Endobronchial ultrasound–guided transtracheal cardiac plexus neuromodulation for refractory ventricular tachycardia

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Introduction

Patients with tachyarrhythmias refractory to standard pharmacologic and catheter ablation treatments have limited therapeutic options and suffer from high morbidity and mortality.[1] Modulation of the autonomic nervous system through surgical cardiac sympathetic denervation consists of a therapeutic strategy for refractory tachyarrhythmias.[2,3] Although cardiac sympathetic denervation has been demonstrated to benefit selected patients resistant to medical therapy and ablation, it is invasive and has variable success rates.

Sympathetic nerves from both stellate ganglia converge to form the deep cardiac plexus (CP), a complex network of nerves that courses along the pretracheal space before reaching out to the heart. CP stimulation to regulate the autonomic cardiac function has been described, but anatomical access to this location has been a critical barrier.[4,5] The advent of endobronchial ultrasound (EBUS) has allowed unprecedented access into the pretracheal region, where agents like botulinum toxin may be used to suppress tachyarrhythmias, as seen with cardiac surgery in animal models and a human pilot study.[6] Although EBUS-guided blockade of the CP has been reported in animal models,[7] it has never been described in clinical settings. We present a refractory case of ventricular tachycardia (VT), which transiently resolved with EBUS-guided transtracheal needle injections of lidocaine and botulinum toxin into the CP. To our knowledge, this is the first case of successful bronchoscopic-guided block of the autonomic nervous system.

KEYWORDS Bronchoscopy; Cardiac plexus; EBUS; Neuromodulation; Transtracheal block; Ventricular tachycardia
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KEY TEACHING POINTS

- Cardiac sympathetic denervation has been shown to benefit patients with refractory ventricular arrhythmias.
- Nerves originated from both thoracic sympathetic chains converge to form the deep cardiac plexus (CP), which descends towards the heart through the pretracheal space.
- Minimally invasive cardiac neuromodulation via CP blockade may have a potential role in the treatment of ventricular arrhythmias when other therapies have been exhausted.

Case report

A 44-year-old woman with a complex history of Takayasu arteritis and ischemic cardiomyopathy was admitted to our institution for the management of recurrent VT and multiple implantable cardioverter-defibrillator (ICD) shocks.

With a history of extensive vascular disease and aortic root and arch replacement owing to aortic insufficiency, she had her postoperative course then complicated with ventricular fibrillation arrest, which resulted in the implantation of a single-chamber ICD. She did well for 13 years, when she had her aortic valve replaced again, owing to bacteremia and dehiscence. She developed heart failure along the follow-up (NYHA class III), and 3 weeks before admission to our institution she was complaining of fatigue, lightheadedness, and palpitations, which culminated in a local hospital admission owing to 2 ICD shocks. Medical therapy was adjusted and included amiodarone (300 mg/day) and low-dose metoprolol (12.5 mg/day). After 2 weeks, VT again recurred, and another ICD shock was reported.

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The day before being transferred to our institution, she was admitted into an outside center with a pulseless VT, requiring 2 rounds of cardiopulmonary resuscitation. Once recovered, the patient was transferred to the cardiac care unit in incessant VT despite the use of continuous intravenous amiodarone.

Once in our institution, the patient continued to present recurrent polymorphic and monomorphic VTs (Figure 1). Multiple antiarrhythmic drugs (amiodarone, lidocaine, mexiletine, ranolazine) and overdrive pacing failed to control VT, and several electrical cardioversions were required. Cardiac catheterization was also attempted but was unsuccessful owing to arterial anatomy and difficult access. She had a coronary computed tomography angiogram, which revealed that both of her saphenous vein grafts, placed during the first valve replacement, were occluded; however, no coronary intervention was indicated owing to anatomic constraints and patent collateral vessels. Transthoracic

