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ELECTROPHYSIOLOGY
Case Report

Initial Experience with Fractionation Mapping in the Identification of Vagal Ganglionated Plexus During Cardioneuroablation

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ABSTRACT

This is a series case report of five symptomatic patients presented with diagnosis of sinus bradycardia, first and second degrees atrioventricular (AV) blocks, that were referred to pacemaker implantation. During the screening, a functional cause for the bradycardia and AV blocks were documented by treadmill stress test, 24-hour Holter monitoring and atropine test. After the confirmation of the diagnosis, patients were submitted to cardioneuroablation on an anatomical basis supported by a tridimensional electroanatomical fractionation mapping software. The technique and the acute and short-term results of the cardioneuroablation are described.

KEYWORDS: Cardioneuroablation; Electroanatomical mapping; Syncope; Bradycardia; Atrioventricular block.

INTRODUCTION

A series of five symptomatic patients that presented with dizziness, blurred vision, pre-syncope and/or syncope and were referred to the institution for pacemaker implantation is reported. Their diagnosis was sinus bradycardia associated with first degree atrioventricular (AV) blockade and sinus pauses in three patients, and in the other two ones second and high-grade AV blocks were the causes of symptoms. After the screening, patients were sent to Electrophysiology (EP) Laboratory to perform a cardioneuroablation (CNA). All patients signed the informed consent form according to the standards of our institution, which follows national and international standards. The study was approved by the Research Ethics Committee of the Institution.

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CASES REPORTS

Between September 2020 and February 2021, CNA was performed in five patients from 38 to 59-years-old, three males, with no history of major cardiovascular diseases. Two patients had mild to moderate obstructive sleep apnea with regular use of Continuous Airway Positive Pressure (CPAP). All patients before the performance of CNA were screened with 24-hour Holter monitoring, transthoracic echocardiography, and treadmill stress test, that showed a functional and reversible cause of the symptoms (Table 1). The mean follow was 4.8 (2-8) months.

Table 1. Pre-ablation 24-hour Holter monitoring features.

Holter pre-ablation	HR – Lower (bpm)	HR – Medium (bpm)	HR – Upper (bpm)	Longer pause (sec)	1st Degree block	2nd Degree block	High Degree Block	SDNN	PNN > 50
Patient 1	45	68	101	1.43	yes	no	no	144	8.76
Patient 2	46	89	119	3.9	no	no	no	128	6.08
Patient 3	29	59	117	3.3	yes	yes	yes	245	19
Patient 4	32	55	129	3.9	yes	yes	yes	312	16
Patient 5	43	71	139	3.22	yes	no	no	221	10.22
Mean features	33.2	68.4	121	3.15	-	-	-	210	12.01

HR: heart rate.

The CNA[1] was based on an anatomic approach using the recording system (EP Tracer recording system — Cardiotek, Netherlands) and supported by a tridimensional (3D) anatomical mapping system EnSite Velocity 5.0 (St. Jude Medical/Abbott, United States), to target and ablate the ganglionated plexus (GP) located in the right and left atria. In all patients, a baseline EP study was performed prior to ablation along with high-frequency stimulation in right and left internal jugular veins, at the level of the carotid sinus, to demonstrate a vagal response before and after CNA. The EP study had the main objective to determine the atrioventricular Wenckebach point and the effective atrioventricular refractory period, but other measurements were also done at this time (Table 2).

Table 2. Electrophysiologic parameters before and after cardioneuroablation.

Patient	Pre-CNA			Post-CNA		
	Heart rate (bpm)	Atrioventricular Wenckebach (ms)	AV refractory period (ms)	Heart rate (bpm)	Atrioventricular Wenckebach (ms)	AV refractory period (ms)
1	42	430	350	79	340	290
2	45	440	340	93	340	210
3	38	1,356	1,280	65	550	520
4	34	1,440	1,320	66	620	590
5	49	490	390	95	340	290
Mean features	41.6	831.2	736	79.6	438	380

CNA: cardioneuroablation; AV: atrioventricular.

