Computed tomography-based identification of ganglionated plexi to guide cardioneuroablation for vasovagal syncope

Pietro Francia [§ *], MD, Daniel Viveros [§], MD, Giulio Falasconi [§], MD, David Soto-Iglesias [§], PhD, Juan Fernández-Armenta [¶], MD, Diego Penela [§], MD, PhD, Antonio Berruezo [§], MD, PhD

[§] Arrhythmia Department, Teknon Heart Institute, Teknon Medical Center, Barcelona, Spain

* Cardiology Unit, Department of Clinical and Molecular Medicine, Sant'Andrea Hospital, University Sapienza, Rome, Italy

[¶] Puerta del Mar University Hospital, Cádiz, Spain

Running title: Fat pads-guided CNA

Funding: there are no sources of funding to disclose

Conflicts of interest: P.F. received speaker fees from Boston Scientific and research grants from Abbott and Boston Scientific. A.B. is stockholder of Galgo Medical. D.S.-I. is an employee of Biosense Webster Inc. All other authors declared no conflicts of interest.

Address for correspondence

Antonio Berruezo, MD, PhD.

Arrhythmia Department, Teknon Heart Institute

Teknon Medical Center, Barcelona, Spain

E-mail: antonio.berruezo@quironsalud.es

Cardioneuroablation (CNA) is an effective treatment for cardio-inhibitory vaso-vagal syncope (CI-VVS) that is under evaluation as a potential alternative to cardiac pacing in selected patients [1]. The cornerstone of CNA is targeting groups of autonomic ganglia known as ganglionated plexi (GPs) embedded in epicardial fat pads (EFP) that are interconnected via intrinsic nerves with the sino-atrial and atrio-ventricular nodes. GPs are commonly identified by high frequency stimulation (HFS), fractionated electrogram (fEGM), or based on anatomical landmarks [1-5]. Although varying in efficacy, these approaches may be hampered by limited sensitivity and specificity, unintended AF induction, and interpatient variability. CT-assisted CNA [6] and CT-based identification of EFP to target GPs during AF ablation [7] have been reported. We sought to assess feasibility of CT-based EFP-guided CNA in patients with CI-VVS.

We enrolled 12 patients (6 males, 53±13 years) with multiple episodes of CI-VVS. Ten had head-up tilt-test (HUT) with cardioinhibitory response (type 2A in 3 patients, type 2B in 5, mixed response in 2). One patient had a negative HUT and one did not undergo the test. These two patients experienced spontaneous transient symptomatic high-degree AV block. Patients underwent EP study, including atropine test, that ruled out organic sinus and AV node dysfunction. After discussion with patients on management options, CNA was proposed prior to committing to pacing. The study was approved from the Ethic Committee and informed consent was obtained.

Contrast-enhanced CTs displaying right, left atrial (LA) anatomy, aorta and EFP near the area of anticipated GPs [8] with attenuation -190 to -30 HU were segmented and exported using ADAS3D software (Galgo Inc). The following GPs were identified as EFP: left superior GP (LSGP) between left superior pulmonary vein (PV) and LA appendage, Marshall tract GP (MTGP) in the carina between left PVs, left inferior GP (LIGP) posteriorly to the left inferior PV, inferior paraseptal ganglionated plexus (IPSGP) between the posterior wall of LA and coronary sinus, superior paraseptal ganglionated plexus

(SPSGP) between the right superior PV and superior vena cava, right inferior GP (RIGP) between the two right PVs, and aorta-superior vena cava GP (Ao-SVC GP).

On the day of CNA, anatomical map of the LA was acquired using CARTO 3 (Biosense Webster, Diamond Bar, CA) and fused with CT. EFP areas were searched for fEGMs (≥4 deflections) but ablated independently from fragmentation. The ablation end-point for each GP was defined as abolition of RF-induced vagal response for left PV GPs, an increase in basal HR ≥25% for SPSGP, RIGP and Ao-SVC GPs, and shortening of AH interval for IPSGP. In case RF over EFP did not elicit autonomic response, we targeted the closest GP area based on anatomical landmarks. Left PV GPs were ablated first, followed by right PV GPs, IPSGP, and Ao-SVC GP.

