Cardioneuroablation for Vasovagal Syncope and Atrioventricular Block: A Step-by-Step Guide

Tolga Aksu[1], Dhiraj Gupta[2], André d'Avila[3], and Carlos A. Morillo[4]

[1]Yeditepe Universitesi Hastanesi
[2]Liverpool Heart and Chest Hospital NHS Foundation Trust
[3]Beth Israel Deaconess Medical Center
[4]University of Calgary Department of Cardiac Sciences

February 28, 2022

Abstract

Catheter based cardioneuroablation is increasingly being utilized to improve outcomes in patients with vasovagal syncope and functional atrioventricular block. There is now increasing convergence amongst enthusiasts on its various aspects, including patient selection, technical steps, and procedural end-points. This pragmatic review aims to take the reader through a step-by-step approach to cardioneuroablation: we begin with a brief overview of the anatomy of intrinsic cardiac autonomic nervous system, before focusing on the indications, pre- and post-procedure management, necessary equipment, and its potential limitations.

Introduction

Vasovagal syncope (VVS) is the most common cause of syncope clinically characterized by bradycardia and/or hypotension, mediated by parasympathetic overactivity and/or sympathetic withdrawal, respectively (1). Similarly, some cases of atrioventricular block (AVB) may be related to vagal hyperactivity in which paroxysmal AVB is accompanied by a significant slowing of sinus rate; also referred to as functional AVB because there is no intrinsic abnormality in the atrioventricular conduction system (2). Functional AVB is typically associated with well-identifiable triggers and characteristic prodromal symptoms like VVS.

Although the reflex is benign and occurs in otherwise healthy persons, frequent episodes or events without prodrome are debilitating, can lead to injuries and affect long-term quality of life (QOL). There are limited non-pharmacological and medical therapies proven effective in randomized clinical trials (3, 4). Pacing is indicated in a select population of patients > 40 years with refractory VVS and documented asystole (5). However, the role of cardiac pacing for the prevention of syncope recurrences remains controversial due to difficulties to exclude potential role of the hypotensive/vasodepressor component during the episode. No studies have specifically investigated the effect of cardiac pacing in patients with functional AVB.

Small open-label cohort studies have shown that catheter ablation of ganglionated plexi (GPs) or cardioneuroablation (CNA) can have salutary effects in some patients with VVS and functional AVB. In this article, we aim to provide a detailed description of CNA, including a brief review of the anatomy of intrinsic cardiac autonomic nervous system (ANS), indications, pre- and post-procedure management, necessary equipment, and potential pitfalls.

Anatomy of Intrinsic Cardiac Autonomic Nervous System

The human heart contains more than one and a half thousand autonomic ganglia (5) which cluster in anatomically well-defined areas known as GPs (6). While ablation of autonomic ganglionic plexi (GPs) causes permanent damage because neurons are amitotic and cannot be replaced, ablation of myocardial and

endocardial efferent nerve fibers will only cause a transient effect due to the regeneration capability of nerve fibers. As such, from a clinical electrophysiologist's perspective, understanding the difference between GPs and the pathway of innervation from autonomic ganglia to the heart is important to create a framework for ablation therapies so as to directly target neuromodulation of intrinsic cardiac ANS.

Based on Armour's GP nomenclature the following atrial locations contain most GPs: (1)superior right atrial GP; (2) superior left atrial GP; (3) posterior right atrial GP; (4) posteromedial left atrial GP; (5) interatrial septal GP; and (6) posterolateral left atrial GP (6). The vein of Marshall may also be considered part of the intrinsic cardiac ANS because parasympathetic fibers from the vein of Marshall innervate surrounding left atrial structures and the coronary sinus (7). Figure 1 schematically illustrates distribution of major atrial GPs which are usually targeted during CNA based on 3D mapping.