An endocardial bipolar 3D anatomical was performed with a 20-pole circular mapping catheter (AFocus II St. Jude Medical/Abbott, United States), to prove the presence of a normal atrial tissue with (parameters to define scar tissues were a voltage < 0.5 mV and normal tissue > 1.5 mV. The fractionation mapping was analyzed during sinus rhythm, and parameters were all the same in the five patients, standardized at internal and external projections of 8 mm, interpolation of 8 mm, and low-voltage identification of 0.1 mV.

Map was created using combinations of width of 10 msec, refractory time of 30 msec, roving sensitivity of 0.1 mV, and fractionation threshold of 3. Map color scale was set to color areas at or above the fractionation threshold of 3 as white, and these areas were accepted as potential GP sites by the high-fractionated signals found. Ablation procedure was performed using a contact force-sensing catheter TactiCath SE (St. Jude Medical/Abbott, United States) with an Agilis (St. Jude Medical/Abbott, United States) deflectable sheath with power set of 30 Watts and irrigation pump flow of 17 mL/min. Electrical targets for ablation were high-frequency and long-fractionated signals at the distal and proximal ablation dipoles (Fig. 1). A correlation between fractionation mapping and anatomical sites was observed, and were identified as the targets to radiofrequency application since appropriate vagal response was noted while increase in heart rate and normalization of atrioventricular conduction occurred (Table 3).

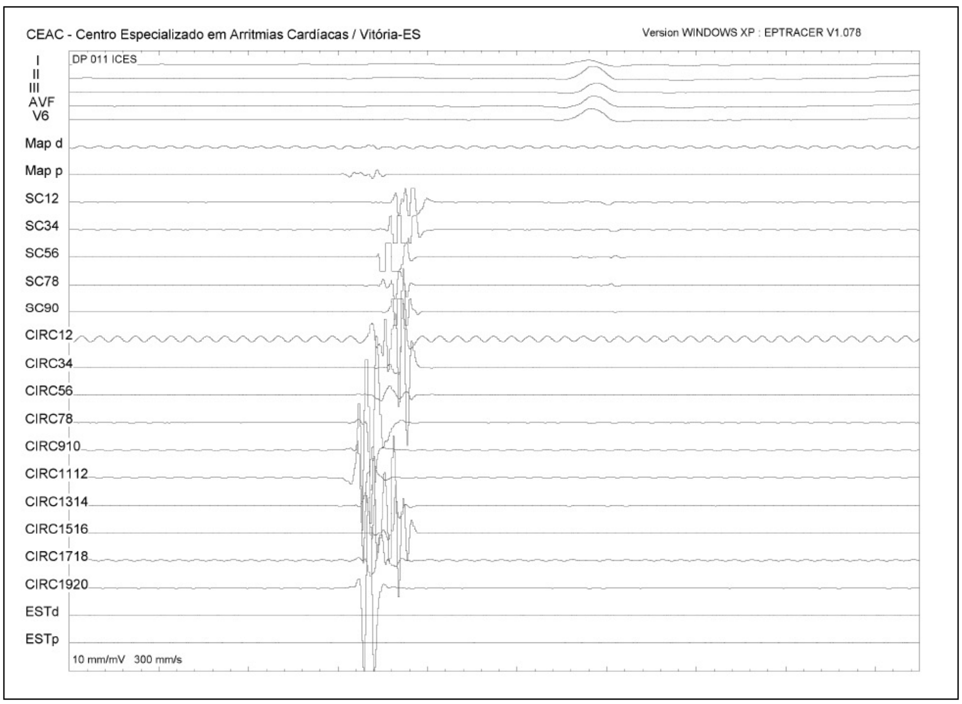


Figure 1. Circular mapping (CIRC) catheter showing the fragmental signal at a ganglionated plexus site (tracing speed of 300 ms/s).

Table 3. Response to heart rate and atrioventricular conduction during radiofrequency applications according to anatomical sites.

