# Ethanol infusion in the vein of Marshall: A potential bail-out strategy in cardioneuromodulation procedures?

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## Introduction

It is well known that the vein of Marshall (VOM) and its neighboring atrial myocardium contain intrinsic cardiac nerves that can induce parasympathetic responses. Relevantly, VOM ethanol infusion can eliminate these parasympathetic responses consistent with regional left atrial denervation. Nevertheless, there is scarce information regarding its role in the setting of cardioneuromodulation procedures.

## Case report

A 53-year-old male patient with history of recurrent syncope in the setting of sinus node dysfunction with concurrent episodes of asystole (Figure 1a) and atrial fibrillation (AF) was referred to our institution for catheter ablation. Both transthoracic echocardiogram and cardiac magnetic resonance rule out the presence of manifest structural heart disease. Although the atropine test performed the day before the procedure (2.5 mg of atropine sulfate given intravenously; dose calculated as 0.04 mg/kg body weight) did not show a significant increase in the resting heart rate (HR) (from 50 to 61 beats/min), owing to the presence of AF, the patient was scheduled for pulmonary vein isolation (PVI) plus cardioneuroablation (CNA). At that time, the patient was under oral anticoagulation, without beta blocker or any other antiarrhythmic drug. The procedure was performed using mild sedation with midazolam and additional fentanyl boluses. Mapping and ablations were performed using a 3.5 mm irrigated-tip catheter (Navistar ThermoCool SmartTouch; Biosense Webster, Diamond Bar, CA). Initially, 3-dimensional virtual anatomy of the right and left atrium was created using the CARTO 3 fast anatomic mapping system (Biosense Webster, Diamond Bar, CA). PVI was performed in the standard fashion aiming to cover the location of the main epicardial ganglia plexus (GP) (roof of the left superior pulmonary vein [PV] between the vein and the left atrial appendage, roof of the left inferior PV, anteriorly and superiorly to the right superior PV, anteriorly to the right inferior PV in left atrium) and posteroinferior GP at the level of coronary sinus ostium. Multiple ablations (power control, 35 W in the posterior wall, 45 W in anterior, with a target contact force of 10–30 g) aiming to achieve local electrogram attenuation and ablation index (Biosense Webster, Diamond Bar, CA) of 400–500. After PVI, the area of the superior vena cava GP (medial lower part of superior vena cava) was targeted (Figure 1c–1e). During the latter, insignificant

### KEY TEACHING POINTS

- Vein of Marshall (VOM) ethanol injection could represent a bail-out therapy in cases refractory to conventional cardioneuroablation, particularly in the setting of patients with concomitant atrial fibrillation.
- In this scenario, the underlying mechanism seems to be different from the disturbances seen in patients with pure cardioinhibitory response.
- Reducing even normal parasympathetic tone by means of VOM ethanol injection may result in a clinically relevant modulation of the intrinsic autonomic tone.