A total of 84 EFP were ablated in 12 patients (median RF applications: 2, IQR:1-3; time:57 s, IQR:33-77). Response to RF for each EFP is shown in **Figure 1**. Overall, 25 (30%) EFP responded to RF. SPSGP displayed the highest rate of RF response (100%) and the most consistent correlation between EFP position and post-RF HR increase (**Figure 1**). Five additional GPs (6%) responded close but outside the EFP, at the level of the predicted area (EFP-RF distance: 5.5±1 mm). Therefore, out of 25 GPs that responded to RF, 20 (80%) were effectively ablated over the EFP. RF delivery did not induce any response in 54 (64%) GPs either at the level of the EFP or at the predicted anatomical location.

After CNA, atropine was administered showing flattened HR response (from 75±24 to 78±24 bpm) without substantial changes of sinus or AV node function in all but one patient, who still displayed significant HR increase (from 72 to 126 bpm). There were no procedure-related complications. Nine patients had follow-up >4 months (median:5, IQR:4-9), without syncope recurrences.

This study shows that CT-based EFP-guided CNA for CI-VVS is feasible, can assist RF delivery with high precision, and has the potential to overcome the interpatient variability that affects CNA when performed solely by anatomic landmarks. Some EFP may not show autonomic response to RF due to previous successful ablation of a GP concealing subsequent GPs' response. Alternatively, some CT-

identified EFP might not contain GPs, as we didn't use direct methods (i.e. extracardiac vagal stimulation) to prove EFP innervation. Of note, we did not target areas with vagal innervation (i.e., left interatrial septum) [9] not associated with EFP. Further larger studies with longer follow-up are required to improve CT-based identification of GPs and our understanding of GP pathophysiology.