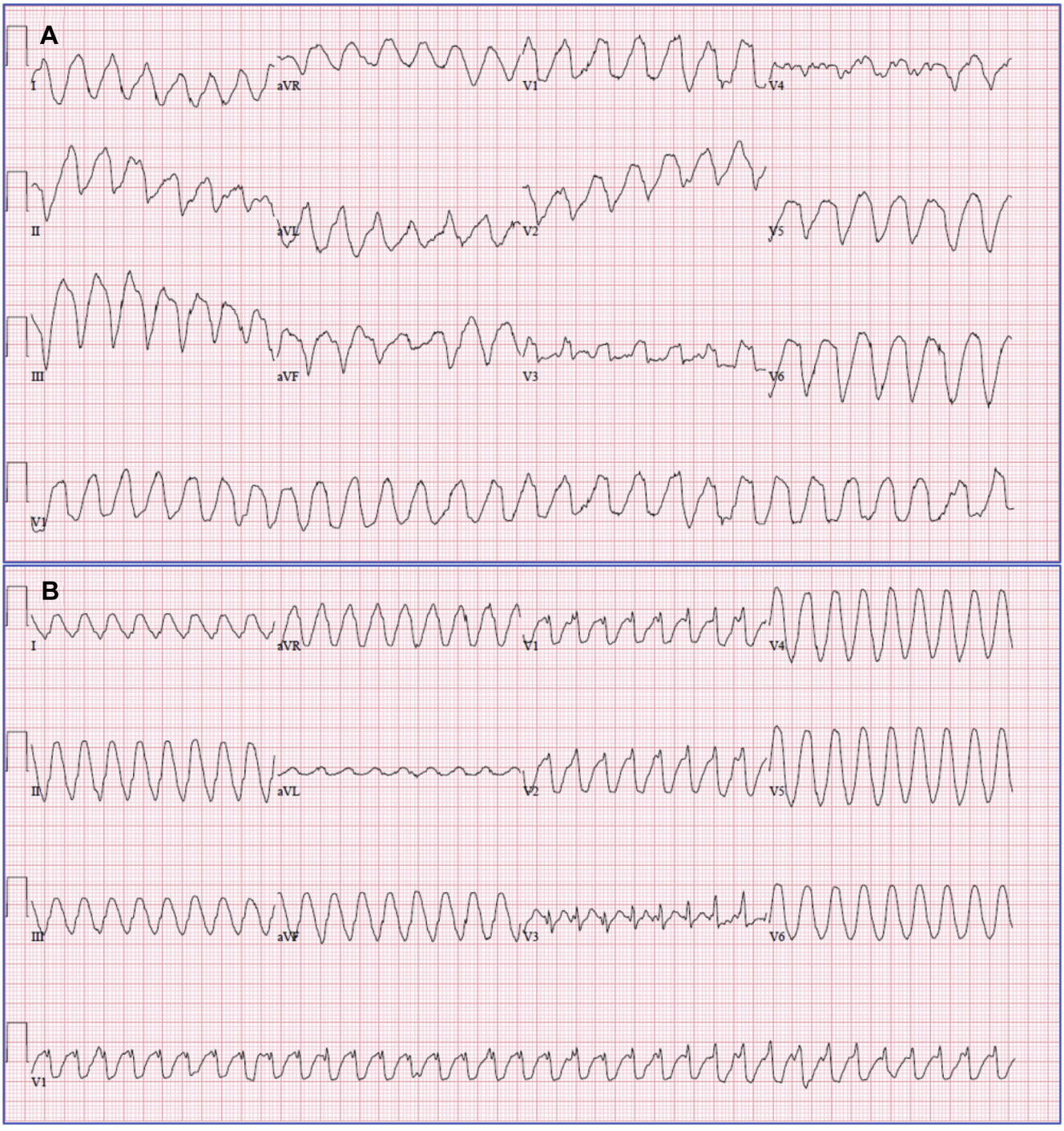

Figure 1 Refractory ventricular tachycardia (VT). **A:** Polymorphic VT associated with prolonged QT interval (proarrhythmia). **B:** Recurrent monomorphic VT targeted during VT ablation procedure.

echocardiogram showed severe biventricular dysfunction (left ventricular [LV] ejection fraction of 20%–25%).

Extensive antiarrhythmic therapy resulted in sinus bradycardia, periods of junctional rhythm, and QT interval prolongation. Both the reduced LV function and the incremental need for pacing led to worsened heart failure symptoms (single-chamber ICD—asynchronous and exclusive right ventricular pacing). Additionally, given that higher pacing rates were required as an attempt to shorten QT interval and thus mitigate recurrent polymorphic VT, her pacing system was upgraded to a biventricular ICD. During the procedure, the patient developed hemodynamically unstable VTs, which were treated with electrical cardioversions. Despite that, later at night the patient developed a VT storm and ultimately went into cardiac arrest, requiring prolonged resuscitation; emergent support with venoarterial extracorporeal membrane oxygenation (VA-ECMO) with LV vent was instituted. Along the next 10 days, multiple attempts to wean the patient off VA-ECMO support failed, as they often resulted in incessant VT requiring multiple electrical cardioversions.