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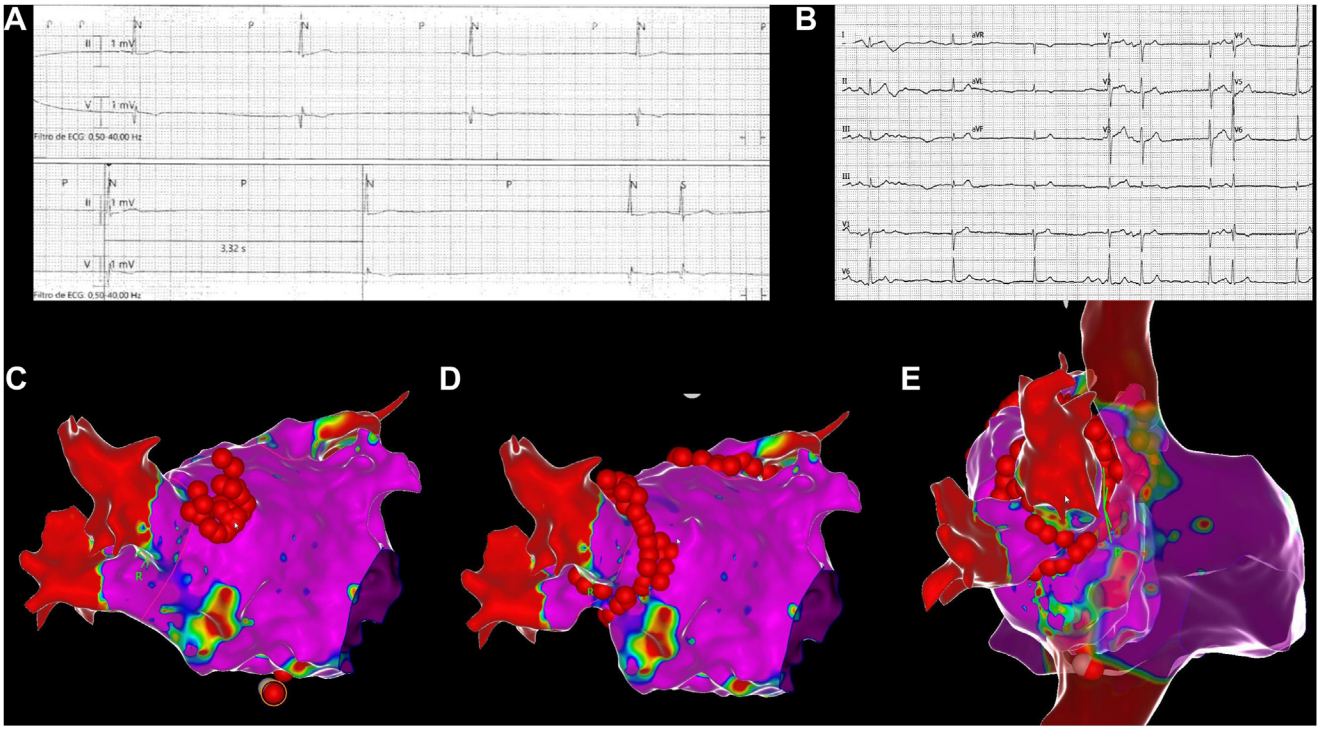


**Figure 1** **a:** Tracing showing some of the episodes of sinus node arrest/nodal rhythm. **b:** Episodes of atrial fibrillation preablation. **c:** Right anterior oblique view depicting the radiofrequency (RF) lesions applied at the level of the superior vena cava–ganglia plexus (medial lower part of vena cava). **d:** Right anterior oblique view illustrating the RF applications in the left atrium. **e:** Simultaneous view of right and left applications.

increase in HR was noticed. Later ablations more inferiorly along the posterior interatrial septum from the left atrium and right atrium were anatomically guided. After no additional increase in HR with further ablations and target anatomic area, the procedure was terminated. Atropine test at the end of the procedure resulted in negligible sinus rate increase (from 54 beats/min to 57 beats/min), which according to published data suggests effective denervation.[1] The patient was discharged home 24 hours after the procedure without complications but required new admission 7 days later for symptomatic sinus bradycardia (despite absence of chronotropic medication). The decision to implant a dual pacemaker was then undertaken. The device was programmed in AAIR-DDDR mode, aiming to avoid unnecessary ventricular pacing. Any AF suppression algorithms or rate drop algorithms were activated. Two months after the implantation, atrial pacing (AP) was predominant, with an AP percentage of 85%. Nevertheless, a few days after this control, the patients required new admission to the Emergency Department owing to left atrial flutter with fast ventricular response. After thorough discussion of the alternatives, the patient was scheduled for a redo procedure. Perimitral reentrant atrial flutter was diagnosed with 3D propagation maps with an evident rotation corresponding to the entire cycle length of the tachycardia. Conventional entrainment mapping confirmed the diagnosis. PVs presented entrance (Figure 2a) and exit block and did not require further applications. Successively, the VOM was cannulated with an angioplasty balloon to deliver 4 1-mL infusions of 98% ethanol, as previously reported[2] (Figure 2b). Voltage map was repeated after VOM ethanol infusion (Figure 2c), exhibiting an inferolateral scar. Additional endocardial radiofrequency ablation at the mitral annulus was needed to achieve bidirectional mitral isthmus block. This was also verified by differential pacing. No other additional lesions were then performed. The patient was discharged home under oral anticoagulation and colchicine 0.5 mg every 24 hours for 8 weeks. Three months after the second ablation procedure, the patient was seen in the outpatient clinic. Remarkably, the percentage of AP had decreased to 14.8% (Figure 3a). The electrocardiogram showed a stable sinus rhythm at 78 beats/min (Figure 3b) and he expressed a marked improvement in his functional class (based on patient's subjective perception along with an increase in the device daily activity [curve a.5 in Figure 3a], neither a quality-of-life test nor functional examination was performed). The atropine test confirmed the persistence of denervation. Unexpectedly, pacemaker interrogation displayed a change in the average diurnal/nocturnal HR ratio (Figure 3a, tracing a.4) post VOM as compared to the first procedure and a slight increase in the HR variability (Figure 3a, tracing a.6).