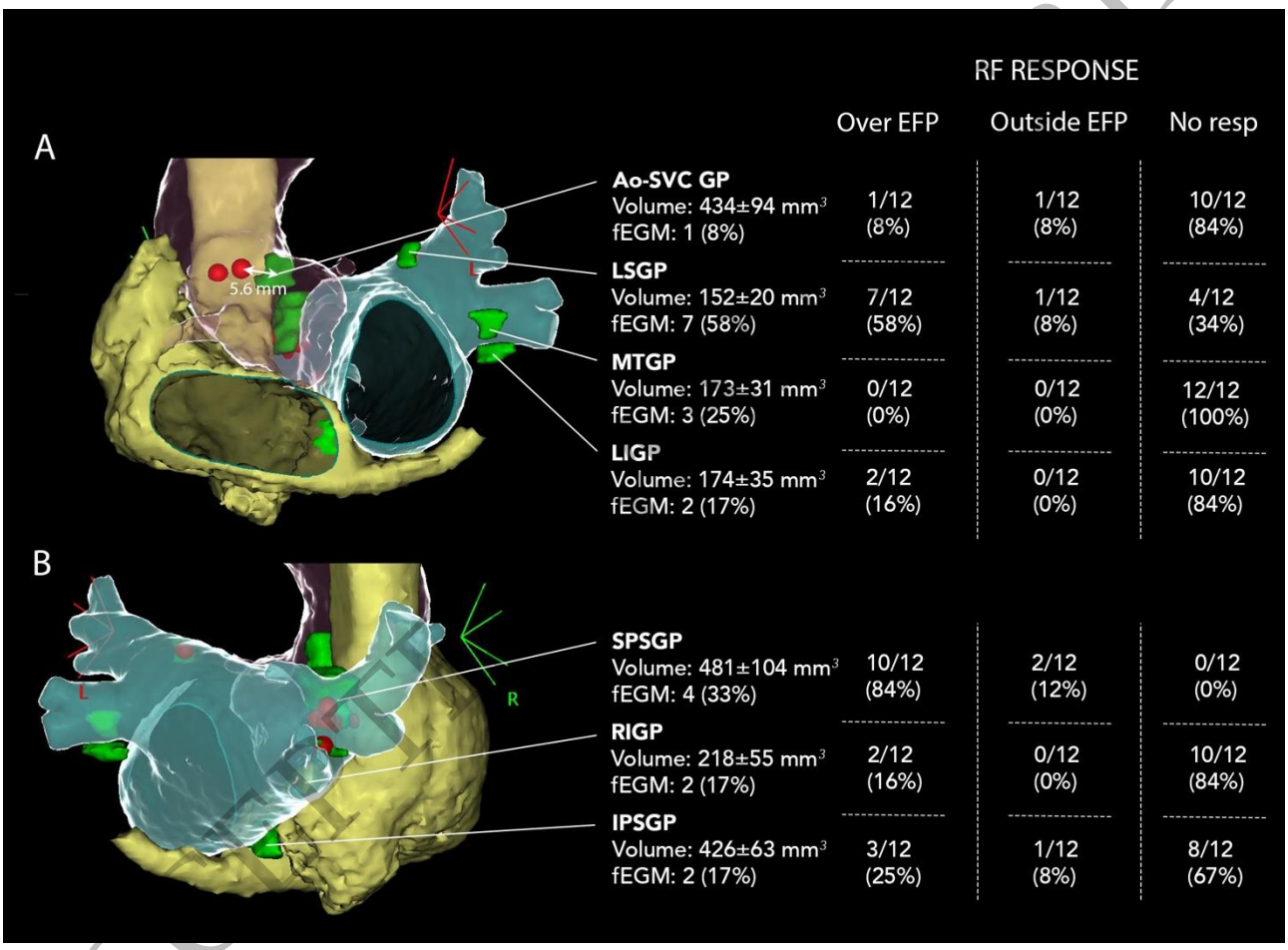


Figure 1. Anatomic localization of EFP and corresponding GPs. For each GP, RF response is reported according to the application site (over EFP, outside EFP, no response). **A.** Disagreement between EFP and effective RF site at the level of the Ao-SVC GP. **B.** In the same patient, effective RF over the EFP at the level of SPSGP.

References

[1] Pachon JC, Pachon EI, Lobo TJ, Pachon MZ, Vargas RN, Jatene AD. "Cardioneuroablation"--new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. *Europace* 2005; **7**: 1-13.

[2] Vandenberk B, Lei LY, Ballantyne B, Vickers D, Liang Z, Sheldon RS, et al. Cardioneuroablation for vasovagal syncope: A systematic review and meta-analysis. *Heart Rhythm* 2022.

[3] Pachon JC, Pachon EI, Cunha Pachon MZ, Lobo TJ, Santillana TG. Catheter ablation of severe neurally meditated reflex (neurocardiogenic or vasovagal) syncope: cardioneuroablation long-term results. *Europace* 2011; **13**: 1231-1242.

[4] Pachon M JC, Pachon M EI, Lobo TJ, Pachon MZ, Vargas RN, Pachon DQ, et al. A new treatment for atrial fibrillation based on spectral analysis to guide the catheter RF-ablation. *Europace* 2004; **6**: 590-601.

