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EDITORIAL COMMENT

Management of life-threatening ventricular arrhythmias: What is going on with autonomic neuromodulation

Manejo de arritmias ventriculares potencialmente fatais: o papel da modulação autonómica

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Electrical storm (ES), characterized by recurrent and frequent episodes of potentially life-threatening ventricular arrhythmias (VA), is a relatively common condition, primarily seen in patients with structural heart disease and implantable cardioverter-defibrillators (ICD).[1] It is a complex severe clinical situation, associated with high mortality and low quality of life.[2]

Electrical storm management has evolved over the years, with anti-arrhythmic drugs, introduced in the 1950s, followed by the ICD in the 1980s. In the 21st century, radiofrequency catheter ablation, three-dimensional electroanatomic mapping and advanced cardiac imaging have provided a better understanding of the arrhythmic mechanisms, allowing substrate modification, and refining ES management. However, ES is still associated with significant residual morbidity and mortality.

In recent years, more attention has been given to autonomic nervous system dysregulation as a perpetrator of arrhythmias, and to the role of innovative techniques of neuromodulation in the prevention and treatment of refractory recurrent VA.

Studies over the last decades have provided evidence of the relationship between the autonomic nervous system (ANS) and arrhythmias. In fact, cardiac autonomic innervation exerts a profound influence on the heart's electrical activity, with derangement of ANS being considered an important contributor to the initiation, maintenance and cessation of arrhythmias.[3]

Complex mechanisms, different for specific arrhythmias, are involved in this modulatory process. In the presence of myocardial injury, cardiac sympathetic activation may turn into sympathetic overdrive and exacerbate VA by increasing myocardial oxygen demand, enhancing trigger activity, reducing the duration of action potential and increasing dispersion of repolarization. On the other hand, parasympathetic influences can slow velocity conduction, prolong ventricular effective refractory periods and mitigate ventricular ectopy. Cardiac disease may lead to an imbalanced ANS function, combining sympathoexcitation with parasympathetic withdrawal, which destabilizes cardiac electrophysiology, facilitating the development of VA.[4]

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Autonomic modulation therapy using non-pharmacologic techniques designed to decrease sympathetic and increase parasympathetic activity, has been used with promising clinical benefits. Presently, autonomic modulation is recommended by the 2022 European Guidelines in the acute management of ES.[1]

This editorial discusses briefly recent advances in clinically used neuromodulatory therapies for the management of recurrent VA and ES.

Percutaneous stellate ganglion blockade (PSGB) entails the percutaneous injection of local anesthetics into either the left or both stellate ganglia, obtaining temporal inhibition of both efferent and afferent neural pathways to the heart and mitigating sympathetic stimulation.[5] It can be achieved using the anatomical, or anterior, approach (Moore technique)[6] or the lateral, ultrasound-guided approach.[7]

Anesthetics used for this technique usually consist of a combination of a fast-acting drug (e.g. lidocaine) with a long-acting drug (e.g. bupivacaine or ropivacaine), which has the advantage of combining a rapid anti-arrhythmic effect onset with longer-lasting protection.[5] PSGB using a catheter for continuous infusion of lidocaine or another anesthetic may be particularly helpful in case there is a need to stabilize the patient for a longer timeframe.[8]

A recent systematic review of 38 patients with ES showed that PSGB resulted in a significant decrease in VA burden and number of external and ICD shocks from an average of 12 to 1 VA episodes per day.[9] In another meta-analysis, PSGB appears to be effective and safe for the treatment of ES, with approximately 1 in 2 patients exhibiting complete suppression of VA for 72 hours, and an 80% mean relative reduction in VA burden.[8]

The main value of PSGB in ES is the feasibility of the procedure at the bedside, which could prove invaluable in the management of unstable ES patients as a bridge for other therapies such as catheter ablation.[5] However, its main disadvantage relates to the transient effects due to the pharmacokinetics of local anesthetics. Moreover, its effect is not circumscribed to the heart, potentially dampening sympathetic tone to the head, neck, and diaphragm.