## Discussion

Under our point of view, this case highlights the potential atrial denervation achieved by means of VOM ethanol injection, which could represent a bail-out therapy in refractory cases to conventional CNA. The effect on AP observed in our patient is in line with existing data. It is well known the role of

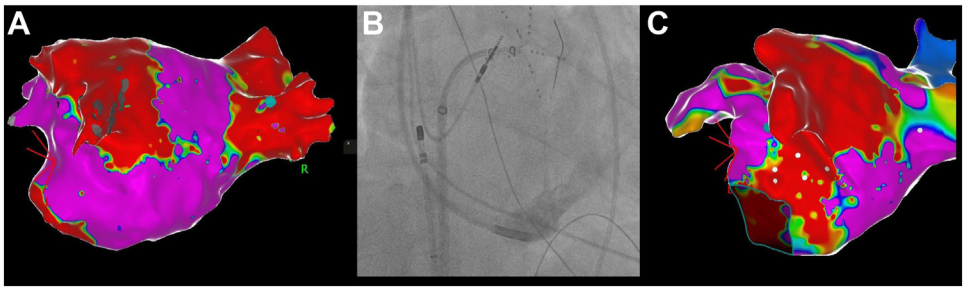


**Figure 2** **a:** Voltage map of the left atrium (cut-off 0.20–0.50 mV) at the time of the procedure in atrial flutter rhythm. **b:** Venogram of the vein of Marshall (*arrow*). **c:** Electroanatomical map (left atrium lateral view) after venous ethanol ablation and focal radiofrequency endocardial applications at the annular level.

VOM as a source of ectopic beats that could initiate AF and of dual sympathetic and parasympathetic innervation[3] of arrhythmogenic potential. Accordingly, VOM represents a therapeutic target in AF ablation procedures. Moreover, Baez-Escudero and colleagues[4] demonstrated not only how the VOM and its neighboring atrial myocardium contain intrinsic cardiac nerves that can induce parasympathetic responses, but also that VOM ethanol infusion eliminated parasympathetic responses and AF induction, consistent with regional left atrial denervation. This effect might have been responsible for the modification in the percentage of AP of our patient, which was not achieved after the first procedure despite extensive biatrial ablation. Remarkably, this first ablation, although it did not increase the HR, led at least to a partial denervation based on the fact that vagal response was completely abolished after atropine. Nevertheless, this might not be a reliable endpoint of CNA in the present case owing to the insufficient response to atropine shown previous to the CNA procedure. In any case, a central, vagally mediated phenomenon seemed implausible and most likely, the patient presented a predominant intrinsic component of the sinus node dysfunction, explaining also the irrelevant HR increase after denervation. This is not the first time that this phenomenon is presented, and several cases of successful CNA in patients with intrinsic conduction disturbances have been reported. For instance, Bulava and colleagues[5] presented the positive response to CNA for the treatment of atrioventricular (AV) conduction disturbances caused by radiofrequency catheter ablation of the slow pathway in a patient with AV nodal reentry tachycardia. In their patient, reducing even "normal" parasympathetic tone resulted in normalization of AV conduction, which could have been the mechanism explaining the response to CNA of our patient. In this line, Flautt and colleagues[6] reported a case of CNA used to treat high-degree AV block in a patient with an orthotopic heart transplant, which supports primary activation of intrinsic cardiac nerves without central nervous system

