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MULTIMEDIA REPORT

Electroanatomic-mapping-guided cardioneuroablation versus combined approach for vasovagal syncope: a cross-sectional observational study

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Abstract

Purpose This study was designed to assess the efficacy of electroanatomic-mapping (EAM)-guided cardioneuroablation (CNA) vs combined approach for vasovagal syncope (VVS).

Methods Twenty patients with VVS refractory to conventional treatments who underwent CNA in our institution were enrolled in the study. Twelve of these patients underwent recently introduced EAM-guided CNA using signal-based approach while 8 patients underwent combined CNA using a combination of high-frequency stimulation and spectral analysis. Both atria and coronary sinus were divided into seven segments to categorize distribution of ganglionated plexi in ablation sites. Clinical responses were evaluated and compared in terms of prodromal symptoms and syncope recurrence rates. Electrophysiological parameters and heart rate variability (HRV) analysis were used to evaluate procedural response.

Results Procedural endpoints were achieved in all cases without any serious adverse events. Compared with the combined approach group, EAM-guided CNA was related to a shorter procedure and fluoroscopy times ($p < 0.001$). The mean number of ablation points in each anatomical segment was comparable between groups. The prodromal symptoms demonstrated a significant and comparable decrease after CNA. Median event-free survival was comparable between groups ($\chi 2 = 0.03$, $p = 0.87$). There was no new syncopal episode in any case at the end of 6-month follow-up. In the combined approach group, new syncope episodes occurred in two cases after 12-month follow-up. HRV parameters indicating parasympathetic activity were comparably decreased after ablation in both groups.

Conclusion This pilot study shows that EAM-guided CNA strategy is feasible and safe in VVS patients resistant to conventional therapies.

Keywords Parasympathetic · Bradycardia · Vagal ganglia · Atrial fibrillation · Ganglionated plexi · Fat pad

1 Introduction

Vasovagal syncope (VVS) is the most common form of syncope [1]. The underlying pathophysiology of VVS is intermittently impaired cardiovascular reflexes causing sympathetic withdrawal-mediated hypotension and/or parasympathetic hyperactivity-based bradycardia, triggered by prolonged standing or exposure to emotional stress, pain, or medical procedures [2]. There is no optimal treatment strategy currently available among patients with VVS [3]. Therefore, alternative treatment modalities are needed for this population.

Ganglionated plexi (GPs), located adjacent to the sinus node and atrioventricular (AV) junction, contain a variety of sympathetic and parasympathetic neurons [4–6]. Demonstration of an increase in sinus rate or AV conduction properties following various radiofrequency catheter ablation

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(RFCA) procedures has led to the introduction of the idea that ablation of GPs might be achieved by endocardial RFCA [7, 8]. The technique was attempted for the first time by Pachon et al. [9], who reported their initial experience on 21 patients with highly symptomatic VVS, functional high grade AV block, and sinus node dysfunction.

To our knowledge, different strategies were used by different authors to map GPs and identify ablation targets: (1) high-frequency stimulation (HFS) [10, 11]; (2) purely anatomic localization [12, 13]; (3) atrial electrogram (EGM) characteristics [9, 14, 15]; and a combination of these strategies [16]. While atrial EGM-based strategies require additional equipment, the others have low specificity to detect GPs [17]. In our early experience, we used a combination of HFS, spectral EGM analysis, and empirical anatomic ablation to detect GPs in a mixed patient population [18]. Despite promising short-term follow-up results, we still needed additional equipment to convert atrial EGMs to spectral potentials and apply HFS in that technique. To counteract these limitations, we used a fractionated EGM-based ablation strategy and named the technique as EAM-guided CNA [19]. The feasibility and safety of EAM-guided CNA in VVS has not been studied, yet.

In the current study, we aimed to determine safety and feasibility of, as well as clinical response to this novel modality in short- and mid-term follow-up in comparison with the conventional method in carefully selected patients with VVS.

2 Methods

2.1 Study population

Twenty patients with VVS refractory to conventional treatments who underwent CNA in our institution were enrolled consecutively in this cross-sectional observational study. Twelve of these patients underwent EAM-guided CNA while 8 patients underwent combined CNA. Primary outcomes of safety and feasibility were assessed [18]. The study was approved by our local ethics committee. Informed consent was obtained from all patients prior to participation in the study. The study was performed in compliance with the Declaration of Helsinki.

The major inclusion criterion is recurrent syncope episodes (at least three episodes in preceding 6 months) accompanied by type 1 or type 2B response according to the New Vasovagal Syncope International Study (VASIS) classification in Head-up tilt table test (HUT) [20]. The main inclusion and exclusion criteria and details of HUT test protocol are provided in supplementary tables (eTables 1 and 2) [21]. Medication of the patients was carefully reviewed before and after the procedure and during follow-up visits. Antiarrhythmic drugs and drugs which alter autonomic nervous system function were not allowed in the participants. All patients received post procedural oral anticoagulation for 3 months with a target international normalized ratio of 2–3.

2.2 Electrophysiological study

All procedures were performed under conscious sedation with intravenous administration of midazolam. Three different femoral vein punctures were performed for insertion of a decapolar 6F steerable electrode catheter in the coronary sinus, a quadripolar electrode catheter His region, and an irrigated ablation catheter into the right atrium (RA) or left atrium (LA) depending on the ablation site. Unfractionated heparin was infused (100 IU/kg bolus) intravenously, and the activated clotting time, measured every 30 min, was maintained between 300 and 400 s. Surface ECG and bipolar EGMs were continuously monitored and recorded (EP-WorkMate Recording System, St. Jude Medical Inc.). Intracardiac EGMs were filtered from 30 to 500 Hz and measured at a sweep speed of 150 mm/s for the conventional electrophysiological study (EPS). Programmed atrial and ventricular stimulation ruled out sustained arrhythmias, primary conduction system dysfunction, and sick sinus syndrome.