Patient Selection for Cardioneuroablation

Although most patients with VVS can be treated with patient education and non-pharmacological measures, a minority of patients with severe forms, such as those with very frequent syncope affecting quality of life, recurrent syncope without prodromal symptoms which exposes the patient to a risk of trauma, and syncope occurring during a high-risk activity may require interventional therapies (8). The current guidelines suggest that cardiac pacing should be considered in patients aged >40 years with frequent recurrent reflex syncope when bradycardia-syncope correlation is confirmed by implantable loop recorder (ILR) (class IIa) or head-up tilt test (HUTT) (class IIb). However, while permanent pacing does appear to be beneficial for some patients, syncope may recur because of the coexistence of a vasodepressor reflex, which is present to some degree in virtually all patients. Also, no data is available to support the use of pacemakers in patients with VVS under the age of 40. Although, in all large cohorts related to CNA (9-11), VVS cases were included according to HUTT results, we recently demonstrated that ILR implantation may be used to select suitable candidates for CNA (12). Therefore, similarly, demonstration of bradycardia-syncope correlation by HUTT or ILR in patients that continue to experience frequent and burdensome VVS recurrences may be applied for CNA case selection. In our current approach, we prefer the Newcastle protocol which includes tilting to 70 degrees for a passive unmedicated phase of 20 minutes, and if positivity/discontinuation criteria are not reached, administration of 300-400 μg sublingual nitroglycerine at the 20th minute, followed by an additional 15-20 minutes of standing to select potential candidates for CNA (13). The patients should not be tilted down prior to developing syncope as this may reduce the proportion of patients that actually end up manifesting asystole > 3sec. It may be possible to make particularly strong recommendations for CNA in patients <40 years of age, and those with the cardioinhibitory or mixed type of VVS. Our practical decision pathway for the management of VVS is summarized in Figure 2.

Atropine sulfate as a vagolytic is a competitive antagonist of actions of acetylcholine and other muscarinic agonists that accelerates both sinus node and atrial myocyte automaticity and increases the speed of atrioventricular conduction. Theoretically, CNA should mimic sinoatrial and atrioventricular nodal effects of atropine. Therefore, to define procedural endpoint and to predict potential results of ablation, pre-procedure atropine response should be checked in all cases at least 24 hours prior. An atropine response test should be attempted in all VVS cases and only patients demonstrating a positive response should be selected as candidates for the procedure. The test is carried out after 4 hours of fasting. Intravenous atropine sulfate 0.04 mg/kg is administered for 30 min under continuous electrocardiogram recording, and a sinus rate increase of [?]25% or a sinus rate [?]90 bpm in the first 20 min after infusion is considered a positive response (9).

According to the 2018 American College of Cardiology/American Heart Association/Heart Rhythm Society guideline, permanent pacing should not be performed in patients with asymptomatic functional AVB (14). However, the guidelines recommend pacing in patients with symptomatic AVB attributable to a known reversable cause like vagal overactivity if AVB does not resolve despite treatment of the underlying cause. Because functional AVB usually occurs in younger population, these patients are particularly vulnerable to long-term complications and challenges from pacemakers and they may need several interventions over their lifetime. Additionally, there are legitimate concerns over lead malfunction, pacemaker dependency and right ventricular pacing induced cardiomyopathy. CNA can potentially overcome these limitations. In a patient

with paroxysmal AVB, to determine the functional or vagal nature of the AVB, the relationship between sinus rate and AVB should be carefully evaluated. Functional AVB is usually characterized by a sinus node slowing before and during AVB episode or a progressive PR prolongation before AVB episode (15). In case of a negative Holter despite existence of typical symptoms, external or internal loop recorders should be preferred to rule out the presence of paroxysmal AVB and to establish a symptom–rhythm correlation. The patients demonstrating second- or advanced-degree AVB in 3 successive resting ECGs should be considered as persistent AVB. To differentiate intrinsic from functional AVB, atropine challenge (0.04 mg/kg, max 3 mg) and exercise stress test should be attempted. Complete resolution of AVB during atropine administration and exercise stress testing should be demonstrated in all cases (16). Regardless of the paroxysmal or persistent nature of AVB, an electrophysiological study with overdrive atrial pacing is indicated to exclude infra- or intra-Hisian AVB (17). In all AVB cases, pacemaker implantation as well as CNA should be discussed with the patient as treatment options. Despite the investigational nature of a CNA strategy in this cohort, the benefits of preserving physiological ventricular stimulation with a CNA procedure should always be considered.

