

High-density mapping of the slow pathway in a patient with atrioventricular nodal reentry given intranasal Etripamil during the NODE-1 study

William C. Choe, MD,* Sri Sundaram, MD, FHRS,* Charles Boorman, MA,[†] Nate Mullins, FCE,[†] Pirouz Shamszad, MD, FAAP, FACC,[‡] Francis Plat, MD[§]

From the *Section of Cardiac Electrophysiology, South Denver Cardiology Associates, Littleton, Colorado, [†]Abbott, St. Paul, Minnesota, [‡]Medpace Inc, Cincinnati, Ohio, and [§]Milestone Pharmaceuticals Inc, Montreal, Quebec, Canada.

Introduction

High-density (HD) mapping of tachycardias can be helpful in identifying the circuits in complex arrhythmias. It has also been shown to be helpful in identifying the slow pathway in atrioventricular nodal reentrant tachycardia (AVNRT). We participated in the NODE-1 study, which was a multi-center, placebo-controlled, double-blinded, dose-ranging phase II study comparing 4 doses of intranasal Etripamil to placebo for the conversion of induced supraventricular tachycardia.¹ Etripamil (Milestone Pharmaceuticals Inc, Montreal, Quebec, Canada) is a novel short-acting L-type calcium channel blocker effective in terminating supraventricular tachycardia by primarily affecting AV nodal conduction. During testing on 1 of the subjects, serial high-density mapping of the slow pathway region was performed.

Case report

A 62-year-old woman with recurrent documented narrow complex tachycardia presented for radiofrequency ablation. She was consented to the NODE-1 study. The study was approved by our local Investigational Review Board.

A routine electrophysiology study was performed. Josephson fixed curve quadripolar catheters (Response, St. Jude Medical, Minnetonka, MN) were placed in the right atrium and the right ventricle. A steerable decapolar catheter (Livewire, St. Jude Medical, Minnetonka, MN) was placed in the coronary sinus (CS) and used as a reference catheter.

KEYWORDS AV node reentry; NODE-1; 3D anatomic mapping; Etripamil; Ablation; High-density mapping (Heart Rhythm Case Reports 2017; ■:1-4)

William Choe and Sri Sundaram are consultants and recipients of an investigator-initiated research grant from St. Jude Medical. South Denver Cardiology Associates participated in the NODE-1 study and received grant support for enrollment from Milestone Pharmaceuticals. Charles Boorman and Nate Mullins are employees of Abbott. Pirouz Shamszad is an employee of Medpace Inc. Francis Plat is the CMO of Milestone Pharmaceuticals. **Address reprint requests and correspondence:** Dr William C. Choe, South Denver Cardiology Associates, 1000 South Park Dr, Littleton, CO 80120. E-mail address: williamc@southdenver.com.

A 2-2-2-mm spaced steerable octapolar catheter (Biosense Webster, Diamond Bar, CA) was placed in the His bundle region. Before induction of tachycardia, HD mapping along with 3-dimensional mapping of the right atrial septum around the slow pathway region was performed with the octapolar catheter and the EnSite Velocity system (St. Jude Medical, St Paul, MN). Baseline measurements were made. AV node Wenckebach was 330 ms. During AV node effective refractory period determination, there was a jump from the fast to the slow pathway and tachycardia was induced with a cycle length of 373 ms. Septal VA time was 61 ms and ventricular overdrive pacing just below the cycle length of the tachycardia induced a V-A-V response with a tachycardia cycle length > 110 ms, all consistent with typical AVNRT.

Once tachycardia was confirmed to be AVNRT, the patient was randomized in the NODE-1 protocol. The protocol specifies that the tachycardia be sustained for 5 minutes and then study drug given via intranasal route. Within 90 seconds after inhalation of the study drug, tachycardia terminated. At predetermined time points required in the study (3, 15, and 30 minutes post drug inhalation) pacing maneuvers were attempted and additional HD mapping of the slow pathway region was also repeated with the octapolar catheter.

HD mapping was not part of the NODE-1 protocol but is routinely performed in our AVNRT cases at our center. With the 2-mm spaced octapolar catheter, we manually obtained and annotated multiple points at each location in the atrial septum. An average of 1154 points were collected (range, 820–1375) and 489 points annotated (range, 384–624) to create the maps. By manually adjusting the voltage setting in cases with a slow pathway, a low-voltage bridge can be noted in the slow pathway region reaching from below the level of the CS os toward the compact AV node.² This low-voltage atrial signal represents the fractionated electrogram, which can be targeted for ablation (Figure 1).

