Long-Term Outcomes of Cardioneuroablation with and without Extra-Cardiac Vagal Stimulation Confirmation in Severe Cardioinhibitory Neurocardiogenic Syncope

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Abstract

Background Cardioneuroablation (CNA) is a novel therapeutic approach for functional bradyarrhythmias, specifically neurocardiogenic syncope or atrial fibrillation, achieved through endocardial radiofrequency catheter ablation of vagal innervation, obviating the need for pacemaker implantation. Originating in the nineties, the first series of CNA procedures was published in 2005. Extra-cardiac vagal stimulation (ECVS) is employed as a direct method for stepwise denervation control during CNA. **Objective** This study aimed to compare the long-term follow-up outcomes of patients with severe cardioinhibitory syncope undergoing CNA with and without denervation confirmation via ECVS. **Method** A cohort of 48 patients, predominantly female (56.3%), suffering from recurrent syncope (5.1±2.5 episodes annually) that remained unresponsive to clinical and pharmacological interventions, underwent CNA, divided into two groups: ECVS and NoECVS, consisting of 34 and 14 cases, respectively. ECVS procedures were conducted with and without atrial pacing. **Results** Demographic characteristics, left atrial size, and ejection fraction displayed no statistically significant differences between the groups. Follow-up duration was comparable, with 29.1 ± 15 months for the ECVS group and 31.9±20 months for the NoECVS group (p=0.24). Notably, syncope recurrence was significantly lower in the ECVS group (2 cases vs. 4 cases, Log Rank p=0.04). Moreover, the Hazard ratio revealed a five-fold higher risk of syncope recurrence in the NoECVS group. **Conclusion** This study demonstrates that concluding CNA with denervation confirmation via ECVS yields a higher success rate and a substantially reduced risk of syncope recurrence compared to procedures without ECVS confirmation.

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Background

Cardioneuroablation (CNA) is a novel therapeutic approach for functional bradyarrhythmias, specifically neurocardiogenic syncope or atrial fibrillation, achieved through endocardial radiofrequency catheter ablation of vagal innervation, obviating the need for pacemaker implantation. Originating in the nineties, the first series of CNA procedures was published in 2005. Extra-cardiac vagal stimulation (ECVS) is employed as a direct method for stepwise denervation control during CNA.

Objective

This study aimed to compare the long-term follow-up outcomes of patients with severe cardioinhibitory syncope undergoing CNA with and without denervation confirmation via ECVS.

Method

A cohort of 48 patients, predominantly female (56.3%), suffering from recurrent syncope (5.1±2.5 episodes annually) that remained unresponsive to clinical and pharmacological interventions, underwent CNA, divided into two groups: ECVS and NoECVS, consisting of 34 and 14 cases, respectively. ECVS procedures were conducted with and without atrial pacing.

Results

Demographic characteristics, left atrial size, and ejection fraction displayed no statistically significant differences between the groups. Follow-up duration was comparable, with 29.1 ± 15 months for the ECVS group and 31.9±20 months for the NoECVS group (p=0.24). Notably, syncope recurrence was significantly lower in the ECVS group (2 cases vs. 4 cases, Log Rank p=0.04). Moreover, the Hazard ratio revealed a five-fold higher risk of syncope recurrence in the NoECVS group.

Conclusion

This study demonstrates that concluding CNA with denervation confirmation via ECVS yields a higher success rate and a substantially reduced risk of syncope recurrence compared to procedures without ECVS confirmation.

Keywords: Ablation, Syncope, Cardioneuroablation, Autonomic Nervous System, Pacemaker, Atrial Fibrillation

Abbreviations and Acronyms

AF	Atrial Fibrillation
AF-Nest	Atrial Fibrillation Nests (poorly connected myocardium spots)
AV	Atrioventricular
AVB	Atrioventricular Block
bpm	beats per minute
CNA	Cardioneuroablation
cSNRT	corrected Sinus Node Recovery Time
EARP	Effective Atrial Refractory Period
EAVRP	Effective Atrioventricular Refractory Period
ECVS	Extra-Cardiac Vagal Stimulation
EF	Ejection Fraction
EVRP	Effective Ventricular Refractory Period
GP	Ganglionated Plexus
HFS	High Frequency Stimulation
HR	Heart Rate
LA	Left atrium
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
SNRT	Sinus Node Recovery Time
WP	Wenckebach's Point
AF	Atrial Fibrillation

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Background

Background

Cardioneuroablation represents a novel approach for treating functional bradyarrhythmias and/or atrial fibrillation, including neurocardiogenic syncope[1], utilizing endocardial catheter radiofrequency ablation(RF) of vagal innervation within the atrial walls, obviating the need for pacemaker implantation[2]. It was created in the nineties being the first series published in 2005[3].