How to Perform Cardioneuroablation

Patient preparation and procedure set-up

The patient can undergo CNA procedure under conscious sedation or general anesthesia. We have recently demonstrated that the autonomic nervous tone can be differentially affected by the level of conscious sedation (18). VR during GP ablation was defined on 3 levels: 1) R-R interval increase of >50% (level 1); 2) R-R interval increase of 20-50% (level 2); and 3) R-R interval increase of <20% (level 3). While ablation of the left superior GP caused a level 1 VR in 89.6% of cases in conscious sedation group, level 1 VR was seen in only 22.2% of cases in deep sedation group ($p<0.0001$). Similarly, percentage of patients with level 1 VR during ablation of the left inferior GP was significantly lower in deep sedation group. Once the cut-off for VR was decreased to level 2, the ratio of (+) VR during ablation of the left superior and inferior GPs was similar between groups. Thus, we concluded that R-R interval increase of >20% instead of >50% should be used for definition of VR in cases performed under deep sedation. In our current approach, in conscious sedation, patients receive a combination of fentanyl 50 μg and midazolam 0.02 to 0.06 mg/kg bolus, followed by a 3 to 5 mg/h continuous infusion. In deep sedation, patients receive a bolus injection of midazolam (0.02 to 0.06 mg/kg) over 30 s, followed a minute later by intravenous propofol infusion (1.0 to 2.5 mg/kg; infusion rate, 400-600 ml/h).

Furthermore, some anesthetic agents like ketamine, and mechanical ventilation, in particular positive end-expiratory pressure, may induce a shift in the sympathovagal balance toward sympathetic predominance, which may cause a blunting on VR characteristics during GP ablation (19). Awareness of anesthesia related differences may be important if GP ablation is performed by using VR characteristics during ablation.

A 6 French and one 8 French sheaths are placed in the right common femoral vein and a decapolar steerable catheter is placed in the coronary sinus (CS). Arterial line, urinary catheter or esophageal temperature probe are not routinely used. We start the procedure by performing a bipolar map of the right atrium with a multipolar (The Inquiry AFocusII) or a high-density mapping catheter (Advisor HD Grid and PentaRay®). We delineate the inferior and superior vena cava, and the coronary sinus, and we tag the His potential and phrenic nerve capture sites with high-output pacing of 20mA.

Next, a single transseptal puncture is performed using an 8.5 Fr transseptal sheath (SL1, St. Jude Medical, Minneapolis, MN, USA) and a transseptal Brockenbrough needle (BRK, St. Jude Medical) under fluoroscopic guidance -. A 0.032-inch 200 cm guidewire is advanced to the left superior pulmonary vein and transseptal sheath is replaced with a deflectable sheath [VIZIGO (Biosense Webster, Johnson & Johnson Medical S.p.a., Irvine, CA, USA) or Agilis NxT (Abbott, Chicago, IL, USA)]. Then, a multipolar or a high-density mapping catheter is advanced through the deflectable sheath into the left atrium to perform a fast-anatomical mapping of the left atrium and the pulmonary veins. During fast-mapping, we particularly focus on acquiring contact points between the right superior pulmonary vein and the superior vena cava, and the septal part of lower

left atrium and the coronary sinus ostium.

Mapping of ganglionated plexi during electrophysiological study

Two approaches can be used for selective identification of GPs: (1) high-frequency stimulation (HFS) and (2) electrogram analysis.

Although different groups have defined different settings for HFS application, in our laboratory, HFS is delivered at a frequency of 20 Hz, amplitude 10 V, and pulse duration of 10ms, for 2-5 seconds, aiming to test at least 100 HFS sites evenly distributed around the left atrium, as previously described (20). HFS applications longer than 5 seconds may stimulate sympathetic fibers and mitigate the parasympathetic response. HFS may cause two types of response: a vagal response (VR), defined as a transient ventricular asystole $>$ 3sec, atrioventricular block (second or third-degree), or an R-R interval prolongation by 50%, and a normal response characterized by the absence of any effect or nonsignificant changes on the PR or RR intervals. Theoretically, demonstration of a positive VR differentiates GP sites. The response to HFS should be reproducible at each site. In our laboratory, HFS-guided GP mapping strategy is used only for specific research protocols purposes, the following part of the review will discuss our favored electrogram-guided GP mapping strategy.

Lellouche et al (21) analyzed electrogram characteristics based on VRs during radiofrequency application and demonstrated that the best single predictor of VR during radiofrequency application was the number of electrogram deflections at the ablation site. In our initial work, GP sites were detected through a combination of fast Fourier transform analysis of electrograms and HFS (22). In accordance with Lellouche's observations, radiofrequency application on the sites showing fractionated electrogram pattern caused vagal response in all cases, whereas there was no vagal response in normal atrial myocardium sites during radiofrequency application. Because the better resolution afforded by the usage of higher high-pass filters allowed better appreciation of electrogram fragmentation (23), in our subsequent work, we used band-pass filter settings of 200–500 Hz instead of conventional band-pass filter settings of 30–500 Hz during sinus rhythm and targeted all fragmented electrograms in regions which are anatomically consistent with GPs (24). Compared with previous combined approach, fragmented electrogram-guided GP ablation decreased the procedure and fluoroscopy times while maintaining success rates.