The patient was then referred for VT ablation procedure. Because of the lack of viable percutaneous vascular access, the LV cannula serving as a vent to decompress the left ventricle was used to assess the left ventricle and execute the procedure. Clinical VT (right bundle branch block, superior axis) was easily induced; voltage mapping revealed extensive endocardial scar in the septum and area of delayed conduction in the lateral apical left ventricle. Perfect pace-map match was found in the lateral apical left ventricle, consistent with concealed entrainment and local early mid-diastolic potentials. Extensive ablation was performed not only at the site of the critical isthmus but at other borderline areas extending from basal to apical anterolateral and lateral left ventricle (substrate modification), which rendered the patient noninducible. Despite all efforts, incessant VT early recurred and persisted despite cardioversions. Cardiac sympathectomy was considered, but the patient's unstable condition and systemic anticoagulation on VA-ECMO contraindicated the procedure. Full anticoagulation also precluded us from pursuing stellate ganglion block owing to the risk of accidental vascular injury (contraindication). Through expanded access ("compassionate use"), we pursued EBUS-guided transtracheal needle injection at the bedside. Using a 22 gauge needle, 4% lidocaine (1 mL) and 50 U/mL botulinum toxin (0.2 mL) were injected into 3 different paratracheal regions to acutely interrupt the sympathetic input to the heart via pretracheal blockade of the CP (Figure 2). Immediately after the completion of the first injection, incessant VT slowed and terminated, and sinus rhythm was re-established (Figure 3). The 2 additional injections were performed to extend the area of block. No procedure-related complication was noted. The following day, given the hemodynamic stabilization, the patient was taken into the operating room and had her VA-ECMO removed, remaining free of VT for 5 days before, while being treated with surgical debridement of a catheter-site wound infection, incessant VT resumed. As a result, she was placed back on venovenous ECMO, followed by her family's decision to withdraw ECMO support.