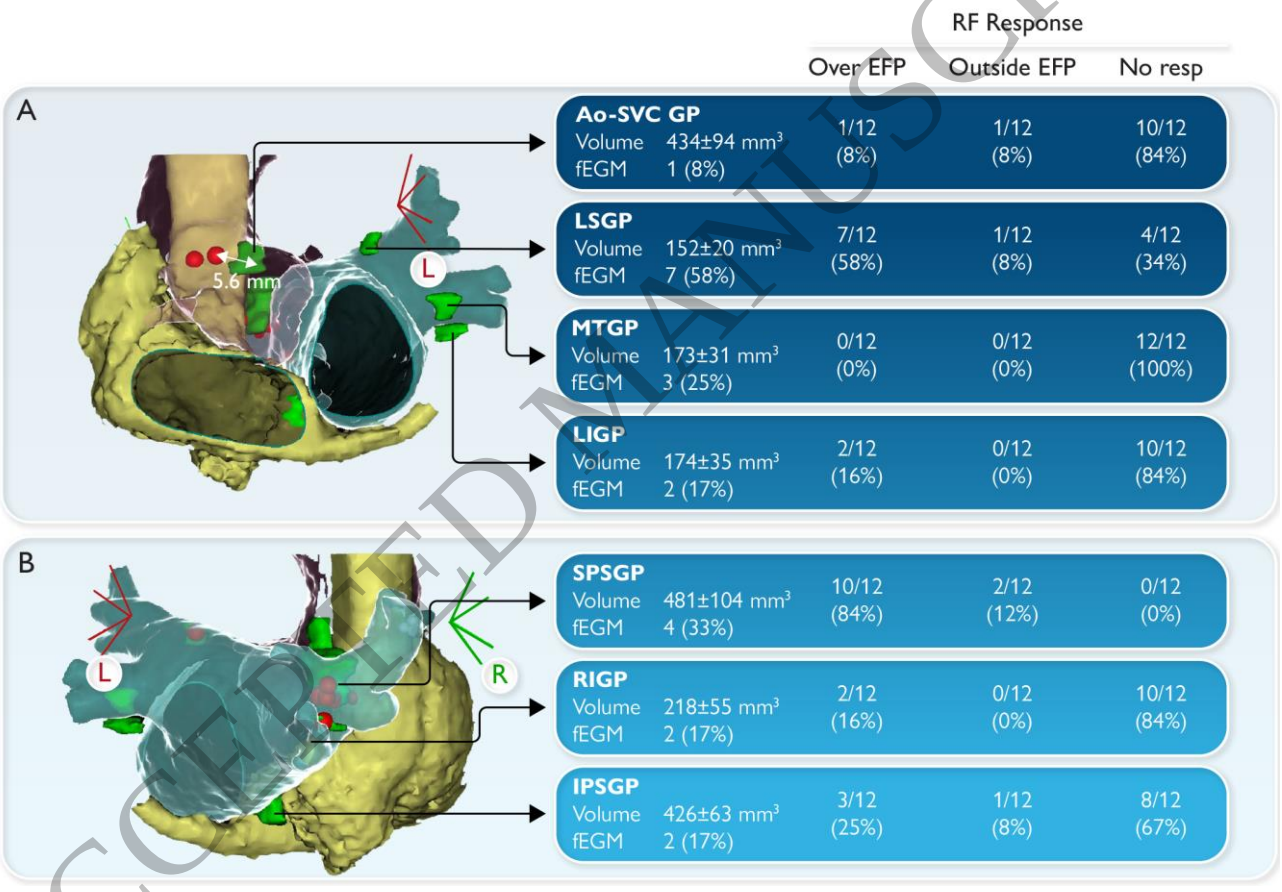
[5] Aksu T, De Potter T, John L, Osorio J, Singh D, Alyesh D, et al. Procedural and short-term results of electroanatomic-mapping-guided ganglionated plexus ablation by first-time operators: A multicenter study. *J Cardiovasc Electrophysiol* 2022; **33**: 117-122.

[6] Debruyne P, Rossenbacker T, Collienne C, Roosen J, Ector B, Janssens L, et al. Unifocal Right-Sided Ablation Treatment for Neurally Mediated Syncope and Functional Sinus Node Dysfunction Under Computed Tomographic Guidance. *Circ Arrhythm Electrophysiol* 2018; **11**: e006604.

[7] Markman TM, Khoshknab M, Santangeli P, Marchlinski FE, Nazarian S. Feasibility of Computed Tomography-Guided Cardioneuroablation for Atrial Fibrillation. *JACC Clin Electrophysiol* 2022; **8**: 1449-1450.

[8] Aksu T, Gupta D, D'Avila A, Morillo CA. Cardioneuroablation for vasovagal syncope and atrioventricular block: A step-by-step guide. *J Cardiovasc Electrophysiol* 2022; **33**: 2205-2212.

[9] Pachon-M EI, Pachon-Mateos JC, Higuti C, Santillana-P TG, Lobo T, Pachon C, et al. Relation of Fractionated Atrial Potentials With the Vagal Innervation Evaluated by Extracardiac Vagal Stimulation During Cardioneuroablation. *Circ Arrhythm Electrophysiol* 2020; **13**: e007900.



Graphical Abstract
170x118 mm (3.1 x DPI)