As well as PSGB, thoracic epidural anesthesia (TEA) is a bedside available procedure that involves the percutaneous injection of a local anesthetic to block sympathetic fibers that innervate the heart. It blocks segments C8 to T4 bilaterally, therefore inhibiting fibers that are proximal to both the left and right stellate ganglia.[10]

A small clinical study on TEA for ES displayed a remarkable >80% reduction in VA in 6 out of 8 patients.[10] However, the dose of TEA is difficult to titrate as there are no easy-to-use markers other than an assessment of its efficacy in arrhythmia control. Much like PSGB, its effect is also transitory and dependent on the pharmacokinetics of the local anesthetics. In a recent European survey, PSGB or TEA were available only in a small proportion of centers, with the large majority (82.5%) performing PSGB.[11]

In the early to mid-20th century, surgical sympathectomy was one of the first attempts at neuromodulation for the treatment of VA. In the 1960s, cardiac sympathetic denervation (CSD) emerged as a therapy for refractory VA, with greater evidence of benefits in congenital long QT syndrome and catecholaminergic polymorphic ventricular tachycardia.

It is a procedure that permanently eliminates cardiac sympathetic input through the mechanical disruption of all neural transmission through the left or bilateral thoracic ganglia. Both left CSD and bilateral CSD are typically performed via video-assisted thoracoscopic surgery and involve the removal of the lower half of the stellate ganglion, as well as the T2 to T4 ganglia of the thoracic sympathetic chain.

In patients with structural heart disease and ES (with previous VT ablation performed in 66% of the cases), bilateral CSD demonstrated greater efficacy than left CSD in reducing the arrhythmic burden, with a one-year ICD shock-free survival of around 50%.[12]

The main disadvantage of bilateral CSD compared to the left CSD technique is a potential reduction in heart rate and chronotropic competence since the sinus node is primarily innervated by right-sided nerves.[13] It remains a safe procedure, provided the patient is managed by a multidisciplinary team of thoracic surgeons, cardiologists and anesthesiologists.

In the 2000s, renal artery denervation (RDN) was mainly used for the management of resistant arterial hypertension. It is performed via selective angiography of the renal artery and catheter ablation, with radiofrequency applied to its branches, resulting in inhibition of the afferent renal sympathetic pathway, which decreases efferent sympathetic overactivation on a systemic level.[14]

A recent meta-analysis, encompassing 121 patients who underwent RDN for the treatment of VA or ES, demonstrated a significant reduction of ICD therapies and frequency of VA episodes.[15] RDN is considered a safe procedure, not associated with increases in complications post-procedure, without evidence of deterioration in renal function, even in patients with chronic kidney disease.[16]

The small amount of clinical data on RDN as an anti-arrhythmic therapy is promising. However, the procedure has yielded mixed results in its trials for hypertension treatment, likely due to inconsistent degrees of technical success and suboptimal anatomical targets. These challenges must be overcome if RDN is to be effectively applied to the treatment of VA.

Transcutaneous electromagnetic stimulation (TcMS) is a noninvasive, nondestructive technique, using an electromagnetic field via electric low-level stimulation, capable of modulating nervous system activity, already in use for a variety of diseases such as depression, and neurodegenerative aphasia. More recently, it has gained interest in the management of arrhythmias, such as atrial fibrillation and VA.

Low-level tragus stimulation targets the auricular branch of the vagus nerve, an afferent nerve that relays information to central vagal projections in the brain stem and other higher centers, which, after being activated, send an efferent signal to the heart via the vagus nerve. This approach decreases sympathetic tone in humans.[17]

In animal models, TcMS, using a device that utilizes current to produce an electromagnetic pulse that is delivered at low-frequency approximation to the stellate ganglion, has been shown to modify arrhythmia risk by targeting cardiac sympathetic innervation.[18] A recent double-blind, randomized trial was conducted to characterize the effects of a single session of TcMS, using magnetic stimulation delivered

via a figure-of-8 coil positioned in the approximation of the left stellate ganglion for patients with ES. In the 24-hour period after the procedure, VA recurred in 4 of 14 patients in the TcMS group versus 7 of 12 patients in the sham group.[19]

The ongoing Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Premature Ventricular Complexes (TREAT PVC) multicenter study will evaluate the effects of low-level transcutaneous stimulation on frequent premature ventricular complexes in patients without structural disease.[20]

In conclusion, in recurrent VA and ES management, autonomic modulation therapies have emerged as a promising ally, reflecting the interface between physiology, mechanisms underlying arrhythmias and technical novelties. The disturbances of the intricate relation of sympathetic and parasympathetic forces underpin the genesis of VA. Procedures such as PSGB, TEA, CSD, RSD and TcMS offer an innovative paradigm to restore autonomic balance and reduce the arrhythmic burden in these high-risk patients.

As research continues in larger clinical studies to unveil the full potential of autonomic modulation, we may find invaluable adjunct therapies for VA management.

Conflicts of interest

The authors have no conflicts of interest to declare.

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