To create a voltage gradient map to identify the slow pathway bridge, the high voltage is set at 1.5 mV and dynamically adjusted. Then the minimum voltage value is dynamically adjusted from 0.1 mV until a compressed band of

KEY TEACHING POINTS

- Three-dimensional voltage gradient mapping can help identify the slow pathway.
- Etripamil is a novel short acting L-type calcium channel blocker effective in terminating supraventricular tachycardia by primarily affecting atrioventricular nodal conduction. We report on the electroanatomic characteristic changes of the slow pathway region using high-density voltage gradient mapping on 1 subject during phase II testing of NODE-1.
- Voltage gradient mapping of the atrial septum in the triangle of Koch has been reported as a method of identifying the slow pathway region to target for ablation.

heterogeneous colors appears between the spectrum of red and yellow. The values below the lower value will display as gray and voltages above maximum value will be purple. All maps displayed in the figures use the same voltage gradient values. The low-voltage bridge is the area of heterogeneous color compression (between red and yellow), which may be between 2 gray areas representing an area of tissue that has higher signals than its surrounding area, or it may represent a narrow band of compressed colors between the gray area (low-voltage signals) and the purple area (high-voltage signals). This low-voltage bridge has been shown to correlate with slow pathway function.²

Atrial pacing down to AV block cycle length was performed at the prespecified time points (3, 15, and 30 minutes). There was a marked change in the AV block cycle length from baseline of 330 ms to 550 ms 3 minutes after inhalation of Etripamil. Figure 2A shows loss of the voltage in the slow pathway region at 3 minutes post inhalation. There was gradual improvement in the block cycle length