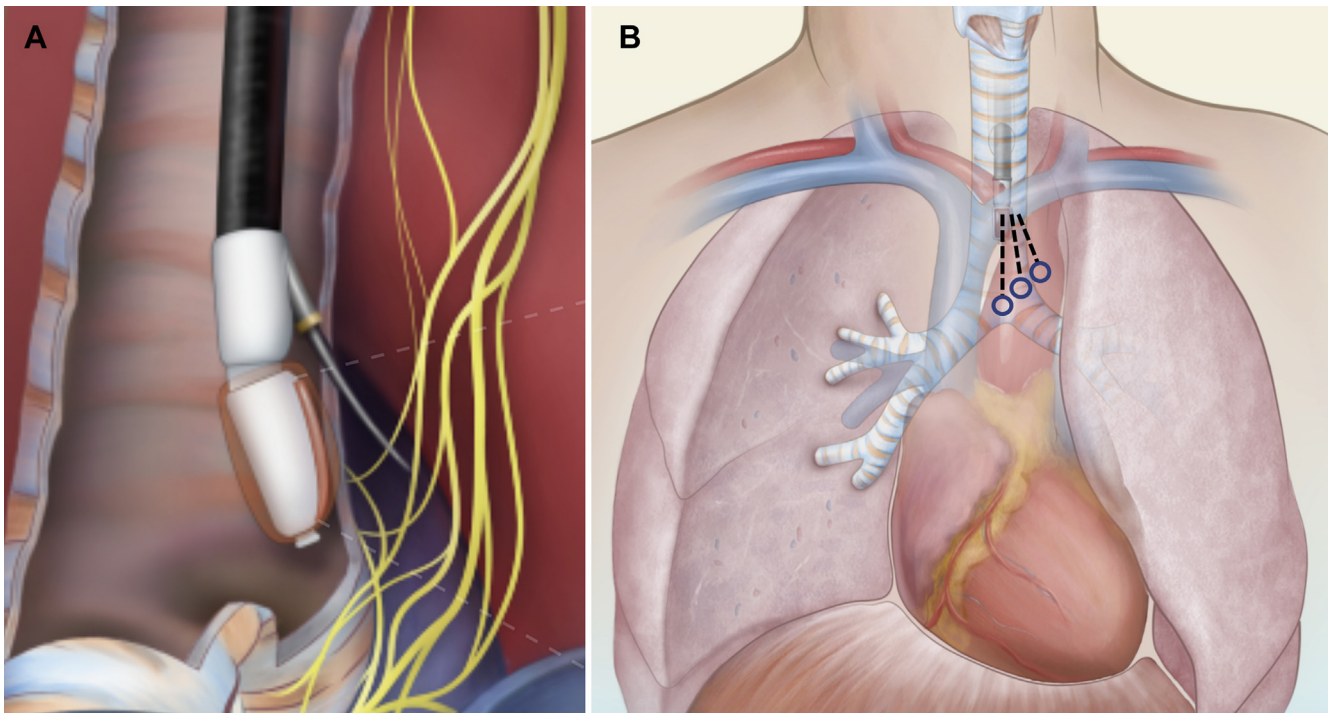

Figure 2 Endobronchial ultrasound–guided transtracheal blockade of the cardiac plexus. **A:** Under real-time ultrasound imaging of the pretracheal space, the needle is positioned through the anterior tracheal wall into the aortopulmonary window. **B:** Three injections were performed along the pretracheal region, from the anterior wall to the left paratracheal region.

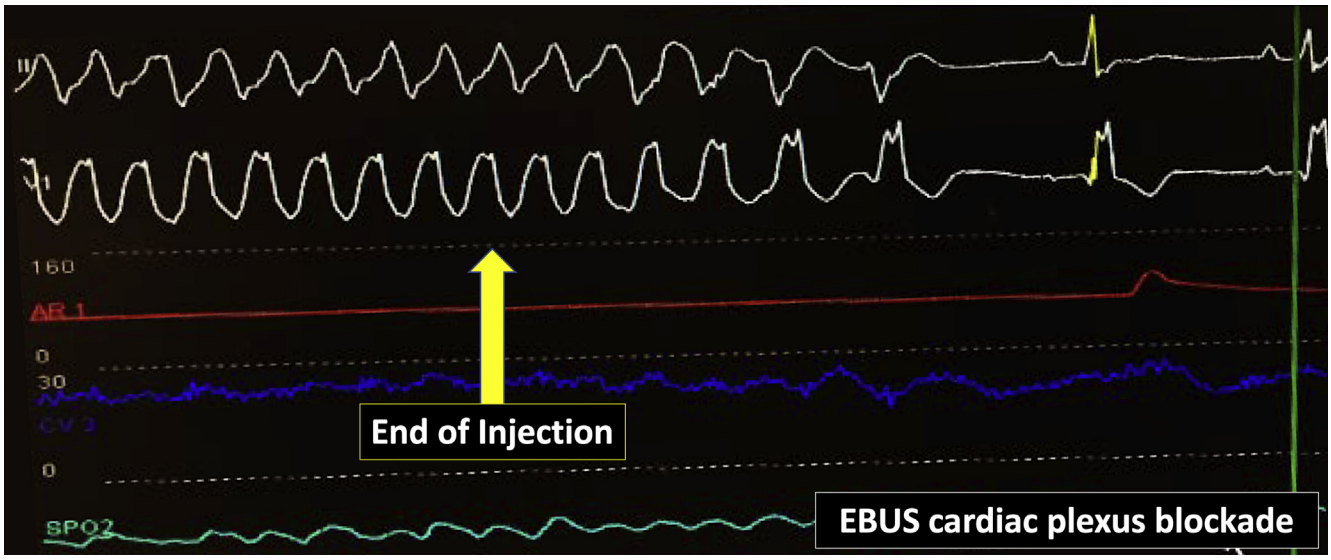

Figure 3 Termination of ventricular tachycardia (VT). Cardiac monitor showing polymorphic VT, followed by slowing and termination of VT at the end of the first endobronchial ultrasound–guided transtracheal injection of lidocaine and botulinum toxin into pretracheal cardiac plexus (*arrow*).

Discussion

Long-term benefits of cardiac surgical sympathectomy have been demonstrated by Vaseghi and colleagues[8] in a large series of patients with refractory ventricular arrhythmia. Herein, we report the first human case of transtracheal EBUS-guided neuromodulation for refractory VT by locally blocking deep CP.