2.3 Mapping and ablation of ganglionated plexi

2.3.1 Electroanatomic-mapping-guided cardioneuroablation

After creating three-dimensional electroanatomic maps of both atria using EnSite NavX™ Cardiac Mapping System (EnSite Velocity, St Jude Medical, Abbott, Sylmar, CA, USA), bipolar endocardial atrial EGMs were evaluated for amplitude and number of deflections at filter settings of 200–500 Hz and a sweep speed of 400 mm/s. Amplitude was defined as the voltage difference between highest and lowest deflections of each EGM. Number of deflections was determined by counting the number of turning points (positive to negative direction or vice versa) in each EGM. All EGMs were divided into the following subgroups: (1) normal atrial EGM, which demonstrates deflection number of less than 4; (2) low-amplitude fractionated EGM (LAFE), which demonstrates greater or equal to four deflections and amplitude of less than 0.7 mV; and (3) high-amplitude fractionated EGM (HAFE), which demonstrates greater or equal to four deflections and an amplitude greater or equal to 0.7 mV (Fig. 1) [22]. Specific EGM characteristics of the regions of parasympathetic ganglia in paroxysmal atrial fibrillation patients were previously defined [14]. In this present work, the sites demonstrating HAFE or LAFE pattern in a region that is consistent with probable localization of GPs were tagged as ablation targets (Fig. 1) [22]. Both atria were included in the analysis. Other sites demonstrating LAFE pattern were accepted as scar tissue and excluded from the assessment. Final empirical anatomic ablation was performed between the aortic root and the medial

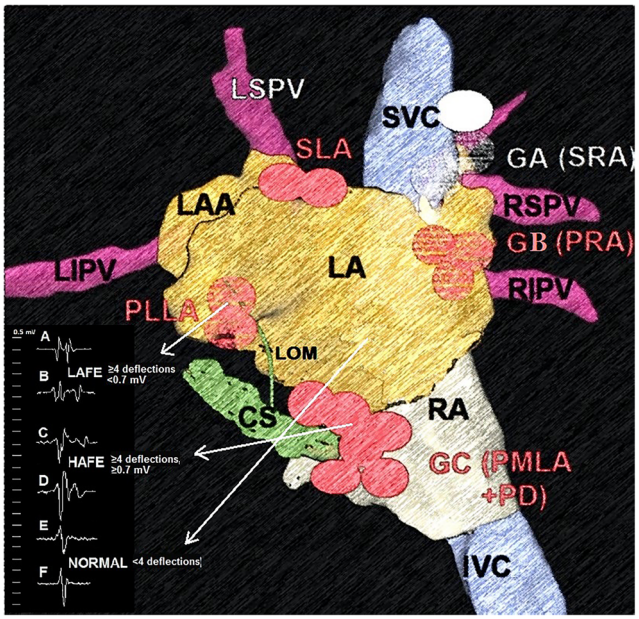

Fig. 1 A modified schematic view of ganglionated plexi according to animal and human studies. The figure demonstrates commonly used location sites for ganglionated plexi and different electrogram patterns seen in atria. A-B, C-D, and E-F demonstrate HAFE, LAFE, and normal atrial electrogram patterns, respectively. Please see text for details related to definition of different electrogram patterns. Please pay attention similar anatomical localization of ganglion A and superior or anterior right ganglion, ganglion B and posterior or inferior right ganglion, and ganglion C and posteromedial left atrial ganglion + posterior descending ganglion or inferior left ganglion. The figure was modified from our previous work with the permission of the editor in chief [22]. *CS* the coronary sinus, *GA* ganglion A, *GB* ganglion B, *GC* ganglion C, *HAFE* high-amplitude fractionated electrogram, *IVC* the inferior vena cava, *LA* the left atrium, *LAA* the left atrial appendage, *LAFE* low-amplitude fractionated electrogram, *LIPV* the left inferior pulmonary vein, *LOM* the ligament of Marshall, *LSPV* the left superior pulmonary vein, *PMLA* posteromedial left atrial ganglionated plexus, *PLLA* posterolateral left atrial ganglionated plexus, *PRA* posterior right atrial ganglionated plexus, *RA* the right atrium, *RIPV* the right inferior pulmonary vein, *RSPV* the right superior pulmonary vein, *SLA* superior left atrial ganglionated plexus, *SRA* superior right atrial ganglionated plexus, *SVC* the superior vena cava

superior vena cava, between the right pulmonary veins (PVs) and RA, and in the inferoposterior interatrial septum if procedural endpoints were not achieved. Radiofrequency current was applied in a point-by-point fashion in power-controlled mode with an open irrigated-tip catheter (Theraphy Coolflex, St. Jude Medical Inc., St. Paul, MN, USA). Radiofrequency energy was limited to 35 watts (W) along the posterior wall and roof under an irrigation flow rate of 17 mL/min, and 40 W in the remaining areas. Continuous flow during mapping was 2 mL/min.

2.3.2 Combined approach

The data of this group was retrospectively retrieved from our previously published cohort [18]. The three-dimensional geometry of RA and LA was created using the same mapping system. The sites demonstrating fibrillar pattern were tagged on mapping system. Subsequently, HFS was delivered to the tagged sites with a frequency of 20 Hz, amplitude of 0.1–1 mA, and pulse duration of 1–10 ms for 5 s per each site (3510 multiprogramming stimulator, St. Jude Medical). A positive vagal response (VR) was defined when HFS induced any of the following phenomena: transient ventricular asystole, AV block, or an increase in mean R-R interval of 50%. The sites showing a positive VR were assigned as ablation targets. Radiofrequency energy was delivered with a power of up to 35 W and a maximum temperature of 43 °C with a cooling rate of 18 mL/min until elimination (< 0.1 mV) of atrial electrical potentials. After each RFCA application, HFS was repeated immediately at the ablation sites. If a positive VR was still recorded, the field of RFCA applications was extended to an adjacent site to form a cloudlike shape until the response was no longer observed. Final empirical anatomic ablation was performed between the aortic root and the medial superior vena cava, between the right PVs and RA, and in the inferoposterior interatrial septum.

