an anchoring stitch is placed through the generator header and pectoralis muscle; this secures the generator to the chest wall. The pectoralis fascia and soft tissues of the chest, as well as the platysma and subcutaneous structures of the neck, are then closed.

Once the surgical incision sites have been closed, the programming wand, within a sterile drape, is placed over the generator and used to perform electrodiagnostic testing using the PDA. The anesthetist monitors the patient's vital signs during testing and is able to detect bradycardia/asystole if they occur. If during testing, the diagnostic parameters are unsatisfactory, the neck incision is reopened to adjust/confirm electrode placement, and/or the chest wall incision is reopened to check contact of the electrode with

the generator. The electrodiagnostic testing is repeated until satisfactory data is collected. The NCP is then programmed by a neurologist to the initial stimulating parameters, and the neck and chest wall are closed completely using Dermabond.

Generator Revision

At each clinic visit, the generator and battery are assessed; the battery life can vary depending of the programmed stimulation parameters, but average expected battery life is 7–10 years. It is desirable to replace the generator, if indicated, prior to end of battery life, as this ensures continuous, uninterrupted VNS therapy. If the generator is changed at the end of battery life, the stimulation settings will have to be set to the baseline minimal settings and titrated up again. To change the generator the patient undergoes general anesthesia, antibiotic administration, and is positioned with their left neck and chest exposed to the surgeon. After surgical preparation, the neck and chest wall incisions are reopened. Dissection is carried down to the generator capsule in the chest wall, using Bovie cautery at low-coagulation settings. The electrode must be avoided. The generator is then removed, and the electrode is disconnected after the set screws have been loosened. Depending on whether the electrode is monopolar or bipolar, the appropriate replacement generators are attached using the torque screwdriver. The positive electrode is identified by a white mark proximal to the connector; this is introduced into the inferior lead channel (closest to the titanium portion of the generator). After tightening the set screws, the generator is placed back in the chest wall, and the incision is closed. Electrodiagnostic testing is then performed using the programming wand, covered by a sterile drape. Once testing is satisfactory, the chest wall is closed using Dermabond.

Lead Revision

If electrodiagnostics detect lead failure, the neck incision is reopened by blunt dissection. The electrodes are followed through to the helical coils; safe removal of electrodes has been demonstrated in cases where the vagal nerve and electrodes are covered by fibrotic tissue.

Avoidance and Management of Complications

Infection

The most frequent surgical complication is generator or lead implant site infection. In a meta-analysis of five controlled clinical trials, 2.86% of patients developed infection (Baumgartner and Von Allmen 2011). In the clinical trial that lead to FDA approval of VNS therapy, of 254 adult patients, surgical infection occurred in three patients (Handforth et al. 1998). In a separate study of 102 pediatric patients, 4% developed wound infection (Kirse et al. 2002); in a study of 69 patients with VNS implantation, three patients developed wound infection (Kabir et al. 2009). As a result, the risk of infection is speculated to be higher in children compared to adults (Morris et al. 2013). Fluid accumulation at the generator implantation site can occur with or without infection in 1–2% of patients (Wheless 2011). Infections are prevented with intravenous antibiotic administration prior to surgery, as well as postoperatively. If infection occurs, majority of infections resolve with intravenous antibiotics, aspiration of fluid collection with antibiotic coverage, and if indicated explantation of lead or generator.

Vocal Cord Abnormalities

In a meta-analysis of patients who underwent VNS implantation, 5.6% of patients developed vocal cord paralysis. Vocal cord paralysis was transient in most and persisted in 0.7% for over 1 year (Kahlow and Olivecrona 2013). A prospective study following 13 patients who underwent preimplantation and postimplantation laryngeal electromyography, videolaryngoscopy, maximal phonation time, Voice Handicap Index, and Consensus Auditory-Perceptual Evaluation of Voice, determined six patients developed vocal cord dysfunction 2 weeks after surgery. Five of the patients had electromyographic abnormality prior to VNS implantation, and they all experienced vocal cord paresis 3 months after implantation. As a result, patients who have preexisting vocal cord abnormalities are at greater risk for long-term vocal paresis, and this is a relative contraindication for

VNS therapy (Baumgartner and Von Allmen 2011).

Vocal cord dysfunction may occur due to excess manipulation of the vagus nerve, with subsequent damage to the vagal artery and its arterioles (Fernando and Lord 1994). In most cases, resolution occurs over several weeks.

Cardiac Rhythm Abnormalities

Bradycardia and ventricular asystole have been observed to occur intraoperatively during electrodiagnostic testing of the lead and generator. This is estimated to occur in one in 800 patients. The anesthetist in the operating room should be informed prior to electrodiagnostic testing being commenced, allowing for observation of vital signs. Management of asystole involved administration of intravenous atropine and switching the VNS off. In some individuals, VNS at low settings can be tolerated. Model 106 is contraindicated in patients with clinically meaningful arrhythmias managed by devices or medications interfering with normal heart rate responses.

Dyspnea/Obstructive Sleep Apnea

Pulmonary function does not significantly change with VNS therapy in patients without lung disease, despite widespread visceral efferent innervation by the vagal nerve. However, dyspnea can occur during stimulation in patients with underlying pulmonary disease (Handforth et al. 1998; Lötvall et al. 1994). It has also been reported that patients with obstructive sleep apnea may experience increased apneic event during VNS stimulation (Cyberonics Inc 2016). These can be managed with positive pressure treatment or by altering VNS stimulation parameters.

Magnetic Resonance Imaging in Patients with Vagus Nerve Stimulation Implants

Cyberonics, Inc. have advised magnetic resonance imaging (MRI) to not be performed in patients with a magnetic resonance body coil in the transmit mode. The heat induced in the lead by MRI can cause injury (Cyberonics Inc 2016). We have developed a protocol that allows safe MRI to be performed in patients with VNS. The patient is informed of FDA concerns of imaging, and informed consent for MRI with VNS is obtained. The device is switched off, and imaging is performed using a 1.5 Tesla MRI machine. Only the patient's brain is imaged, and the scan is performed with a GE quad head coil. After completing the MRI scan, the VNS is reprogrammed to the same settings as before the scan.

Conclusion

VNS is a safe and effective treatment for patients with medically refractory epilepsy, not amenable to surgical resection. The VNS is also indicated for adjunctive treatment of chronic or recurrent depression in patients over the age of 18. VNS use has expanded to be effective in children younger than 12 years age, to patients with tuberous sclerosis complex, and patients with failed resective surgery. The use of VNS therapy has demonstrated better long-term seizure control and improved quality of life outcomes in palliative patients.

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