Procedural steps of electrogram-guided ganglionated plexus mapping and ablation

After creation of 3D mapping of both atria, fragmented bipolar endocardial atrial electrograms are evaluated for number of deflections at filter settings of 200–500 Hz by using the ablation catheter. This setting is available in WorkMate Claris system (St Jude Medical, Abbott, St. Paul, MN, USA). In Prucka Cardiolab system (GE Healthcare, Wauwatosa, WI), 100–500 Hz can be selected as default setting (18). The EGMs demonstrating greater or equal to 3 deflections in regions which are anatomically consistent with GP sites are tagged as ablation targets (Figure 3). Although both atria are included in the analysis, ablation is started at the left atrium. After all GP targets have been identified in the left atrium, we deliver radiofrequency ablation of targeted areas in the following order: the superior left atrial GP; the posterolateral (inferior) left atrial GP; the Marshall tract GP (MTGP) on the endocardial aspect of the vein of Marshall; the superior right atrial GP; and the posterior (inferior) right atrial GP (Figure 3). If the heart rate after left atrial GP ablation reaches the pre-ablation atropine response test, we do not perform additional ablation in the right atrium. Otherwise, we perform empirical ablation around the posteroseptal wall of the superior vena cava for the superior right atrial GP site (Video 1). We have recently demonstrated that different GP sites demonstrate different neuromodulation characteristics during radiofrequency application (25). While ablation around the left-sided GPs causes a VR (Video 2 and 3), ablation of the superior right atrial GP increases heart rate acutely without any VR (Video 4). Furthermore, we demonstrated that right side first strategy may cause an attenuation of VR ablation around the left-sided GPs (26), and hence our preference for starting from the left sided GPs. Ablation of the inferior right atrial GP is not related to a significant VR regardless of ablation strategy.

In the human heart, the superior right atrial GP supplies epicardial nerves to the sinoatrial nodal neural

network, and it is likely that ablation around this area first affects endocardial and myocardial postganglionated nerve fibers before affecting epicardial ganglia which likely causes an increase in heart rate by blocking parasympathetic innervation of the sinoatrial node without vagal discharge effect (27). In patients with atrioventricular block, the posteromedial left atrial GP should also be targeted because postganglionated nerves from the posteromedial left atrial GP extend towards the interatrial septum and presumably supply the atrioventricular nodal region (28). We have recently demonstrated that ablation around the posteromedial left atrial GP resulted in 1:1 atrioventricular conduction in 13 (76.4%) of 17 patients with persistent second-degree atrioventricular block (Video 5) (17). However, we may need to extended ablation to other GP sites if desired atrioventricular response is not achieved after ablation around the posteromedial left atrial GP (Video 6).

We have recently compared the acute procedural characteristics and clinical success rates with fragmented-guided GP ablation in patients with vagally mediated bradyarrhythmias performed by first-time operators and those of a single high-volume operator center with an international multicenter registry from 16 sites (29). The proctor (TA) reviewed the electrograms and 3D maps in real time and opined on the suitability of ablation sites in all cases who were done by virtual proctoring. Although the procedure time was longer in the first-time GP ablation group, acute procedural success was achieved in all cases without any major adverse events. At a mean follow-up of 8.0 +- 3 months, none had recurrent syncope.

Use of a software to map ganglionated plexus sites

Despite promising results with the visual electrogram-guided GP ablation strategy, there are concerns regarding reproducibility of this technique, especially amongst relatively inexperienced operators. In this regard auto-algorithm software identifying fractionated areas may aid in developing more careful mapping to localize GPs. The Ensite Precision^{TM} (Abbott) system includes the fractionation mapping software that provides an algorithm to detected fragmented areas. Although there is some similarity with the CFAE (complex fractionated atrial electrogram) settings, the cycle length of atrial fibrillation is not taken into account in this new software. Fractionation mapping software was first used to detect critical ablation sites during sinus rhythm in a patient with vagal atrial fibrillation by our group (30). Mapping parameters were standardized at internal and external projections of 7 mm, interpolation of 7 mm, low-voltage identification of 0.1 mV. The Inquiry AFocusII (Abbott) catheter with 4-mm electrode spacing collected fractionated signals over 5 s. A baseline noise threshold of 0.05 mV was applied to exclude background system noise. Fractionation map was created using possible combinations of width (5 msec), refractory time (30 mses), and roving sensitivity (0.1 mV). Based on these parameters, the algorithm assigned each electrogram a fractionation score. The map color scale was set to color areas at or above the defined fractionation threshold as white (suggestive of fractionated electrogram) and below as purple (suggestive of nonfractionated electrogram). Acute atrial fibrillation termination was achieved during ablation in the fractionated areas (white) around the superior right atrial GP site. We have also reported this technique during sinus rhythm (31). The map color scale was set to color areas at or above the fractionation threshold of 2 as white. White areas were accepted as potential GP sites and were compared areas which were visually detected by our fragmented electrogram-guided method. Distribution of white areas demonstrated a close similarity with ablation points that were detected using visual fragmented EGM-based strategy (Figure 4). In our cases, ablation catheters (FlexAbility(r), Abbott) were used for mapping. Other groups have demonstrated similar procedural results with Virtual/remote real-time proctoring during the case by high-density mapping catheters (32, 33). However, the technique is still not validated in larger patient groups and multicenter studies are needed to confirm this benefit.