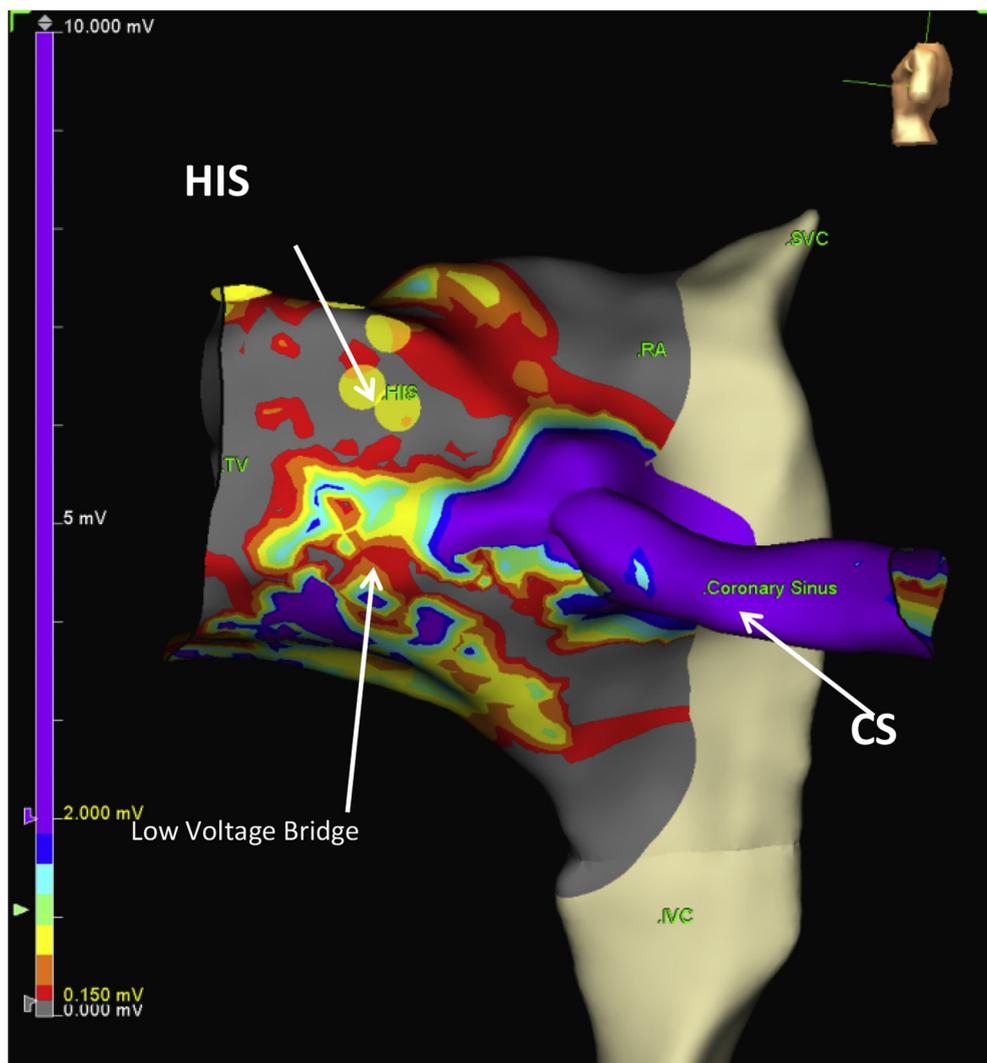


Figure 1 Baseline sinus rhythm voltage map. Image is left lateral view. Adjustment of the voltage settings show heterogeneous colors (between red and yellow), which represent the low-voltage bridge (slow pathway). This area is between areas of no voltage (gray) and high voltage (purple). Yellow dots represent the His region. CS = coronary sinus.

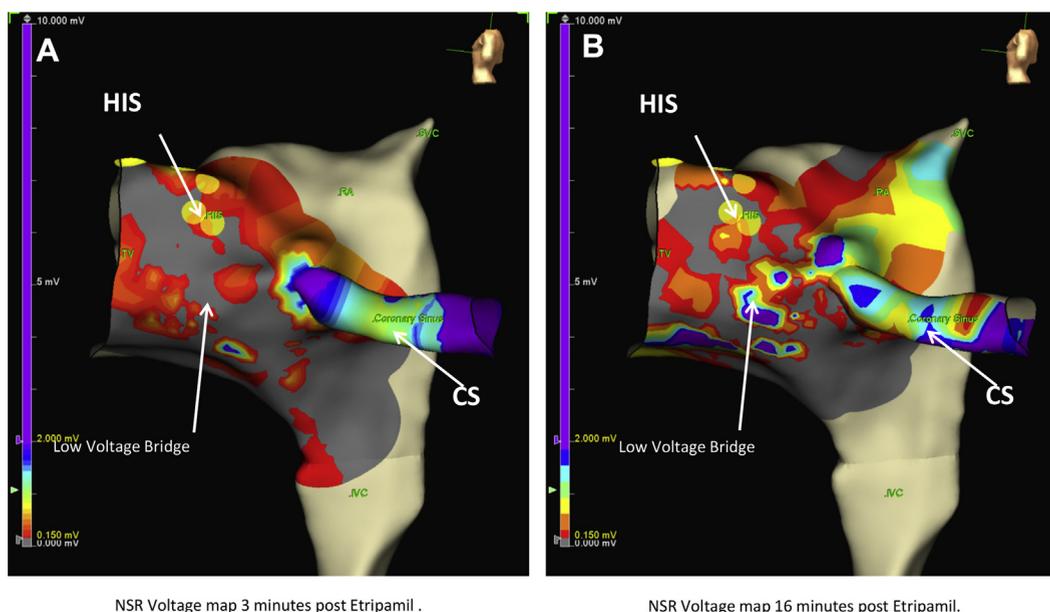


Figure 2 Etripamil sinus rhythm voltage maps. **A:** Voltage map 3 minutes after Etripamil showing loss of low-voltage bridge voltage. **B:** Sixteen minutes post Etripamil showing return of voltage in the low-voltage bridge region. CS = coronary sinus.

from 490 ms down to 450 ms at 15 and 30 minutes, respectively. Correlating to the improvement in block cycle length, there is return of voltage in this area, as shown in [Figures 2B](#) and [3A](#).

After 45 minutes, catheter ablation of the slow pathway was performed using a 4-mm Safire ablation catheter (St. Jude Medical, Minnetonka, MN) delivering up to 30 W, 50°C for 60 seconds, targeting the low-voltage bridge in [Figure 3A](#). Junctional beats were noted in the area predicted by our voltage map. After a 30-minute waiting period, tachycardia could not be induced post ablation with or without isoproterenol infusion, and HD mapping was again

performed. [Figure 3B](#) shows loss of the bridge and the lack of voltage 30 minutes post ablation in this area.²

Discussion

We report on the electroanatomic effects of intranasal Etripamil on the slow pathway. HD noncontact mapping of the AVNRT circuit has been previously reported.³ Voltage mapping of the atrial septum has also been reported to be another method of identifying the slow pathway.^{3,4} In patients with AV node reentry, with adjustments in the voltage settings, a discrete low-voltage channel appears in the low posterior