RF ablation attenuates the vagal innervation in the atrial walls and in the epicardial ganglion plexuses (GPs) leading to the abolition or substantial attenuation of the cardioinhibitory reflex.[3],[4],[5] , allowing many patients to be treated without the need for pacemaker implantation[6],[7],.

Despite widespread use worldwide, demonstrating good reproducibility,[5],[8],[9]continuous refinement of the technique remains imperative. In this sense, it is essential to have a hard endpoint that can be used as a standard in all services, allowing an objective and rational comparison of results, regardless of the denervation technique used.

To establish a standardized endpoint and ensure procedural rationality, we introduced the extracardiac vagal stimulation in 2015.[10]. This tool allows for the assessment of the effectiveness of vagal denervation and determines whether further ablation is necessary to achieve complete acute elimination of the vagal effect, thereby serving for validating vagal denervation, which is considered the gold-standard endpoint of the procedure.

Some aspects deserve to be considered:

1. Safe methods for visualizing GPs remain elusive and are inferred through indirect means[3],[11];

2. A significant proportion of vagal innervation extends beyond the main GPs[12];

3. Individual variability in innervation levels introduces unpredictability in the anatomical approach[12];

4. High-frequency endocardial stimulation identifies only distal innervation sites and does not assess global vagal innervation, which is the primary driver of the cardioinhibitory reflex[13];

5. Vagal reinnervation occurs to varying degrees in all cases[14],[15] underscoring the importance of comprehensive denervation during the initial procedure to minimize the risk of recurrence.

In this study, we aimed to investigate whether Cardioneuroablation, coupled with the elimination of the vagal effect induced by extracardiac vagal stimulation (ECVS), can enhance long-term outcomes.

Objective

The objective of this study was to compare the long-term follow-up of patients with severe cardioinhibitory syncope who underwent CNA, with or without confirmation of denervation via ECVS.

Method

Study population

We enrolled a cohort of forty-eight patients presenting with isolated neurocardiogenic syncope characterized by a pronounced cardioinhibitory component. Among them, 27 (56.3%) were female, and they had a documented history of recurrent syncope episodes (5.1±2.5 per year) causing significant impairment in their quality of life, despite prior attempts at clinical and pharmacological interventions. All patients received comprehensive information regarding available therapeutic options and elected to undergo CNA rather than pacemaker implantation.

Inclusion Criteria:

Patients were required to meet the following criteria:

1. Diagnosis of neurocardiogenic syncope with a substantial cardioinhibitory component resulting in symptoms impacting quality of life;
2. Age ranging from 15 to 70 years;
3. Refractoriness, impracticality, or ineffectiveness of pharmacological treatment or pacemaker implantation;
4. Willingness to provide written informed consent, participate in the study, and comply with the follow-up protocol.

Exclusion Criteria:

Those who meet any of the following criteria were not included:

1. Previous cardiac surgery.
2. Presence of cardiomyopathy (EF < 55%; LA > 42mm).
3. Left ventricular hypertrophy (wall thickness >1.2 cm), valvular, or coronary artery disease.
4. Contraindication for the use of anticoagulants (heparin or NOAC).
5. NYHA Heart Failure Class > I.
6. Cerebrovascular or important organic or metabolic disease.
8. Current or possible pregnancy in the next 3 months.

Extracardiac Vagal Stimulation (ECVS)

The amount of vagal denervation was progressively evaluated by stepwise ECVS in the group ECVS. It was obtained without dissection or direct contact with the vagus nerve according to the original technique[10]. A quadripolar EP catheter was advanced by the superior vena cava and internal jugular vein, up to the right or left jugular foramen, Figure 1-B,D. Generally, this place is the closest one to the vagus nerve, Figure 1-C. ECVS was attained by pulsed electric field between the pole 1 and 3 of the quadripolar catheter with amplitude of 1V/kg body weight up to 70V with 50 microseconds width and a frequency of 50Hz for 5 seconds, within the jugular vein, Figure 1-A.