2.4 Mapping of the phrenic nerve

Right phrenic nerve is close to the superior vena cava (SVC) superiorly and adjacent to the lateral border of the entrance of the inferior vena cava to RA inferiorly. It is well known that damage to the phrenic nerve occurs usually during RFCA on the posterolateral aspect of SVC. In our routine approach, we performed ablation in septal side of SVC. Therefore, we did not apply high amplitude pacing to check capture in the right phrenic nerve. If HAFE or LAFE EGMs were detected in the lateral aspect of SVC, capturing in the right phrenic nerve was assessed before ablation attempt (eFigure 1).

2.5 Evaluation of distribution of ablation points

To categorize GPs distribution in ablation sites, both atria and coronary sinus were divided into the following seven segments: the left superior segment consisting of the left superior PV and superior left atrial GPs, the left inferior segment consisting of the left inferior PV and posterolateral left atrial GPs, the right superior segment, the right inferior segment, the interatrial septal area, the superior vena cava area, and the coronary sinus area (Fig. 2). Groups were compared according to distribution of ablation points.

2.6 Endpoints

In EAM-guided CNA group, the first procedural endpoint was the near complete elimination of all targeted atrial EGMs. For this aim, we performed ablation in the targeted sites until the amplitude of the EGMs decreased to less than 0.1 mV.

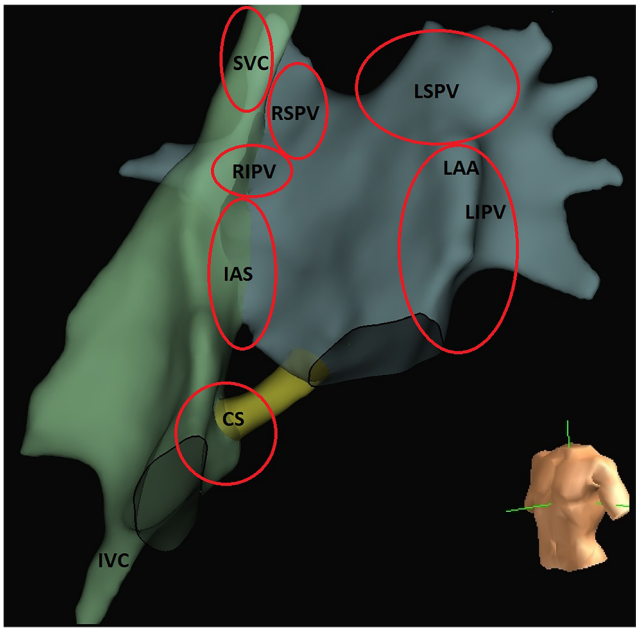

Fig. 2 Schematic view of biatrial segmentation protocol. In order to categorize ganglionated plexi distribution in ablation sites, both atria and coronary sinus were divided into the following seven segments: the left superior segment consisting of the left superior pulmonary vein and superior left atrial ganglionated plexi, the left inferior segment consisting of the left inferior pulmonary vein and posterolateral left atrial ganglionated plexi, the right superior segment, the right inferior segment, the interatrial septum side, the superior vena cava side, and the coronary sinus side. *CS* the coronary sinus, *IVC* the inferior vena cava, *LAA* the left atrial appendage, *LIPV* the left inferior pulmonary vein, *LSPV* the left superior pulmonary vein, *RIPV* the right inferior pulmonary vein, *RSPV* the right superior pulmonary vein, *SVC* the superior vena cava

Elimination of positive VR to ablation was the second procedural endpoint. In combined approach group, procedural endpoints were elimination of EGMs on fibrillar atrial myocardium sites and elimination of positive VR to HFS in any site which demonstrated positive response in the pre-ablation attempt.

2.7 Instantaneous autonomic evaluation

2.7.1 Electroanatomic-mapping-guided cardioneuroablation

Electrophysiological measures of sinoatrial node and AV node functions were consistently recorded throughout the study, immediately before and after every radiofrequency pulse applied to all targeted sites: sinus rate, atrial-His (A-H) interval (defined as the time from earliest reproducible rapid atrial deflection in the His bundle catheter to onset of the His deflection). As it is for HFS, a progressive slowing of the sinus rate by 50% or the development of a second or third degree AV block was accepted as significant parasympathetic response.

After each radiofrequency application, the locations of sites associated with significant parasympathetic response were recorded for evaluation of EGM characteristics at those sites. If more than one radiofrequency applications were performed at the same or close anatomical site, we included the first response in the analysis. Basal cycle length (BCL), AV nodal Wenckebach point (AV WP), A-H interval, sinus node recovery time (SNRT), and corrected sinus node recovery time (cSNRT) were measured in the baseline setting and after CNA.

2.7.2 Combined approach

To reveal whether there is any relationship between EGM characteristics of ablation points and parasympathetic response, at each radiofrequency application sites, positive and negative parasympathetic response were retrospectively assessed by two experienced operators (K.Y. and S. E. G.). The same electrophysiologic parameters as in the combined approach group were measured at baseline and after CNA.

2.8 Follow-up

2.8.1 Electroanatomic-mapping-guided cardioneuroablation

Clinical assessments, 12-lead ECG, and 24-h Holter-monitor recordings were obtained at baseline and 1, 3, and 6 months after the ablation procedure. Electrocardiograms and Holter-monitor recordings were assessed by experienced clinicians (T.E.G., K.Y., S.B., or S.E.G.). All patients underwent HUT at 6 months after CNA. All the patients were asked to record a diary of their symptoms such as dizziness, fatigue, or palpitation and/or syncope episodes. All new syncopal episodes were carefully documented.