Deep CP is positioned adjacent to the trachea near the level of the bifurcation of the mainstem bronchi, coursing along a confined space between the pulmonary artery, aortic arch, and anterior wall of the trachea (aortopulmonary window). Given the proximity of the CP to the trachea, the EBUS bronchoscope allows to safely access this otherwise prohibited region under real-time visualization of adjacent structures. Once location is confirmed, a 2-mm-diameter needle is advanced and local injection of chemical agents performed. To our knowledge, no attempts have been made to utilize bronchoscopy for transtracheal CP neuromodulation in clinical settings.

Modulation of the cardiac autonomic nervous system by electrical stimulation of either parasympathetic or sympathetic cardiac nerves have been described as potential therapeutic modalities for arrhythmias.[9,10] However, as the cardiac function is modulated by the balance of cardiac sympathetic and parasympathetic nerve activity, further animal studies have been conducted to evaluate the feasibility of electrical stimulation of the CP, where the parasympathetic and sympathetic cardiac nerves converge. Kobayashi and colleagues[4,5] have demonstrated that in canine models, both epivascular and less invasive endovascular CP stimulation induced significant and selective increase in LV contractility and cardiac output with no increase in heart rate. Furthermore, the CP is contiguous with the pulmonary plexi at the level of the tracheal bifurcation, with potential modulatory effect on the pulmonary vascular and bronchial tone. As such, neuromodulation of the CP may have extended therapeutic implications for the treatment of pulmonary diseases, such as pulmonary hypertension and asthma, both yet to be determined.

Our research group investigated the safety and feasibility of the bronchoscopic sympathetic block of the autonomic nervous system in large animal models and utilized such experience in this single human case.[7] Corroborating our preclinical results, the procedure was revealed to be safe, without complications, despite full anticoagulation. The rationale of combining lidocaine and botulinum toxin relies on the differences in terms of time-to-effect and half-life between the 2 drugs. Whereas lidocaine induces fast but short-term neural block, with an average half-life of 1–2 hours, the botulinum toxin is associated with a more prolonged effect, although it may take days to be effective. Though we recognize that botulinum toxin–induced parasympathetic block is the rule at the postganglionic level, and that there are no robust data to support its use for this purpose, especially in this location, there is some evidence that suggests that botulinum toxin can also act to reduce the noradrenergic response. Nonspecific dose-dependent sympathetic inhibition in vitro, and evidence of retrograde axonal migration of botulinum toxin from peripheric administration to central nervous system, all collectively account for a potential associated antinoradrenergic effect derived from botulinum toxin injection.[11–14] Also, preliminary preclinical data showed that the injection of botulinum toxin into the epicardial fat, a structure densely innervated mainly by postsynaptic cholinergic neurons activated by presynaptic acetylcholine, was associated with a significant reduction of the ventricular arrhythmia burden within 1 hour after myocardial infarction induction, which is a period wherein an increase in sympathetic tone is well recognized.[15] By virtue of that, as an effort to deliver an acute but more sustained sympathetic block, the 2 medications were combined with complementary roles. Given the rapid resolution of the

refractory VT, lidocaine is suspected to be the main therapeutic agent. Nevertheless, whether some degree of delayed changes in sympathetic-parasympathetic balance derived from the botulinum toxin contributed to the 5-day VT-free survival is unclear.

As the pretracheal CP harbors both sympathetic and parasympathetic innervations, the occurrence of selective sympathetic block in this case is debatable. Because we had not performed any pre- or postprocedural assessment to confirm nerve block, such as local stimulation, we can only assume that there was a predominant sympathetic block, given the obtained response (VT termination). However, we cannot discard the possibility that some degree of concomitant parasympathetic block occurred. Yet, since the injection terminated the tachycardia and neither a bradycardic response nor further decrement of hemodynamic status was observed, we believe that there was no clinically significant parasympathetic block.

Although EBUS has been clinically utilized for aspiration of lymph nodes and masses in the mediastinum, its potential utilization to locally access and manipulate other structures such as nerves is novel. Our case supports the concept that EBUS bronchoscopy can be utilized for nonsurgical access and manipulation of the CP; however, additional investigations are needed to better understand and optimize this technique.

Conclusion

We describe the first human case of successful bronchoscopic CP neuromodulation for refractory tachyarrhythmia. Further investigation is still warranted to determine the value and safety of this minimally invasive approach of cardiac neuromodulation.

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