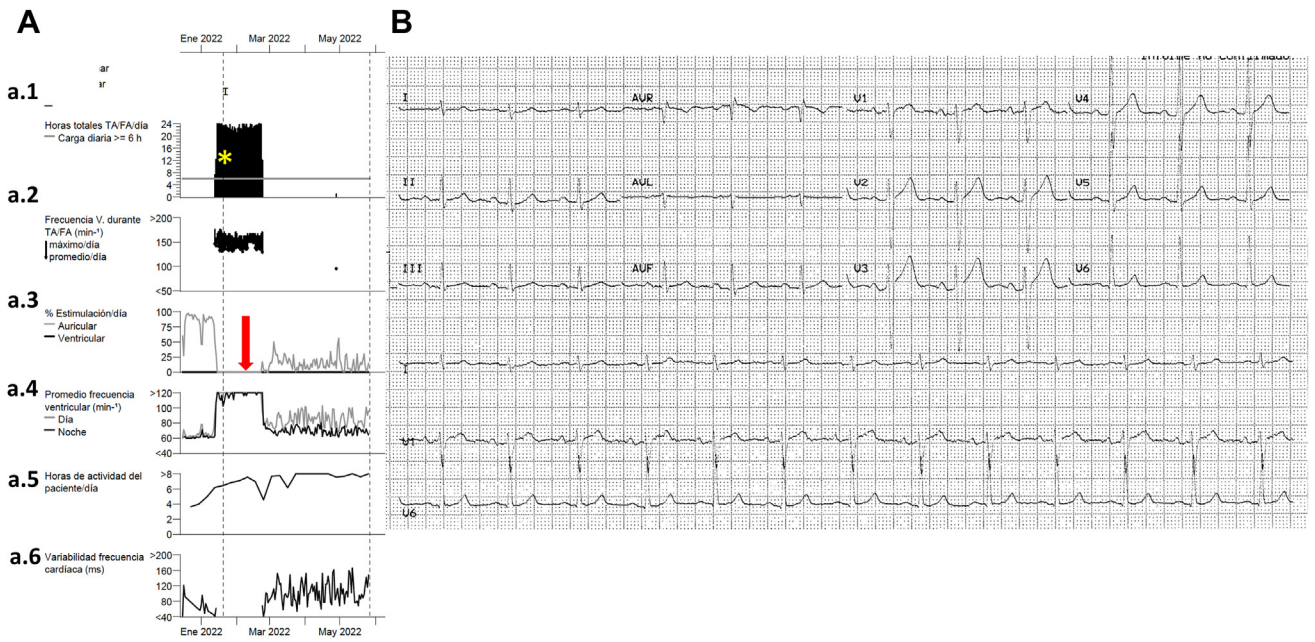


**Figure 3** **a:** Pacemaker interrogation performed 3 months after vein of Marshall ethanol infusion (*red arrow*) showing atrial tachycardia burden (*yellow asterisk*) 2 months after the first ablation (December 2021) with the significant reduction in atrial pacing immediately after the second procedure: **a.1:** total time in atrial tachycardia; **a.2:** heart rate during atrial tachycardia; **a.3:** percentage of atrial and ventricular pacing; **a.4:** mean ventricular heart rate (day and night, respectively); **a.5:** patient activity (in hours); **a.6:** heart rate variability.

influences as a mechanism of functional AV block. This conceivable different underlying mechanism could explain the unexpected behavior regarding the diurnal/nocturnal HR ratio and HR variability of our patient, as compared to the classical indication in which a decrease in HR variability is seen after CNA. Moreover, the predominant AP (85%) pre-VOM could have also played a role in the effect seen in the diurnal/nocturnal ratio and the HR variability.

It is clear that VOM ethanol infusion results in a nonpredictable and extensive lesion that might not be justified in the setting of patients without AF. Nevertheless, an important implication of the effect seen in our patient is that VOM ablation might be considered as a bail-out therapy in refractory cases, particularly in those patients with associated AF, a situation in which VOM ethanol infusion also increases the likelihood of remaining free of AF.[2] We consider that based on the initial atropine test and with the current available data, this case does not represent a classic indication for CNA, and it would have never been performed outside the setting of concurrent PVI. The ultimate role of VOM ethanol infusion in CNA procedures remains to be determined and would only be established in a randomized clinical trial assessing its additional effect over the standardized approach proposed by Pachon and colleagues.[7]

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