2.8.2 Combined approach

The prospective follow-up consisted of a clinical evaluation (at discharge, 1 month, 3, 6, 12, and 24 months), ECG (at discharge, 1 month, 3, 6, 12, and 24 months), Holter monitoring (at discharge, 1 month, 3, 6, 12, and 24 months), and HUT (at 6 months and in case of symptoms). Patients were asked to contact their physician any time they had any prodromal symptoms such as dizziness, fatigue, or palpitation. All new syncopal episodes were carefully documented.

2.9 Heart rate variability analysis

To detect autonomic nervous system effects of the CNA procedure, heart rate variability (HRV) parameters were analyzed and compared using a commercially available software algorithm (DMS Cardioscan Holter system, DM Software Inc., Beijing, China) before the procedure and at all follow-up

visits. Time-domain and frequency-domain parameters were used for HRV analysis. Time-domain parameters are (1) rMSSD: 24 h close together normal cardiac cycle difference value mean square root; (2) PNN50: the percentage of difference of close together RR intermediate > 50 ms account total RR intermediate; (3) SDNN: standard deviation of all R–R intervals; (4) SDANN: standard deviation of the averages of the R–R intervals in all 5-min segments of R–R intervals; and (5) SDNN index: the mean of all the 5-min standard deviations of N–N (normal R–R) intervals during the 24-h period. Frequency-domain parameters consist of (1) low-frequency power (LF), (2) high-frequency power (HF), and (3) ratios of low-frequency power/high-frequency power (LF/HF).

2.10 Statistical analysis

SPSS software for Windows (release 17.0.0, SPSS, Chicago, IL, USA) was used for statistical analysis.

Continuous variables were reported as mean ± standard deviation or median (minimum-maximum). Comparisons between the EAM-guided CNA and combined approach groups were carried out using a Mann–Whitney *U* test. Categorical variables were reported as the number (percentage) of participants and compared by a Pearson chi-square test or Fisher exact test. Wilcoxon signed-rank test was used to analyze the changes in heart rate and heart rate variability after the ablation procedure. Recurrent syncope or prodromal symptoms were compared using a Kaplan–Meier analysis. Event-free survival patterns in combined versus EAM-guided CNA groups were compared with Breslow test. Statistical significance was reached at a $p < 0.05$.

3 Results

3.1 General characteristics of the patients

Twenty patients (aged 36.0 ± 12.8 years; 50.0% female) were enrolled in this study. The detailed demographics of the enrolled participants are listed in eTable 3. There were no statistical differences between the EAM-guided CNA ($n = 12$) and combined approach ($n = 8$) groups except for gender. There was a significant female dominance in combined approach group (66.6 vs 12.5%, respectively). Fourteen of 18 cases demonstrated cardioinhibitory response in HUT. There were two patients with mixed response in both groups. In one of cases of combined approach group, situational syncope was accompanied by VVS which was related with defecation. In one of the case of EAM-guided CNA group, paroxysmal atrial fibrillation episodes were detected on Holter recordings. Therefore, additional ablation was performed to achieve complete PV isolation in this case.

3.2 Procedural characteristics of the patients

Compared with the combined approach group, the patients in the EAM-guided CNA had a shorter procedure time, a shorter fluoroscopy time, and a shorter pre-procedural SNRT (Table 1). No statistical difference was observed between the two groups regarding the other electrophysiological parameters. Five patients (25%) required temporary pacing via the right ventricle due to prolonged ventricular asystole during radiofrequency application (Movie 1). No phrenic nerve palsy, inadvertent ablation of slow pathway, or AV block was seen related with the procedure. Procedural endpoints were achieved in all cases. The detailed procedural characteristics of patients are listed in Table 1.

3.3 Electrogram characteristics and distribution of ablation points

Mean number of points per map in the left and right atria was comparable between groups (eTable 4). In combined approach group, ablation points were retrospectively evaluated for atrial EGM characteristics. Although the existence of fractionated EGM was not an absolute requirement in the combined approach group, all 295 ablation points (a mean 36.8 ± 4.6 per patients) demonstrated fractionated EGM pattern. The mean number of ablation points in each anatomical segment was comparable between groups (eTable 4). In both groups, majority of fractionated EGMs were detected at the insertion of the right PVs and at the superior vena cava insertions or surrounding the coronary sinus ostium in the left and right atria, respectively. Number of ablation points on the interatrial septum was higher in the EAM-guided CNA group at a borderline statistical significance. When the EGM characteristics in each segment are closely observed, the ratio of LAFEs to HAFEs was higher in the EAM-guided CNA group (Table 2). Both HAFEs and LAFEs were detected in all anatomical segments. As an exception, there were no LAFE on the left inferior segment in combined approach group.

3.4 Holter recordings and heart rate variability analyses

Changes in HRV parameters from baseline to post-ablation among the groups are shown in Table 3. In both groups, minimum and mean heart rates were significantly increased after ablation. The relative changes in HRV parameters from baseline to post-ablation and at first, third, and sixth months after ablation were comparable in two groups. Although the vagal tone showed a slow recovery, it remained significantly attenuated at the end of 6-month follow-up when compared with the pre-ablation period. Panels a, b, and c in Fig. 3 demonstrate HRV metrics positively correlated with parasympathetic tone while panel d demonstrates LF/HF which is positively

Table 1 Comparison of electrophysiological parameters between groups

	Electroanatomical guided cardioneuroablation	Combined approach	*P* value
Procedure time, min	75 ± 9	121.2 ± 16	*< 0.0001*
Fluoroscopy time, min	15.1 ± 5	32.5 ± 6	*< 0.0001*
The need for temporary pacing, %	25	25	1
Baseline electrophysiological parameters			
BCL, ms	1119.5 ± 143	1238.7 ± 112	0.09
SNRT, ms	1561.6 ± 233	1810.5 ± 105	*0.01*
cSNRT, ms	512 ± 102	572.5 ± 117	0.15
AV node WP, ms	332.5 ± 61	323.7 ± 36	0.72
AH interval, ms	140.2 ± 19	147.5 ± 32	0.78
Electrophysiological parameters after cardioneuroablation			
BCL, ms	726.4 ± 108	701.8 ± 58	0.48
SNRT, ms	1026.2 ± 138	1083.7 ± 51	0.76
cSNRT, ms	364.5 ± 45	381.8 ± 22	0.23
AV node WP, ms	216.6 ± 18	207.5 ± 20	0.43
AH interval, ms	90 ± 10	78.1 ± 13	0.06