Ablation Settings and Endpoints

Radiofrequency current should be applied in a point-by-point fashion in power-controlled mode with an open irrigated-tip catheter. Radiofrequency energy is limited to 35 watts along the left atrial posterior wall and roof, and to 40 watts in the remaining areas for duration of at least 30 seconds at each site. The ablation endpoint for each GP is defined as the complete elimination of all targeted EGMs and elimination of positive VR following ablation at any site that demonstrated positive response in the previous ablation attempt(s).

In patients with VVS, achievement of 75% of the sinus rate that was detected during pre-ablation atropine response test may be accepted as clinical endpoint. In patients with functional atrioventricular block, the clinical endpoints should be as follows: in patients with persistent atrioventricular block, achievement of 1:1 atrioventricular conduction; in patients with paroxysmal atrioventricular block, achievement of at least one of the following: 75% of the final PR interval that was recorded during pre-ablation atropine response test, a reduction in PR interval of greater than 25%, or achievement of final sinus rate of <75% of that was recorded during the pre-ablation atropine response test.

Pachon et al (34) used extracardiac vagal stimulation (ECVS) to evaluate procedural endpoints. As a main advantage of the technique, denervation effect of sinus and atrioventricular nodes can be evaluated in real-time. Furthermore, response to ECVS might be more specific to quantify the vagal denervation than simple increase in the heart rate (34). However, this technique requires the ECVS hardware whose availability is limited.

Future implications

Some important questions remain unanswered. Long-term outcomes of GP ablation over a 5-year horizon or longer have not yet been reported. Randomized controlled trials comparing CNA and conservative therapy, and between CNA and pacing are required to demonstrate efficacy and safety of the technique. Because positive results of pacemaker implantation demonstrated a powerful placebo/expectation effect in the VVS population, there are similar concerns with CNA, and sham-controlled trials may help to quantify the placebo effect. Finally, it should be kept in mind that neuromodulation of ANS might be associated with procedural risks, either in terms of procedural complications or the potential for off-target effects like enhanced susceptibility to ventricular arrhythmias (35). Until we collect more data from prospective randomized studies, it is reasonable to proceed with caution in ablating these structures.

Conclusions

Cardioneuroablation appears to be a safe and efficacious procedure to improve outcomes in patients with VVS and functional atrioventricular block. Many skills that are required to perform CNA safely and effectively are already within the skillset of many electrophysiologists, and development of automated software to identify possible GP sites should decrease the learning curve. Well-designed controlled randomized trials are needed to further the field of CNA.

References

1. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, et al; ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39:1883–1948.

2. Alboni P, Holz A, Brignole M. Vagally mediated atrioventricular block: pathophysiology and diagnosis. Heart. 2013;99:904–908.

3. Sandhu RK, Raj SR, Thiruganasambandamoorthy V, Kaul P, Morillo CA, Krahn AD, Guzman JC, Sheldon RS; Secondary Writing Committee, Banijamali HS, MacIntyre C, Manlucu J, Seifer C, Sivilotti M. Canadian Cardiovascular Society Clinical Practice Update on the Assessment and Management of Syncope. Can J Cardiol 2020 Aug;36(8):1167-1177

4. Sheldon R, Faris P, Tang A, Ayala-Paredes F, Guzman J, Marquez M, Morillo CA, Krahn AD, Kus T, Ritchie D, Safdar S, Maxey C, Raj SR; POST 4 investigators. Midodrine for the Prevention of Vasovagal Syncope : A Randomized Clinical Trial. Ann Intern Med. 2021 Oct;174(10):1349-1356.