Anatomical ablation response	LA: LPV Carina	LA: LSPV/LAA	LA: RIPV Inferoanterior	LA: RPV Anterior	RA: SPV/Septal	RA: Coronary sinus ostium
Patient 1	-	-	AV	HR	HR	AV
Patient 2	-	HR	AV	HR	HR	AV
Patient 3	AV	-	-	HR	HR	-
Patient 4	-	-	-	HR	HR	AV
Patient 5	AV	HR	AV	HR	HR	AV

LA left atrium; LPV: left pulmanary veins; LSPV: left superior pulmonar vein; LAA: left atrium appendage; RIPV: right inferior pulmonary vein; RPV: right pulmonar veins SPV: superior vena cava; RA: right atrium; HR: heart rate; AV: atrioventricular.

As a successful treatment was achieved by the discretion of the physician performing a new EPS, high-frequency stimulation in right and left internal jugular veins and a challenge of 2 mg of atropine were performed (Table 4), to prove the lack of parasympathetic response.

Table 4. Post-ablation 24-hour Holter monitoring features.

Holter pre-ablation	HR – Lower (bpm)	HR – Medium (bpm)	HR – Upper (bpm)	Longer pause (sec)	1st Degree block	2nd Degree block	High Degree Block	SDNN	PNN > 50
Patient 1	68	84	108	0.88	no	no	no	82	0.08
Patient 2	80	102	147	0.75	no	no	no	78	0.46
Patient 3	62	112	128	0.97	no	no	no	65	0.39
Patient 4	73	98	117	0.82	no	no	no	60	0.5
Patient 5	43	73	116	1.39	no	no	no	78	0.28
Mean features	65.2	93.8	123.2	0.96	-	-	-	72.6	0.34

HR: heart rate.

DISCUSSION

Anatomical study of intact human heart by Armour et al.[2] identified five major atrial location of GPs. They have been given specific names, that are related to their locations:

- On the posterior superior surface of the right atrium adjacent to the superior vena cava and right atrium junction (nominated superior right atrium GP);
- Collection of ganglia on the posterior surface of left atrium between the pulmonary veins (nominated superior left atrial GP);
- On the posterior surface of right atrium adjacent to interatrial groove (nominated posterior right atrial GP);
- On posterior medial surface of left atrium (posteromedial left atrial GP);
- A small atrial one on the posterior lateral surface of left atrium base, on the left side of the atrioventricular groove (nominated posterolateral left atrial GP).

The posterior atrial GP fused and extend anteriorly into the interatrial septum to form the interatrial septal GP. The largest number of ganglia was associated with the two major GP founds on the posterior surface of the two atria.

Pachón et al.[1,3] were the first ones to report CNA through catheter ablation guided by fast Fourier transform (FFT) analysis as an alternative treatment for functional high-degree AV block. In seven out of the 21 patients included in their study, the diagnosis was intermittent high-degree AV block. The procedural endpoint was normalization of AV conduction. In three patients, the procedure was performed only via the right atrium (RA), and one of these patients still experienced nocturnal Mobitz type I AV block after the procedure. Long-term follow-up results presented in another study4 concluded that endocardial radiofrequency (RF) ablation of neural-mediated reflex syncope via both atria has excellent results in some patients and may prevent the need of pacemaker implantation. Anatomical mediated CNA has been increasingly used to treat severe vagal-related arrhythmias worldwide[1,4-7].

Although guidelines indicate pacemaker implantation for cases of symptomatic bradycardias or AV block[8], when patients are mostly young and otherwise healthy, a conservative approach is encouraged. Pacemaker implant in patients with vasovagal syndrome has been a controversial topic, and official guidelines and statement have approached it with the same caution. In vasovagal syncope, studies did not support the role of pacemaker except in selected patients with syncope without clear provocation or provoked with a pause of more than 3 seconds, and/or asymptomatic pause of more than 6 seconds. Furthermore, in the past there was an understanding that cardiac pacing was more likely to help older patients with concurrent sinus node dysfunction (SND). Recently, more cases of patients older than 40 years old treated with CNA have been described worldwide[9,10].