Figure 1

A typical response is transitory asystole and/or AV block, Figure 2-A and B. A new ECVS was repeated under atrial pacing 10 to 20ppm higher than the sinus rate, Figure 2-B. Typical response in all cases is transitory total AV block. The ECVS was performed before ablation to record the basal response, during the procedure for guiding the denervation progression, and at the end to confirm the endpoint, Figure 2-C.

Figure 2

Cardioneuroablation

All cases underwent orotracheal intubation, general intravenous anesthesia controlled by BIS (Brain Index Spectral®) and transesophageal echocardiogram. Parasympatholytic drugs were proscribed for the last two days. A conventional recorder and NAVX-Ensite® Velocity/Precision St Jude/Abbott electroanatomic mapping system were installed. The catheters were deployed under pulsed radioscopy by femoral vein using the Seldinger technique. A duodecapolar catheter was positioned in the coronary sinus. Left atrium was accessed by transseptal puncture. A decapolar circular catheter was used to get the 3D anatomical model, simultaneously achieving fractionation map. Ablation were proceeded by an irrigated RF St Jude/Abbott Flexability catheter by the classical technique for AF ablation with pulmonary vein isolation[16] and for CNA[3],[4] . Coagulation activated time between 300 to 400s was maintained by adjusting intravenous heparin infusion. Ablations were performed in the following anatomical landmarks: at the P zone (left interatrial septum between foramen oval, right pulmonary veins and left atrial roof), at the roof of the coronary sinus, at the Waterston groove and at the regions of the four main PGs[3],[17],[18]. In the latter, prolonged ablations of 1 to 2 minutes were performed to obtain deep epicardial effect, Figure 3.

Figure 3

Patients Groups

ECVS Group: This group comprised 34 cases in which ECVS was performed prior to CNA to record the baseline vagal response. CNA targeted the anatomical landmarks described earlier. Following each step, a repeat ECVS was conducted to assess the degree of denervation. If the anatomical approach proved insufficient, CNA was extended based on fractionation mapping until achieving complete or near-total elimination of the vagal response.

NoECVS Group: This group included 14 cases in which mapping relied on anatomical landmarks and regions rich in AF-Nests, as detected by Fractionation Mapping. The progression of denervation was inferred from the increase in heart rate and the Wenckebach's point. At the conclusion, an atropine test was administered, and the endpoint was deemed satisfactory if there was no response to atropine or if it was not significant.

All patients underwent close monitoring for an average duration of 30.1±16 months, with regular office visits scheduled at 3, 6, and 12-month intervals. Additionally, active communication via phone, email, ECG smartwatch, and social media was maintained to inquire about syncope recurrence and any related symptoms.

Results

The main features of the patients are shown in Table 1.

Table 2 displays the findings, statistical analysis, and results of the invasive electrophysiological study for all patients. No significant differences in electrophysiological parameters were observed between the two groups.

There were no significant differences in demographic features, left atrial size, or ejection fraction as illustrated in Table 1 and Table 2. The annual mean of syncope before the procedure was similar. The mean annual syncope rate prior to the procedure was similar. Electrophysiological parameters also exhibited equivalence, as shown in Table 2. While the mean follow-up duration did not differ significantly, the NoECVS group, which underwent CNA without denervation confirmation by ECVS, experienced a significantly higher number of relapses, as indicated in Table 1 and Figure 4.

The syncope recurrence-free survival curves, Figure 1, demonstrate a significantly lower syncope recurrence rate in the ECVS group with confirmed denervation, as indicated by a Log-Rank p-value of 0.04, Figure 4-A. Furthermore, the Hazard Ratio analysis revealed that the risk of syncope recurrence was five times higher in the NoECVS group, as depicted in, Figure 4-B.

Figure 4

Additional data from the study as presented in Table 3 will be further debated in the discussion.