5. Aksu T, Gopinathannair R, Gupta D, Pauza DH. Intrinsic cardiac autonomic nervous system: What do clinical electrophysiologists need to know about the "heart brain"? J Cardiovasc Electrophysiol. 2021 Jun;32(6):1737-1747.

6. Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec. 1997;247:289-298.

7. Ulphani JS, Arora R, Cain JH, et al. The ligament of Marshall as a parasympathetic conduit. Am J Physiol Heart Circ Physiol. 2007;293: H1629-H1635.

8. Writing Committee Members, Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, Grubb BP, Hamdan MH, Krahn AD, Link MS, Olshansky B, Raj SR, Sandhu RK, Sorajja D, Sun BC, Yancy CW. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2017 Aug;14(8):e155-e217.

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

10. Hu F, Zheng L, Liang E, Ding L, Wu L, Chen G, Fan X, Yao Y. Right anterior ganglionated plexus: the primary target of cardioneuroablation? Heart Rhythm. 2019;16:1545–1551.

11. Aksu T, Guler TE, Bozyel S, Yalin K, Gopinathannair R. Usefulness of post-procedural heart rate response to predict syncope recurrence or positive head up tilt table testing after cardioneuroablation. Europace. 2020;22:1320–1327.

12. Aksu Tolga, Guler Tumer E, Saygı Serkan, Yalin Kivanc. Usage of implantable loop recorder to evaluate absolute effectiveness of cardioneuroablation. J. Cardiovasc. Electrophysiol. 2019 Dec;30 (12):2986–2987.

13. Parry SW, Reeve P, Lawson J, Shaw FE, Davison J, Norton M, Frearson R, Kerr S, Newton JL. The Newcastle protocols 2008: an update on head-up tilt table testing and the management of vasovagal syncope and related disorders. Heart. 2009 Mar; 95(5):416-20.

14. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, Goldschlager NF, Hamilton RM, Joglar JA, Kim RJ, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2019;140:e382–e482.

15. Aksu T, Güler TE, Yalın K. Step-by-Step Cardioneuroablation Approach in Two Patients with Functional Atrioventricular Block. Balkan Med J. 2019 Oct 28;36(6):301-310.

16. Aksu T, Guler TE, Bozyel S, Yalin K. Potential usage of cardioneuroablation in vagally mediated functional atrioventricular block. SAGE Open Med. 2019 Mar 15;7:2050312119836308.

17. Aksu T, Gopinathannair R, Bozyel S, Yalin K, Gupta D. Cardioneuroablation for Treatment of Atrioventricular Block. Circ Arrhythm Electrophysiol. 2021 Sep;14(9):e010018.

18. Aksu T, Yalin K, John L, Osorio J, Winterfield J, Aras D, Gopinathannair R. Effect of conscious sedation and deep sedation on the vagal response characteristics during ganglionated plexus ablation. J Cardiovasc Electrophysiol. 2021 Aug;32(8):2333-2336.

19. Neukirchen M, Kienbaum P. Sympathetic nervous system: evaluation and importance for clinical general anesthesia. Anesthesiology. 2008 Dec;109(6):1113-31.

20. Aksu T, Baysal E, Lakkireddy D, Yalin K, Gopinathannair R. Comparison of Fragmented Electrogram Based Strategy and High Frequency Stimulation for Detection of Ganglionated Plexi. J Atr Fibrillation. 2020 Dec 31;13(4):2440.

21. Lellouche N, Buch E, Celigoj A, et al. Functional characterization of atrial electrograms in sinus rhythm delineates sites of parasympathetic innervation inpatients with paroxysmal atrial fibrillation. J Am Coll Cardiol. 2007;50:1324-1331.

22. Aksu T, Golcuk E, Yalin K, Guler TE, Erden I. Simplified cardioneuroablation in the treatment of reflex syncope, functional AV block, and ainus node dysfunction. Pacing Clin Electrophysiol. 2016; 39:42–53.

23. Pachon MJC, Pachon MEI, Pachon MJC, et al. A new treatment for atrial fibrillation based on spectral analysis to guide the catheter RF-ablation. Europace. 2004;6:590-601.

24. Aksu T, Guler TE, Mutluer FO, Bozyel S, Golcuk SE, Yalin K. Electroanatomic-mapping guided cardioneuroablation versus combined approach for vasovagal syncope: a crosssectional observational study. J Interv Card Electrophysiol. 2019;54:177-188.

25. Aksu T, Yalin K, Bozyel S, Gopinathannair R, Gupta D. The anatomical basis behind the neuromodulation effects associated with pulmonary vein isolation. J Cardiovasc Electrophysiol. 2021 Jun;32(6):1733-1736.