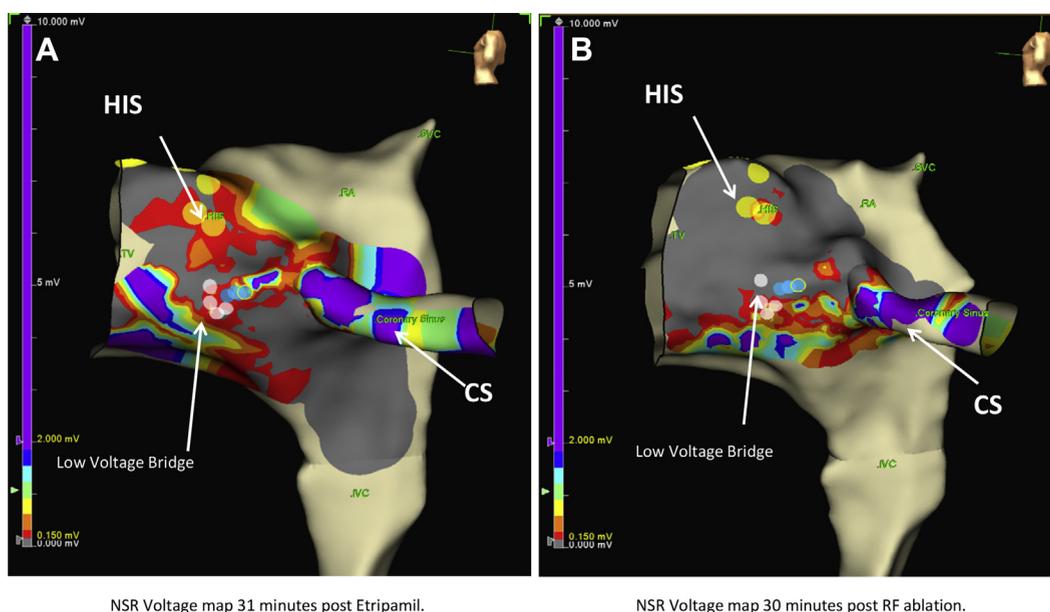


Figure 3 Postablation sinus rhythm voltage maps. **A:** Thirty-one minutes post Etripamil showing the low-voltage bridge. White dots (short test lesions without junctional beats) and blue dots (successful lesions with junctional beats) showing where radiofrequency lesions were delivered. **B:** Thirty minutes post ablation showing loss of low-voltage bridge, which appears similar to [Figure 2A](#), which was 3 minutes post Etripamil. CS = coronary sinus.

atrial septum near the CS os leading toward the compact AV node. Within the low-voltage bridge, typical slow pathway electrograms can be seen. When this area is successfully ablated, the voltage map changes and there is no longer a low-voltage bridge noted in this region.

Etripamil is a L-type calcium channel blocker with a short half-life (<5 minutes). After the study was completed, we were able to confirm that the patient received Etripamil 105 mg and not placebo. Serial HD voltage maps taken over the next several minutes after medication administration shows the dramatic effects that Etripamil has on the slow pathway region. Immediately post inhalation at 3 minutes, the map shows a dramatic loss of voltage in the slow pathway (Figure 2A) similar to the postablation map (Figure 3B), suggesting that Etripamil affects the slow pathway bridge. Over the next several minutes, there is a gradual recovery of voltage in this area along with slow recovery of AV nodal conduction (Figures 2B and 3A). The voltages surrounding

tissue in the CS region and fast pathway region do not seem to be affected as much. Unfortunately, this was the only case in which we were able to perform HD mapping post Etripamil inhalation, because the study closed shortly afterward. Further studies should be performed to evaluate the slow pathway with this medication.

References

1. Efficacy and Safety of Intranasal MSP-2017 (Etripamil) for the Conversion of PSVT to Sinus Rhythm (NODE-1), www.clinicaltrials.gov. NCT02296190.
2. Bailin SJ, Korthas MA, Weers NJ, Hoffman CJ. Direct visualization of the slow pathway using voltage gradient mapping: a novel approach for successful ablation of atrioventricular nodal reentry tachycardia. *Europace* 2011;13:1188–1194.
3. Steinberg BA, Piccini JP. High-density mapping of the tachycardia circuit in atrioventricular nodal reentrant tachycardia. *HeartRhythm Case Rep* 2016; 2:451–453.
4. Lee PC, Tai CT, Lin YJ, Liu TY, Huang BH, Higa S, Yuniadi Y, Lee KT, Hwang B, Chen SA. Noncontact three-dimensional mapping guides catheter ablation of difficult atrioventricular nodal reentrant tachycardia. *Int J Cardiol* 2007; 118:154–163.