Discussion

The data derived from this study indicate that ECVS-guided CNA with vagal denervation confirmation as the endpoint (ECVS group) yields superior long-term outcomes compared to CNA without validation of vagal denervation (NoECVS group), as illustrated in Figure 4. Within this cohort, the ECVS group, which concluded CNA after achieving vagal response abolition[19] exhibited a 91% freedom from syncope recurrence at the 5-year mark. In contrast, the NoECVS group, which performed CNA without ECVS control, had a 63% likelihood of remaining free from syncope during the same period, as depicted in Figure 4-A. The cumulative risk function illustrates a Hazard Ratio (HR) of 4.69, with a 95% confidence interval and a p-value of 0.047, as shown in Figure 4-B. Therefore, in the ECVS group, the probability of syncope recurrence was 4.7 times lower than that in the NoECVS group, which conducted CNA without confirmation of vagal denervation by ECVS.

Rationale of Extracardiac Vagal Stimulation

The rationale for both ECVS and CNA is grounded in the distribution of the cardiac autonomic nervous system[20],[21],[22]. Any medical procedure necessitates a method of control. Consequently, if the procedure aims to achieve vagal denervation, it should monitor and regulate the extent of this innervation and the elimination or reduction of the vagal response[19], Figure 2-C. Furthermore, cardioinhibition typically involves a substantial bilateral vagal response, and the control method must replicate it as closely as possible. In clinical practice, the reproduction of cardioinhibition is achieved through the HUTT, and in the laboratory, the sole method capable of replicating a similar controlled condition is ECVS[10],[19],[23]. Both in spontaneous events and during the HUTT, there is a massive vagal response simultaneously affecting all regions with vagal innervation, particularly the sinus node, AV node, and atrial walls. This condition can be readily reproduced with ECVS as many times as necessary, depending on the operator, as illustrated in Figure 2-A and B. In this method, the extensive vagal stimulation, accompanied by an overdrive of the vagal efferent fibers, enables a clear, objective, and gradual control of the degree of vagal denervation, ultimately leading to the complete elimination of responses in the sinus node, AV node, and even atrial walls[19], Figure 2. Consequently, aside from facilitating the rational conclusion of CNA, ECVS helps prevent over-ablation. Therefore, the significance of ECVS, which is quite intuitive from a rational standpoint, is statistically validated in this study.

CNA without ECVS

Electrophysiological Parameters of Vagal Denervation

In this study, both groups exhibited significant electrophysiological changes in all parameters related to the vagal effect. There was a notable increase in sinus rate and the Wenckebach point, along with a reduction in sinus node recovery time, sinoatrial conduction time, and AV refractory period. All other parameters unrelated to the vagus showed no significant changes, as detailed in Table 2 and Table 3.

The original CNA study we had no ECVS[3]. Ablations were directed towards areas with the highest density of AF-Nests, typically associated with the neuro-atrial interface in normal heart[3],[19],[24],[25]. Additionally, extended ablations were applied to anatomical regions that presumably overlapped with the primary GPs, which also tend to harbor a higher number of AF-Nests. The goal was to achieve sufficient depth for epicardial GP ablation. In cases with a high risk of esophageal thermal injury, mechanical esophageal displacement was performed using a transesophageal echocardiogram transducer. Based on the initial CNA technique, relying on spectral mapping obtained through online spectral analysis[26], we developed the Fractionation Mapping, making the innervation tracking easier and faster[27], Figure 5.

Figure 5

While the ablated points appeared adequate, the depth of thermal effect on the atrial wall and epicardium, and consequently the extent of denervation, could not be measured. The increase in sinus rate and the Wenckebach point, along with the shortening of the AH and EAVRP, serve as important indicators of denervation (as detailed in Table 2 and Table 3); however they represent indirect parameters and do not necessarily indicate a full effect. Immediate results may be achieved by eliminating superficial fibers, but long-term outcomes depend on the disappearance of deep neural bodies. There are numerous instances where, despite modifications in all EP parameters, ECVS reveals a significant residual vagal response[28], often leading to clinical recurrence. In this study, we found that although there was no statistically significant difference in the electrophysiological parameters of acute vagal denervation (as shown in Table 3), there was a significant difference in long-term outcomes, suggesting that immediate electrophysiological response alone may not be enough to predict the long-term efficacy of CNA.

Atropine Test

In the initial study aimed at evaluating vagal denervation, we employed the atropine test (0.04mg/kg up to 2mg intravenously) to ascertain whether any residual vagal tone remained at the conclusion of CNA[3],[29]. However, it should be noted that even in cases of partial CNA, there is an immediate increase in sinus rate, which diminishes the sensitivity of the atropine test as sinus rate rises. Additionally, after atropine infusion, assessing further denervation attempts becomes challenging.

