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Ethanol Infusion in the Vein of Marshall Leads to Parasympathetic Denervation of the Human Left Atrium

Implications for Atrial Fibrillation

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Objectives This study sought to determine whether ethanol infusion in the vein of Marshall (VOM) can ablate intrinsic cardiac nerves (ICN).

Background ICN cluster around the left atrial epicardium and are implicated in the genesis of atrial fibrillation (AF).

Methods Patients undergoing catheter AF ablation underwent adjunctive ethanol injection in the VOM. A multipolar catheter was introduced in the VOM and used for high-frequency stimulation (HFS), either as HFS with P-wave synchronized (SynchHFS), 30 pulses, 100 Hz (n = 8) or as HFS with 3 to 10 s bursts (BurstHFS), 33 Hz (n = 72) at 25 mA for 1-ms duration. Atrioventricular (AV) nodal conduction slowing (asystole >2 s or R-R interval prolongation >50%) and AF inducibility were assessed before and after VOM ethanol infusion. Up to 4 1-ml infusions of 98% ethanol were delivered via an angioplasty balloon in the VOM.

Results SynchHFS induced AF in 8 of 8 patients. In 4 of 8 AF initiated spontaneously without VOM capture. No parasympathetic responses were elicited by SynchHFS. BurstHFS was performed in 32 patients undergoing de novo AF ablation (Group 1) and 40 patients undergoing repeat ablation (Group 2). Parasympathetic responses were found in all 32 Group 1 patients and in 75% of Group 2 patients. After VOM ethanol infusion, parasympathetic responses were abolished in all patients (both groups). There were no acute complications related to VOM ethanol infusion.

Conclusions The VOM contains ICN that connect with the AV node and can trigger AF. Retrograde ethanol infusion in the VOM reliably eliminates local ICN responses. The VOM is a vascular route for ICN-targeting therapies. (J Am Coll Cardiol 2014;63:1892–901) © 2014 by the American College of Cardiology Foundation

Intrinsic cardiac nerves (ICN) can modulate atrial muscle physiology in a pro-fibrillatory manner (1). ICN ablation has been proposed as an adjunctive (2) or stand-alone (3) therapy for atrial fibrillation (AF). Strategies for ICN ablation have involved the use of radiofrequency at endocardial sites where parasympathetic reflexes were elicited or epicardial ablation during surgery or epicardial access. To date, the clinical impact of ICN ablation in the overall procedural success is unclear, in part because of unreliable ablation techniques.

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ICNs cluster in discrete ganglia located in the proximity of the pulmonary veins (PV). The ligament of Marshall is considered part of the ICN (4). It has been shown to contain sympathetic (5) and parasympathetic (6) innervation, and it coincides with regions known to harbor ICN, specifically the left dorsal nerve (7). It becomes the vein of Marshall (VOM) caudally as it connects with the coronary sinus. The ligament of Marshall has been implicated in the genesis of AF by multiple mechanisms: as a source of ectopic beats initiating AF (8–10), as a connection pathway with

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neighboring myocardium and left PV (5,11), and as a source of arrhythmogenic autonomic innervation (5,6). Animal (12) and human (3) surgical open-chest studies have shown that high-frequency electrical stimulation (HFS) at the ligament of Marshall area may induce parasympathetic responses characterized by significant slowing of atrioventricular (AV) nodal conduction and AF induction. It is not known whether the VOM can anatomically connect with the ICN associated with the ligament of Marshall. If so, then the VOM could be used as a closed-chest endovascular route to the ICN for therapeutic purposes. We have developed a technique for retrograde VOM ethanol infusion and have shown its feasibility and safety in humans (13,14). We hypothesized that: 1) HFS performed within the VOM can elicit parasympathetic responses; and 2) the VOM can be used as a vascular route to target these epicardial ICN and regionally denervate the LA with chemical ablation.

Abbreviations and Acronyms

AF = atrial fibrillation

AV = atrioventricular

BurstHFS = high-frequency stimulation using 3- to 10-s bursts at 33 Hz

HFS = high-frequency stimulation

ICN = intrinsic cardiac nerves

SynchHFS = high-frequency stimulation using P-wave-synchronized, 30 pulses, 100 Hz

VOM = vein of Marshall

Methods

Patients. We enrolled 133 patients in the VOM ethanol infusion procedure. Patients were undergoing clinically indicated PV antral isolation (PVAI) and gave consent for adjunctive ethanol injection in the VOM in a protocol that was approved by the local institutional review board, overseen by the Food and Drug Administration (IND #105083), and an external Data Safety Monitoring Board.