Values in italics identify significant *p*-values

AH atrial-His, *AV node WP* atrioventricular node Wenckebach point, *BCL* basal cycle length, *cSNRT* corrected sinus node recovery time, *SNRT* sinus node recovery time

correlated with sympathetic tone. This figure suggests that there is partial recovery in parasympathetic control over heart; however, the values of the variables do not reach the preprocedural levels. LF/HF values demonstrate a scattered pattern and seem to increase in small amounts during follow-up compared to preprocedural levels. Importantly, the changes in HRV parameters were similar in both groups. Time-domain HRV indices related to sympathetic tone such as SDNN, SDANN, and SDNN index demonstrated no significant differences between the pre-procedural and the 6th months of follow-up results.

3.5 Follow-up

In the EAM-guided CNA group, there was no new syncope episode in any case at the end of 6-month follow-up period. The prodromal symptoms demonstrated a significant and comparable decrease after CNA. Median event-free survival was 78 (61.2–94.8) days in combined CNA group versus 78 (63.6–92.3) days in the EAM-guided CNA group. There was no difference in event-free survival patterns between groups ($\chi 2 = 0.03$, $p = 0.87$) (Fig. 4). Furthermore, this effect was constant during follow-up period. In combined approach group, although there was no syncope episode in any patient during the first 12 months of follow-up, two cases admitted to our outpatient clinic with a new syncope episode in 14th and 18th months of follow-up, respectively. On post-event control HUTs, both patients demonstrated vasodepressor response without bradycardia or asystole. Oral midodrine hydrochloride 5 mg/day was administered in both cases to counteract vasodepressor component of VVS. At the end of 6-month follow-up period, they had no new attacks of syncope. Control HUTs were performed again with the patients taking the medication and syncope was not induced even by the administration of sublingual isosorbide dinitrate.

3.6 Procedural safety

Inappropriate sinus tachycardia was observed in two female patients. In one of them, there was no symptom associated with sinus tachycardia and the heart rates gradually decreased during follow-up period. Although the other case was asymptomatic during the first 12 months, she suffered from EHRA class 2 symptoms. The symptoms of the patient disappeared under ivabradine treatment within 3 days.

There were no other procedural complications, including vascular access events, tamponade, pericarditis, phrenic nerve paralysis, or symptoms related to a delay in gastric emptying.

4 Discussion

4.1 Major findings of the current study

The main findings of the current study were as follows: (1) fractionated EGMs may be used to define anatomical location of GPs without using any additional equipment during EPS; (2) both EAM-guided CNA and combined approach might

Table 2 Comparison of electrogram characteristics on ablation sites between groups

	Electroanatomical guided cardioneuroablation				Combined approach				*P* value			
Ablation points	Total, *n*	HAFE, *n*	LAFE, *n*	HAFE/LAFE	Total, *n*	HAFE, *n*	LAFE, *n*	HAFE/LAFE	Total, *n*	HAFE, *n*	LAFE, *n*	HAFE/LAFE
Total, *n*	47.4 ± 26	26.8 ± 9	14.0 ± 4	1.9 ± 0.3	36.8 ± 4	31.2 ± 3	5.8 ± 2	6.2 ± 2.7	0.18	0.20	*0.001*	*< 0.0001*
The left superior segment, *n*	7.0 ± 7	4.4 ± 4	1.0 ± 1	3.7 ± 1.6	2.0 ± 1	1.8 ± 1	0.1 ± 0.3	4[a]	0.11	0.20	0.09	0.85
The left inferior segment, *n*	2.3 ± 5	0.6 ± 1	0.09 ± 0.3	3[b]	0.3 ± 0.5	0.3 ± 0.5	0[c]	_[d]	0.47	1	0.77	_[e]
The right superior segment, *n*	7.2 ± 4	4.3 ± 1	2.0 ± 1	2.5 ± 0.9	6.7 ± 1	5.6 ± 1	1.1 ± 0.3	5.2 ± 1.9	0.73	0.17	0.20	*0.002*
The right inferior segment, *n*	6.3 ± 4	3.5 ± 2	2.0 ± 1	2.2 ± 0.9	4.6 ± 2	4.2 ± 2	0.2 ± 0.4	4.5 ± 0.7	0.38	0.54	*0.01*	*0.036*
The interatrial septum side, *n*	6.7 ± 5	3.4 ± 2	2.3 ± 1	1.4 ± 0.4	3.0 ± 1	2.6 ± 1	0.3 ± 0.5	*2.6 ± 0.5*	*0.051*	0.39	*0.007*	*0.018*
The superior vena cava side, *n*	9.9 ± 3	5.5 ± 1	3.6 ± 1	1.5 ± 0.4	11.6 ± 1	9.2 ± 0.7	2.3 ± 1	4.9 ± 2.9	0.08	< 0.001	0.051	*< 0.0001*
The coronary sinus side, *n*	8.0 ± 4	4.6 ± 3	2.8 ± 1	1.7 ± 0.6	8.5 ± 2	6.8 ± 2	1.6 ± 0.7	4.7 ± 1.9	0.38	*0.012*	0.075	*< 0.0001*

Values in italics identify significant *p*-values

One patient in electroanatomical-guided CNA group who underwent additional circumferential wide antral ablation due to paroxysmal atrial fibrillation was excluded from this analysis

LAFE low-amplitude fractionated electrogram, *HAFE* high-amplitude fractionated electrogram

[a] LAFE was detected in only one case in combined approach group

[b] LAFE was detected in only one case in electroanatomical-guided cardioneuroablation group

[c] There were no LAFE on the left inferior segment in combined approach group

[d] Calculation of HAFE/LAFE ratio was invalid because there were no LAFE on the left inferior segment in combined approach group

[e] There were not enough valid cases to perform the Mann-Whitney Test for HAFE/LAFE ratio of the left inferior segment

effectively prevent recurrent spontaneous syncopal episodes in patients with refractory VVS; (3) compared with the combined approach, EAM-guided CNA may decrease the procedure and fluoroscopy times without affecting curative effect; and (4) the effect of CNA on parasympathetic tone might persist at least 12 months after ablation, as shown by repeated heart rate variability measurements.