26. Aksu T, Guler TE, Bozyel S, Yalin K. Vagal responses during cardioneuroablation on different ganglionated plexi: is there any role of ablation strategy? Int J Cardiol. 2019;304:50–5.

27. Pauziene N, Pauza DH, Stropus R. Morphology of human intracardiac nerves: an electron microscope study. J Anat. 2000;197:437-459.

28. Saburkina I, Rysevaite K, Pauziene N, et al. Epicardial neural ganglionated plexus of ovine heart: anatomic basis for experimental cardiac electrophysiology and nerve protective cardiac surgery. Heart Rhythm. 2010;7:942-950.

29. Aksu T, De Potter T, John L, Osorio J, Singh D, Alyesh D, Baysal E, Kumar K, Mikaeili J, Dal Forno A, Yalin K, Akdemir B, Woods CE, Salcedo J, Eftekharzadeh M, Akgun T, Sundaram S, Aras D, Tzou WS, Gopinathannair R, Winterfield J, Gupta D, Davila A. Procedural and short-term results of electroanatomic-mapping-guided ganglionated plexus ablation by first-time operators: A multicenter study. J Cardiovasc Electrophysiol. 2022 Jan;33(1):117-122.

30. Aksu T, Guler TE. Electroanatomical mapping-guided ablation during atrial fibrillation: a novel usage of fractionation mapping in a case with sinus bradycardia and paroxysmal atrial fibrillation. J Interv Card Electrophysiol. 2020 Mar;57(2):331-332.

31. Aksu T, Yalin K, Gopinathannair R. Fractionation mapping software to map ganglionated plexus sites during sinus rhythm. J Cardiovasc Electrophysiol. 2020 Dec;31(12):3326-3329.

32. Osorio J, Doud DM, Aksu T. Fractionation Mapping by Using a High-density Catheter to Map Ganglionated Plexus Sites During Sinus Rhythm. J Innov Card Rhythm Manag. 2021 Jan 15;12(Suppl 1):7-8.

33. John LA, Mullis A, Payne J, Tung R, Aksu T, Winterfield JR. Cardioneuroablation for cardioinhibitory vasovagal syncope. J Cardiovasc Electrophysiol. 2021 Jun;32(6):1748-1753.

34. Pachon MJC, Pachon MEI, Santillana PTG, Lobo TJ, Pachon CTC, Pachon MJC, et al. Simplified method for vagal effect evaluation in J Interv Card Electrophysiol cardiac ablation and electrophysiological procedures. JACC Clin Electrophysiol. 2015;1:451–60.

35. Jungen C, Scherschel K, Eickholt C, et al. Disruption of cardiac cholinergic neurons enhances susceptibility to ventricular arrhythmias. Nat Commun. 2017;8:14155.

Figure legends

Figure 1

Title. Schematic view of ganglionated plexi (GPs) distribution

Caption. Spheres with different colors demonstrate site of grouping epicardial autonomic ganglia defined as ganglionated plexus (GP). (1) the superior right atrial GP labeled with blue color located on the posterosuperior surface of the right atrium adjacent to the junction of the superior vena cava (SVC) and the right atrium; (2) the superior left atrial GP labeled with red on the posterosuperior surface of the left atrium between the pulmonary veins; (3) the posterior right atrial GP located adjacent to the interatrial groove; (4)

the posteromedial left atrial GP labeled with black color on the posteromedial surface of the left atrium; (5) the interatrial septal GP labeled with green color consisting of fusion and extensions of the posterior right atrial GP and the posteromedial left atrial GP; and (6) the posterolateral left atrial GP (the inferior left atrial GP) labeled with orange color is identified on the posterolateral surface of the left atrium

CS, coronary sinus; IVC, inferior vena cava; LAA, left atrial appendage; LIPV, left inferior

pulmonary vein; PN, phrenic nerve; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava; VOM, the vein of Marshall.