Procedural strategy. After obtaining informed consent, patients were subjected to general anesthesia, and vascular access was obtained. A quadripolar catheter was positioned in the His bundle and a decapolar catheter in the coronary sinus via a femoral vein.

The VOM was cannulated as previously described (13,14). Briefly, the right internal jugular vein was accessed with a 9-F sheath. Then, a sheath designed for left ventricular pacing lead delivery was inserted in this sheath and into the coronary sinus (CPS sheath, St Jude Medical, Minneapolis, Minnesota). A subselector catheter (LIMA angioplasty guide) was then inserted through the CPS sheath and manipulated so that its tip faced posteriorly and superiorly. Angiographic contrast was injected through the LIMA guide, and the VOM was identified as an atrial branch of the coronary sinus that arose at the level of the valve of Vieussens and that was directed posteriorly.

A quadripolar catheter (1.7-F Pathfinder Mini, Cardima, or 4-F IBI [St. Jude Medical]; or 2.4-F over-the-wire [Internova Medical, Chiba, Japan]) was inserted in the VOM through the LIMA guide. This catheter was used to record baseline VOM electrocardiograms and to perform HFS. A transseptal puncture was then performed under intracardiac echocardiographic guidance, and a circular duodecapolar catheter was inserted in the left atrium. Heparin was administered to maintain the activated clotting time between 350 and 400 s throughout the procedure. Three-dimensional maps of the left atrial geometry and regional bipolar voltage amplitude were constructed at baseline and after VOM ethanol administration with either NavX (St. Jude Medical) or Carto 3 (Biosense-Webster, Diamond Bar, California) mapping systems.

High-frequency stimulation protocols. PROTOCOL 1. To avoid atrial capture, VOM HFS was performed during atrial refractoriness (15), delivering atrium-synchronized HFS (SynchHFS; sensing in the proximal coronary sinus) stimulation (30 pulses at 100 Hz). Spontaneous (non-captured) atrial activity was monitored subsequently.

PROTOCOL 2. Prolonged (3- to 10-s) bursts at 33 Hz (BurstHFS) were delivered via the VOM.

Both protocols were delivered at 25 mA of amplitude and 1-ms pulse width. A positive parasympathetic response was defined as either AV block or asystolic pause >2 s or a bradycardic response manifested as R-R interval prolongation by >50% when averaging 15 beats before and after HFS. Local AF inducibility with HFS was assessed pre- and post-ethanol infusion in the VOM. If AF persisted beyond the VOM ethanol administration, local AF inducibility with HFS could not be tested.

VOM ethanol infusion procedure. The quadripolar catheter was then retracted from the VOM, and an angioplasty wire (BMW, Abbott, Abbott Park, Illinois) was advanced into the VOM as distally as possible. A pre-loaded angioplasty balloon (8-mm length, 2-mm nominal diameter [Voyager OTW, Abbott] or 6-mm length, 1.5 mm diameter [Medtronic, Minneapolis, Minnesota]) was advanced over the wire, as distally as possible. Depending on the length of the VOM, up to 4 injections of 98% ethanol (1 cc over 2 min each) were delivered. Starting in the most distal VOM, the balloon was slightly retracted sequentially after each injection so that the last injection was given from the most proximal VOM. After ethanol infusion, the angioplasty wire and balloon were retracted, and the quadripolar catheter was reinserted into the VOM to record signals and repeat HFS with the same protocol used prior to ethanol administration. Ethanol levels were measured in mixed venous blood at the end of the procedure. Beyond VOM instrumentation, the procedure continued with radiofrequency ablation using a Thermocool catheter (Biosense-Webster) navigated with the Artisan robotic sheath (Hansen Medical, Mountain View, California). Radiofrequency ablation with a power of 25 to 35 W and saline irrigation at a rate of 17 to 30 cc/min were performed as needed in each case to isolate the PVs, ablate complex-fractionated potentials, or LA flutters if present.