4.2 Theoretical background of permanent parasympathetic denervation idea

Unlike the previous studies using different modalities to define GPs, the current technique was developed to define a new method that does not require additional equipment, is easily applicable, and has a high degree of accuracy based on the results of Lellouche et al. [14]. The idea aiming detection of GPs through an EGM-guided strategy by conventional electrophysiology equipments was possible based on the following two characteristics: (1) induction of VR by radiofrequency energy occurs with a similar mechanism with HFS application [23]; (2) fractionated EGMs demonstrate higher VR during RFCA than normal atrial EGM sites [14, 23]. As a potential alternative to current strategy, usage of empiric ablation in presumptive anatomic sites may acquire currency. However, in a recently published meta-analysis, we compared recurrence rates between different approaches in patients with VVS and demonstrated that anatomical ablation as a standalone strategy was associated with higher rates of syncopal recurrence [17].

4.3 From the previous techniques to electroanatomic-mapping-guided cardioneuroablation strategy

Despite anatomical considerations, there is still no consensus for the anatomical location and number of GPs according to electrophysiologists. That is why different authors used different approaches such as ablation exclusively in the LA, ablation in both atria, or just in interatrial septum to achieve complete vagal denervation and reported a significant clinical impact [24]. To localize GPs, three different approaches have been used, so far. In the first method, Pachon et al. [9, 25] defined two different atrial myocardium types by studying the spectrum of the endocardial potentials: (1) the fibrillary atrial myocardium which demonstrates GP sites with a heterogeneous spectrum; (2) the compact atrial myocardium which demonstrates a homogeneous spectrum and normal atrial myocytes. Main limitation of the techniques is that the whole atrial endocardium needs to be scrutinized. In the second approach, Yao et al. [11] used HFS to detect only left atrial GPs. They focused specifically on the left superior, left inferior, right anterior, and right inferior left atrial GPs. Despite promising results, this technique has some limitations, too. During

Table 3 Comparison of mid-term changes in heart rate and heart rate variability parameters between groups

Parameters	Electroanatomical-guided cardioneuroablation				
	Pre-procedure	Post-procedure	Follow-up (months)		
			1	3	6
Heart rate (beats/min)					
Minimum	32.5 (18–49)	41 (31–81)	74.5 (52–79)	66 (53–75)	71.5 (52–75)
Mean	65 (38–82)	93.5 (73–103)	94 (71–106)	84.5 (68–96)	89 (66–93)
Maximum	119.5 (103–148)	125.5 (115–142)	135 (118–146)	130 (114–137)	123.5 (109–132)
Heart rate variability					
The time–domain analysis					
rMSSD50 (ms)	67.5 (30–74)	21 (15–28)	25.5 (18–34)	27.5 (20–35)	35.5 (19–43)
pNN50 (ms)	31.5 (8–40)	6 (2–9)	4.5 (2–7)	8 (4–12)	9.5 (4–18)
The frequency-domain analysis					
LF	1270.5 (266–1582)	392 (250–537)	361.5 (287–467)	434 (345–501)	495.5 (405–616)
HF	409.5 (207–471)	66.5 (52–80)	93 (64–119)	83.5 (72–100)	120 (76–154)
LF/HF	3.05 (1.17–4.24)	5.75 (3.3–9.42)	3.52 (2.61–6.58)	3.92 (2.61–6.46)	4.22 (3.09–6.59)
Parameters	Combined approach				
	Pre-procedure	Post-procedure	Follow-up (months)		
			1	3	6
Heart rate (beats/min)					
Minimum	37 (28–46)	71 (64–80)	68 (60–75)	64 (54–73)	60.5 (52–66)
Mean	66 (45–76)	79.5 (68–85)	75.5 (67–84)	72 (62–81)	72.5 (61–76)
Maximum	133 (118–148)	131.5 (120–145)	130.5 (121–151)	132.5 (122–141)	134 (119–149)
Heart rate variability					
The time–domain analysis					
rMSSD50 (ms)	66.5 (56–80)	21.5 (16–31)	23 (18–29)	27 (17–31)	28 (20–31)
pNN50 (ms)	35 (28–45)	3 (2–6)	4.5 (4–6)	6.5 (5–8)	7 (5–8)
The frequency-domain analysis					
LF	1290.5 (1012–1626)	436 (346–522)	463 (354–546)	483 (394–555)	512 (442–612)
HF	412.5 (316–563)	73 (48–101)	79 (59–113)	83.5 (77–115)	93 (81–118)
LF/HF	3.12 (2.89–3.2)	6.02 (5.04–7.21)	5.89 (4.83–6.32)	5.54 (4.48–6.37)	5.36 (4.65–6.28)

There is no statistically significant difference for any parameters between groups

Values are expressed as median (minimum-maximum)