Figure 2

Title. Schematic practical decision pathway for the management of vasovagal syncope according to age

Caption. Both the European and U.S. guidelines recommend pacemaker implantation for patients with recurrent vasovagal syncope older than age 40 years and evidence of symptomatic spontaneous asystole for at least 3 s, or asymptomatic spontaneous asystole for at least 6 s on implantable loop recordings (ILR)*. However, spontaneous asystole in patients with reflex syncope received a slightly different class of recommendation in the U.S. guidelines (Class IIb) when compared with the European guidelines (Class IIa). The European guidelines also provide Class IIb recommendations for pacing in patients older than age 40 years with head-up tilt table (HUTT)-induced asystolic response for at least 3 s without direct parallel U.S**. recommendations. In selected cases, cardioneuroablation (CNA) may be used in patients aged <40 years. However, guidelines do not give any recommendations due to the lack of sufficient evidence from studies in this population. Please see text for details. Yellow, orange, and red boxes indicate our suggestions is useful (class I), is recommended (class IIa), may be considered (class IIb), respectively. CNA, cardioneuroablation; DDD-CLS, dual-chamber closed loop stimulation; DDD-RDR, dual-chamber rate drop response.

Figure 3

Title. Distribution of ablation points in a patient with vasovagal syncope and functional atrioventricular block based on presence of fragmented electrograms in sinus rhythm

Caption. Red and pink spheres demonstrate fragmented electrogram sites. Electrogram examples are shown with red arrows. Please see text for detailed anatomical distribution of GPs.

CS, coronary sinus; IVC, inferior vena cava; LAA, left atrial appendage; LIGP, the posterolateral (inferior) left atrial ganglionated plexu;s LIPV, left inferior pulmonary vein; LSGP,the superior left atrial ganglionated plexus; LSPV, left superior pulmonary vein; MTGP, the Marshall tract ganglionated plexus; PN, phrenic nerve; RIGP, the posterior (inferior) right atrial ganglionated plexus; RIPV, right inferior pulmonary vein; RSGP, the superior right atrial ganglionated plexus; RSPV, right superior pulmonary vein; SVC, superior vena cava.

Figure 4

Title. Fractionation map of the left atrium during sinus rhythm

Caption. The color scale in map reflects the number of deflections of the electrogram from baseline. The sites demonstrating [?] 2 deflection are indicated with white color. Electrogram examples are shown on the right-hand side. Please see text for details.

LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIGP, the posterior (inferior) right atrial GP; RIPV, right inferior pulmonary vein; RSGP, the superior right atrial GP; RSPV, right superior pulmonary vein.

Video legends

Video 1

Title. Three-dimensional view of the left atrial and right atrial structures is seen during ablation for the superior right atrial ganglionated plexus via the superior vena cava

Caption. Intracardiac electrograms are seen during ablation on the superior right atrial ganglionated plexus at the bottom of video. Heart rate increases suddenly during radiofrequency ablation in this site.

Video 2

Title. Three-dimensional view of the left atrial appendage and the left superior pulmonary vein is seen during ablation on the superior left atrial ganglionated plexus

Caption. Intracardiac electrograms are seen during ablation on the superior left atrial ganglionated plexus at the bottom of video. Red dots demonstrate previous ablation points in the same area. There is still positive vagal response with asystole >3s during ablation on the superior left atrial ganglionated plexus.

Video 3

Title. Three-dimensional view of the left superior and the left inferior pulmonary veins is seen during ablation on the inferior (posterolateral) left atrial ganglionated plexus

Caption. Intracardiac electrograms are seen during ablation on the inferior (posterolateral) left atrial ganglionated plexus at the bottom of video. A clear vagal response with a prolongation on RR interval of >50% is seen during ablation in this site.

Video 4

Title. Three-dimensional view of the left atrial structures is seen during ablation for the superior right atrial ganglionated plexus via the left atrium

Caption. Intracardiac electrograms are seen during ablation on superior right atrial ganglionated plexus at the bottom of video. Although there is no effect on the heart rate at the beginning of the ablation with non-fragmented electrogram site, a steep increase of heart rate is seen fragmented electrogram site in the following part of the video.

Video 5

Title. Three-dimensional endocardial surface of the left atrial and right atrial structures and locations of bi-atrial ablation points

Caption. Red, pink and white points indicate the locations of ganglionated plexi based on fragmented electrograms. Intracardiac electrograms are seen during ablation on the posteromedial left atrial ganglionated plexus via coronary sinus at the bottom of video. Mobitz type 1 atrioventricular block completely resolves during radiofrequency ablation in this site.

Video 6

Title. Achievement of 1:1 atrioventricular conduction during ablation on the superior right atrial ganglionated plexus

Caption. The video shows biatrial electroanatomic maps during ablation on the superior right atrial ganglionated plexus. The intracardiac electrograms are shown below. At the beginning of the tracing, atrioventricular (AV) block is seen despite the presence of sinus tachycardia. After 11 seconds of ablation, 1:1 atrioventricular conduction is achieved.