Endocardial High Frequency Stimulation in the Atrial Wall

An alternative approach to monitor CNA involves High-Frequency Stimulation (HFS) of the GPs via the endocardium[18,13]. While this method holds significant academic value in various applications, including AF ablation[30]. it presents certain challenges specific to CNA. Apart from the inherent issues associated with point-by-point sequential assessment and frequent AF induction, HFS primarily assesses specific areas of innervation and cannot provide an estimate of the global innervation resulting from extensive vagal cardioinhibition. In other words, HFS examines individual branches rather than the entire neural network.

Radioscopy Time The average duration of radioscopy in the CNA+ECVS group was slightly longer than in the CNA group (13.6±11 vs. 13.1±3.2 minutes, p=0.87), but the difference was not statistically significant. However, there was greater data dispersion in the ECVS group. This variation was due to cases in which the vagal effect was rapidly eliminated by anatomical ablation, while in others, it was necessary to expand CNA until vagal effect abolishment or maximum reduction was achieved.

Denervation and Reinnervation versus CNA

Cardiac innervation is highly primitive and exhibits a substantial capacity for reinnervation[15,31]. It is estimated that reinnervation may recover between 30% to 60% of the basal innervation. Consequently, the broader the initial procedure, the greater the potential for long-term success[32].

In this study, we observed that the electrophysiological parameters of denervation were equally achieved in both groups. There is no doubt that both techniques induced significant acute denervation. However, it became evident that there was indeed a difference in the extent of denervation and in preventing reinnervation. This conclusion is supported by the fact that in the NoECVS group, the risk of relapse was five times higher with a high level of statistical significance. Moreover, relapses occurring between 10 and 25 months in this group suggest reinnervation. This finding is crucial because we may observe an initial apparent denervation response, likely due to superficial effects, without the elimination of deep GPs and micro-GPs. Naturally, the absence of more extensive elimination of these GPs may facilitate reinnervation and significantly increase the likelihood of relapse.

Limitations

A limitation of this study is the relatively small number of patients in the NoECVS group (2 cases). This can be reasonably explained by the stringent patient selection criteria applied to both groups, and it underscores the ethical concerns regarding uncontrolled CNA without ECVS confirmation. However, the statistical analysis demonstrates that the two groups are sufficiently equivalent and suitable for comparison. It is crucial to recognize that patient selection was rigorously conducted, and the number of cases with predominantly cardioinhibitory neurocardiogenic syncope is inherently limited, as only severe cases with complete resistance to conservative treatment were included. Additionally, only cases performed by three highly trained operators were included to ensure maximum equivalence and technical reproducibility of the procedures.

Conclusion

Controlled CNA with extra-cardiac vagal stimulation, aiming for the complete elimination of the vagal response in the sinus and atrioventricular nodes, achieves a significantly higher long-term success rate than procedures performed without confirming vagal response elimination via extra-cardiac vagal stimulation. The risk analysis demonstrates that confirmed acute elimination of the vagal response through extra-cardiac vagal stimulation reduces the chances of syncope recurrence by at least fivefold.

Compliance with Ethical Standards

Disclosure: There is no disclosure

Funding: None

Ethical approval: The study was approved by the hospital ethical committee

Informed Consent: Patients were informed about the benefits and risks of the procedure, as well as alternative therapies, and were included as long as they fully agreed and signed the consent form.

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Tables

Table 1 - Basic characteristics and statistical comparison of patients

	Group ECVS	**Group NoECVS**	p
	CNA with ECVS	**CNA without ECVS**	
N	34	14	
Age	35.8 ± 18	37.9±10	0.68
Genre	20 F (58.8%)	7F (50%)	0.57
Weight	70.1 ± 14	67.6±16	0.66
Heigth	168.4 ± 11	166.1±6	0.55
BMI	24.4 ± 4	23.9±4	0.75
Syncope	5.1 ± 2.7	4.9±2.3	0.78
LA	34.1 ± 4.5	33.4±3.5	0.86
EF	65.6 ± 4.6	66.1±4.7	0.78
Mean Syncope/year	5.1 ± 2.7	4.9 ± 2.3	0.78
Radioscopy Time	13.6±11	13.1±3	0.87
Follow-up (months)	29.1 ± 15	31.9±20	0.24
Syncope Recurrence	2	4	0.03

Table 2 - Electrophysiological features. HR: Heart Rate; cQT: Corrected QT; WP: Wenckebach Point (ppm); SNRT: Sinus Node Recovery Time; cSNRT: Corrected Sinus Node Recovery Time; SACT: Sino-Atrial Conduction Time; EART: Effective Atrial Refractory Period; EAVRP: Effective Atrioventricular Refractory Period; EVRP: Effective Ventricular Refractory Period.