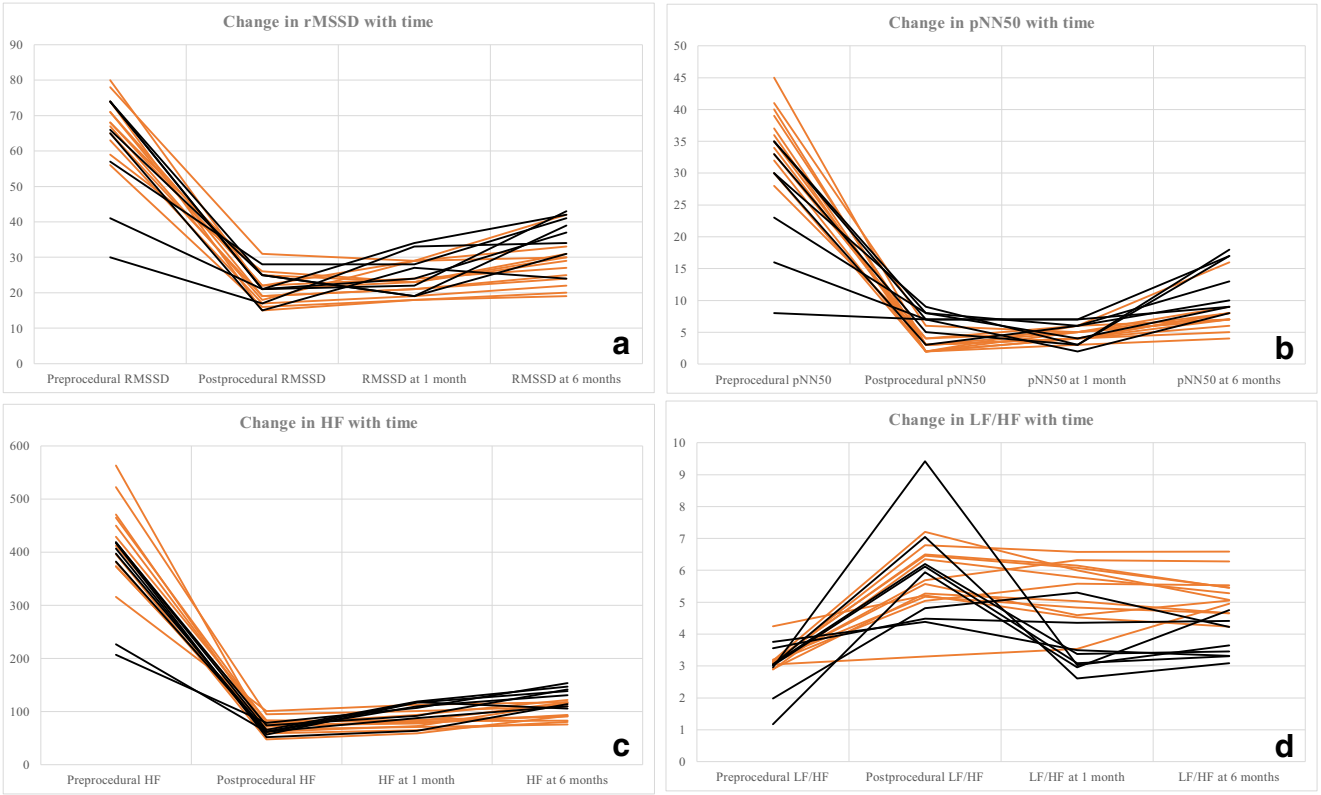

Fig. 3 Chronological changes in the heart rate variability parameters demonstrating parasympathetic tone in electroanatomical guided cardioneuroablation group ($n = 12$) and combined approach group ($n = 8$). Orange and black colors demonstrate electroanatomical guided cardioneuroablation and combined approach groups, respectively

application, concomitant afferent autonomic nerves stimulation may cause a significant sensation of discomfort and lead negative dromotropic or chronotropic effects due to unpleasant sensation. This necessitates the usage of general anesthesia. Another limitation is if a selective ablation in positive VR sites is aimed, HFS should not only be applied to empirically determined sites but also in all atrial myocardium sites. After completing ablation in the relevant areas, complete resolution of positive VR should be demonstrated. Furthermore, there is still no consensus on the best HFS protocols and criteria for positive VR. Lastly, repeated HFS applications may cause inadvertent atrial fibrillation induction in some cases. In the last technique, authors performed RFCA in empirically identified sites [23]. This approach seems less time-consuming than the previous two methods because mapping is required to a lesser extent. However, it was found related to higher recurrence rates in our recently published meta-analysis [17].

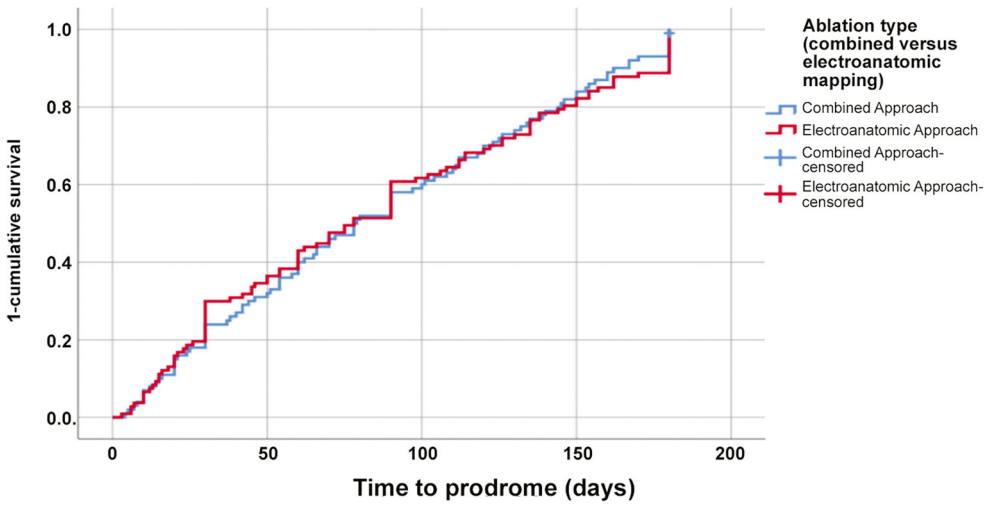

Fig. 4 Kaplan–Meier curves of recurrent prodromes in electroanatomical guided cardioneuroablation and combined approach groups. Please see the text for explanations

Considering all these limitations, we tried to find an easily understandable and applicable GP detection method which does not require additional equipment. We previously demonstrated that all the EGMs on the RF application sites demonstrate either a HAFE or LAFE pattern [18]. So, we only targeted HAFE and LAFE sites in the current study. Compared with the combined approach strategy, EAM-guided-CNA exhibited shorter procedure and fluoroscopy times ($p < 0.001$) and achieved an identical success rate in preventing prodromal symptoms. A possible explanation for this reduction in the procedure and fluoroscopy times is that combined approach requires additional time to apply HFS and to restimulate the ablated targets to verify resolution of positive VR. Also, operator experience may be another contributing factor.