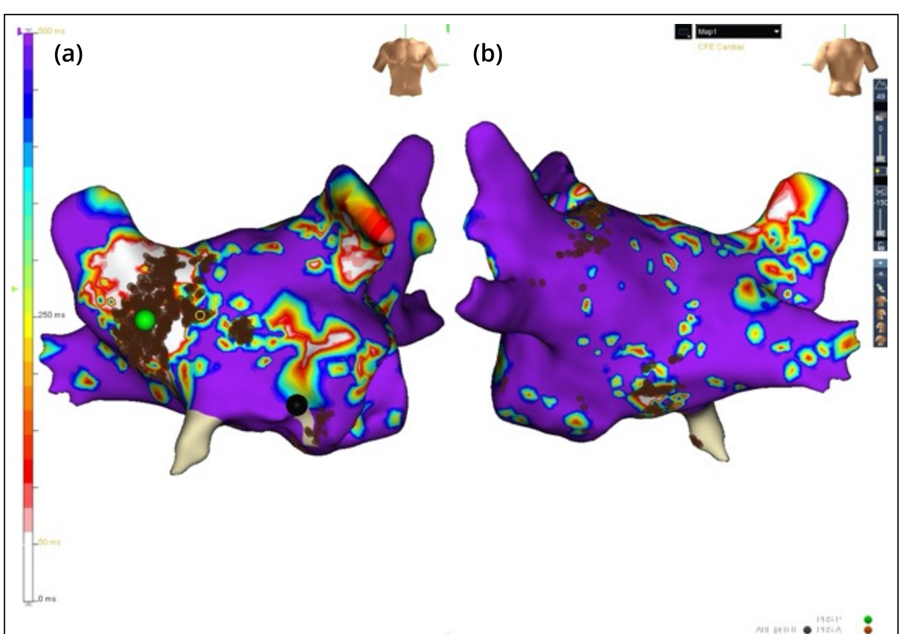
Despite these good results with CNA, it is important to remember that recurrence may occur because an intrinsic cardiac nervous system forms a complex neural network composed of the ganglia plexus and interconnecting axons. Larger ganglia are observed close to the pulmonary vein and serve as autonomic integration centers, modulating cardiac excitability. This widely distributed structure cannot be entirely targeted. A comprehensive approach is required and meant to promote attenuation instead of total vagal blockade, and a step-by-step test with extracardiac vagal stimulation can be a much wiser management during this kind of procedure.

Targeting all the GPs could be a risk if continuous monitoring by extracardiac vagal stimulation is not done, because AV block can get more severe if you denervate only the sinus node with the heart rate increase, so an individualized systematic approach to ensure the objective and success of the CNA is mandatory.

The aims of this case series report were to disseminate and encourage other colleges to perform the CNA, and the use of the complex fractionated electrograms (CFE) map was to help the identification of the anatomical sites of parasympathetic ganglia. The role of fractionation mapping software of EnSite system was detecting the localization of GP during sinus rhythm. Distribution of white areas, which is suggestive for fragmented electrograms (EGMs), demonstrated high similarity with visually selected ablation points. Potential importance of fragmented EGMs during sinus rhythm for the identification of GPs was firstly studied by Lellouche et al.[11]. They found that fragmentation of EGMs was the best single predictor of vagal response during radiofrequency ablation. Fractionation mapping software was previously used to detect localization of GP and critical substrate for continuity of atrial fibrillation[12-14].