4.4 Heart rate variability-based follow-up of vagal denervation

As a quantitative evaluation of the cardiac parasympathetic tone, various HRV-related parameters may be evaluated before and after the procedure [26]. In the time–domain analysis of HRV, rMSSD and PNN50 mainly reflect vagal tone [27]. In the frequency domain analysis of HRV, an increase in HF values shows dominant parasympathetic activity while higher LF values indicate dominance of sympathetic nervous system. But, studies in recent years have shown that parasympathetic activity may also affect the value of LF [27]. Higher LF/HF ratio may indicate an increase in sympathetic activity. In the present work, a significant reduction in the HRV parameters demonstrating parasympathetic tone was noted (Table 3, Fig. 3). The parameters related with sympathetic activity significantly recovered during follow-up, whereas the effect on parasympathetic parameters keep constant. This result may be related with a known anatomical relationship that the neuronal bodies of parasympathetic system are located in GPs, while the same sites only retain axonal fibers of the sympathetic system. So, we may say that unrequited sympathetic activity is not a reality, although post-procedural higher LF/HF ratio may show an increase in sympathetic activity. Additionally, although there was an increase in the minimum and mean heart rates which are accepted as indicators of parasympathetic tone, maximum heart rate which is accepted as an indicator of sympathetic tone was unchanged after the procedure.

4.5 Mid-term clinical outcomes

Survival rates without recurrent syncope were 100% at the end of the 6-month follow-up period in both study groups. Two points regarding the events during follow-up should be taken into consideration. The first is, although the two study groups do not differ with respect to prodromal recurrences, almost all the patients experience at least one prodromal symptom during mid-term follow-up (Fig. 4). According to this, even though findings from the current study suggest that EAM is non-inferior to combined approach in eliminating syncopal episodes, both techniques need to be improved to successfully eliminate prodromal episodes. Secondly, similar to prodromal recurrences, syncopal episodes may recur in longer follow-up periods. So, longer periods of surveillance for syncopal recurrences are warranted.

Although the previous animal studies revealed a trend of potential increase in the vulnerability to atrial or ventricular arrhythmias after ablation of the GPs, no supraventricular or ventricular arrhythmia was detected during the follow-up period. Two cases admitted to outpatient clinic with inappropriate sinus tachycardia. The arrhythmia was symptomatic in one of the two patients. Symptoms were successfully eliminated with ivabradine treatment in this patient. Nevertheless, the proarrhythmic effect of the GP ablation still needs to be addressed in further studies.

At the end of long-term follow-up period, in the combined approach group, two of the eight patients (25%) presented with new syncopal episode, despite persistent findings of parasympathetic denervation on Holter recordings. However, both patients demonstrated vasodepressor response without bradycardia and asystole on post-event control HUTs, whereas there was > 3 s asystole on preprocedural HUTs in both. These patients were started on midodrine hydrochloride and responded perfectly to the drug, completing the study follow-up period event-free.

5 Limitations

The first limitation of the current study is the small size of groups. Main reason is that the modality was performed only in a very small subset of patients resistant to all the currently available treatment options. Secondly, the retrospective and non-randomized nature of the study may be a factor reducing the power of results. The pathophysiology of syncope was not clear in patients with sinus node dysfunction or in some of AV block cases. So, the lack of new syncopal episodes might not indicate absolute clinical success. An attempt to obtain ECG documentation by implantable loop recorder during syncope (symptom-arrhythmia correlation) might increase diagnostic accuracy.

Transient prodromal symptoms persisted in nearly half of the cases. Although our study demonstrated that CNA may be beneficial in even mixed-type or situational VVS as well as cardioinhibitory syncope, it is well known from implantable loop recorder experience that only half of spontaneous VVS episodes are asystolic in nature [28]. So, it is difficult to accept that GP ablation was successful in all VVS cases or ablation also acts directly by counteracting peripheral vasodilatation.

Appropriate patient selection by implantable loop recorder may increase demonstrable benefits and superiority of CNA.

Lastly, it is well known from the atrial fibrillation ablation studies that an increasing amount of fibrosis within the atrial wall may cause formation of a substrate favorable for slow conduction and display EGMs with lower voltage and fragmentation [29]. Therefore, areas displaying LAFE may indicate atrial fibrosis. Although there was no overt structural cardiopathy in any of included patients, these LAFE areas might correspond to areas with altered electrical properties preceding macroscopic structural abnormalities. Also, Jadidi et al. [30] demonstrated that most fractionated EGMs are not related to fibrosis areas and occur at healthy atrial tissue without evidence of fibrosis on magnetic resonance imaging.

6 Conclusion

Fractionated atrial EGM characteristics may be used to define VG sites by using conventional electrophysiological equipment. We demonstrated that high-amplitude fractionated EGMs are associated with greater PR during CNA. With these findings, we suggest that our EAM-guided CNA strategy is noninferior to combined or anatomical approaches regarding procedural and clinical endpoints. Further large-scale randomized studies are needed to support these findings.

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Compliance with ethical standards

Conflict of interest Tolga Aksu has received a live case performance honorarium from Wokshop Registration Office of 21st Prague Workshop on Catheter Ablation. The other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study, although for retrospective type of study formal consent is not required.

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