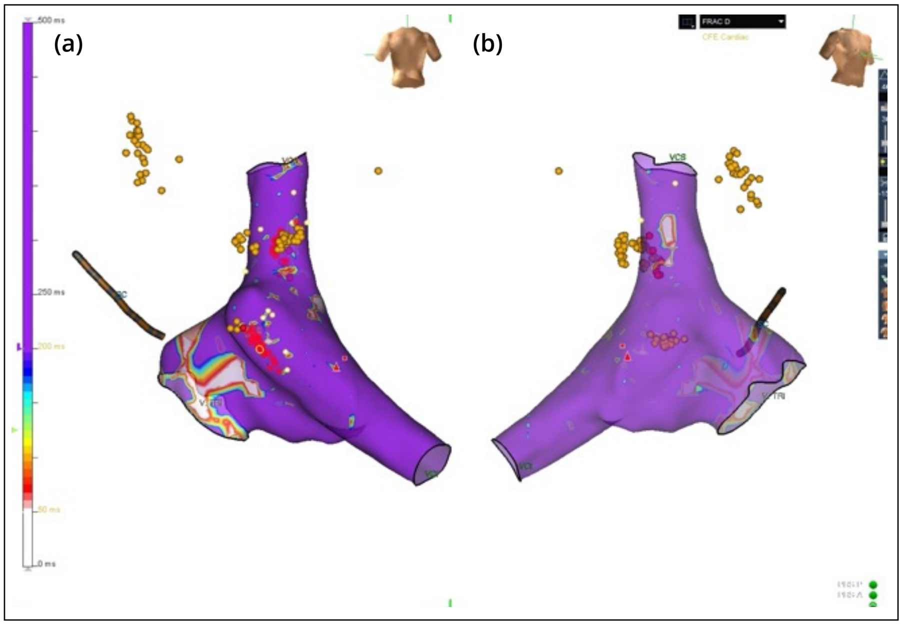
In the present work, fractionation mapping software during sinus rhythm demonstrated a GP distribution pattern which is suitable with anatomical localization. It might be a promising method for detection of GPs to avoid potential low reproducibility of visual methods by low-experienced operators. However, in this technique, mapping parameters like width, refractory time, roving sensitivity, and fractionation threshold should be standardized because, based on these parameters, the algorithm assigns each EGM a fractionation score. The fractionation mapping softwareTM was developed to be used during AF for detection of critical AF substrate[15,16], and the use of definition of localization of GP sites[11] need some validation in further randomized controlled studies with the use of high-frequency stimulation or potentially by nuclear imaging. Therefore, in the present study, ablation points were selected based on previously validated visual method and latter compared the localization of these anatomical sites with the fractionation mapping.

At the left atrium (LA), the fractionation mapping was able to identify a total of 30 places of supposed GPs site, and the anatomical localization of this sites occurred only in 19, so the CFE map identified 11 more than our usual anatomical basis CNA (Fig. 2). At the RA, a total of 17 locations of GP sites in the CFE map and 10 anatomical GPs locations were identified, seven more that the routine of anatomical basis CNA (Fig. 3). In all cases, at least one of the following responses was observed during RF application in the 19 sites at LA and 10 sites of RA; heart rate increase, heart rate reduction and/or atrioventricular conduction normalization. With this analysis, the fractionation mapping softwareTM can have the possibility to help the identification of GPs and guide RF application during the CNA.



CFE: (Complex Fractionated Electrograms) GP: ganglionated plexus; RF: (Radiofrequency).

Figure 2. (a) Anterior view of left atrial CFE map and anatomical GP site and RF application. The CFE Map shows GP sites as white colors and RF application in brown dots. (b) Posterior view of left atrial CFE map.



CFE: (Complex Fractionated Electrograms) GP: ganglionated plexus; RF: (Radiofrequency).

Figure 3. (a) Posterior view of right atrial CFE map and anatomical GP site and RF application. The CFE map shows GP sites as white colors and RF application in red dots (yellow dots indicate left atrium RF applications). (b) Anterior view of right atrial CFE map.

Patients were monitored at the 7th and the 30th day with rest electrocardiogram at both dates and with 24-hour Holter monitoring at the 30-day follow-up (Table 3). All the five subjects were asymptomatic and reported a better outcome after CNA.

CONCLUSION

As in other authors' series cases, results for CNA for the treatment of functional sinus bradycardia and AV blocks are encouraging and excellent. This series of cases showed that the fractionation mapping software™ matched in a good manner with anatomical GP sites and it is a useful and helpful tool for groups that are starting CNA program.

LEARNING OBJECTIVES

- CNA can be reproduced in EP laboratories in selected patients with very good results;
- 'The fractionation mapping software™ is a useful tool for helping the identification and guidance for GP sites localization;
- There is a good relationship between fractionation mapping, anatomical GPs locations and vagal response during RF application.

AUTHOR'S CONTRIBUTION

All authors contributed equally in the study except the corresponding author that collected the data and wrote it.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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Not applicable.

CONFLICT OF INTERESTS

Fabricio Vassallo, Christiano Cunha, Eduardo Serpa, Aloyr Simões Jr. and Hermes Carloni certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. Edevaldo da Silva is an employee of Abbott Brazil, an organization with a financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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