	Group ECVS	**Group NoECVS**	p
	CNA with ECVS	**CNA without ECVS**	
HR	59.1 ± 11.8	61.7±9.9	0.47
PR	159.5 ± 20.9	154.8±22.7	0.49
QRS	101.6 ± 10.9	101.2±8.4	0.92
QT	424.0 ± 43.9	402.5±69.6	0.2
corrected QT	436.4 ± 81.0	421.8 ± 85.8	0.19
WP	146.2 ± 33.6	160.6±31.6	0.19
SNRT	1515.7 ± 501.2	1366.7±274.4	0.32
corrected SNRT	458.2 ± 311.6	392.5±203.0	0.49
SACT	199.0 ± 65.0	177.1±75.1	0.48
PA	29.5 ± 10.6	35.9±16.6	0.11
AH	80.5 ± 20.3	73.4±14.7	0.25
H	20.3 ± 4.0	21.3±3.2	0.98
HV	49.3 ± 5.0	50.8±5.3	0.37
EARP	223.3 ± 28,7	215.7 ± 16.2	0.55
EAVRP	363.1 ± 118.8	328.3 ± 87.9	0.37
EVRP	248.5 ± 27.7	246.6 ± 17.5	0.82

Table 3 - Comparison of pre and post-CNA electrophysiological parameters in the two groups.

	ECVS Group (CNA With ECVS) Pre-CNA	**ECVS Group (CNA With ECVS) Post-CNA**	**ECVS Group (CNA Wit p**
HR	59.1 ± 11.8	84.4 ± 14.5	0.00
PR	159.5 ± 20.9	150.0 ± 19.4	0.07
QRS	101.6 ± 10.9	100.1 ± 11.3	0.61
QT	424.0 ± 43.9	397.6 ± 45.3	0.02

cQT	436.4 ± 81.0	442.1 ± 79.3	0.77
WP	146.2 ± 33.6	172.6 ± 22.4	0.00
SNRT	1515.7 ± 501.2	881.9 ± 264.7	0.00
cSNRT	458.2 ± 311.6	239.3 ± 95.0	0.01
SACT	199.0 ± 65.0	171.4 ± 44.1	0.15
PA	29.5 ± 10.6	25.3 ± 7.4	0.45
AH	80.5 ± 20.3	59.8 ± 19.1	0.00
H	20.3 ± 4.0	19.9 ± 3.2	0.64
HV	49.3 ± 5.0	48.9 ± 4.8	0.75
EARP	223.3 ± 28.8	220.5 ± 29.2	0.83
EAVRP	363.1 ± 118.8	275.2 ± 69.8	0.00
EVRP	248.5 ± 27.8	250.5 ± 28.6	0.82

Figures

Figure 1

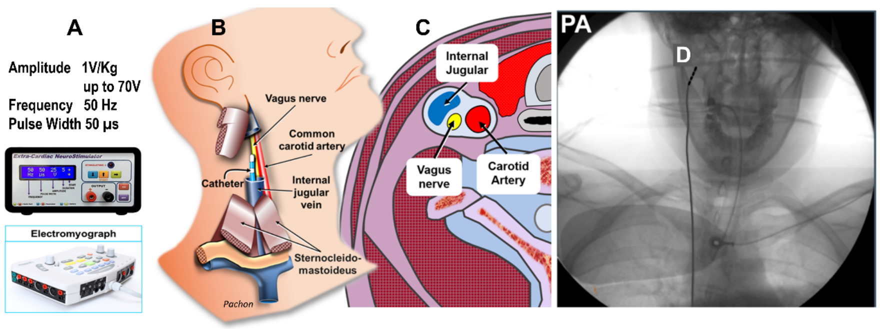


Figure 2

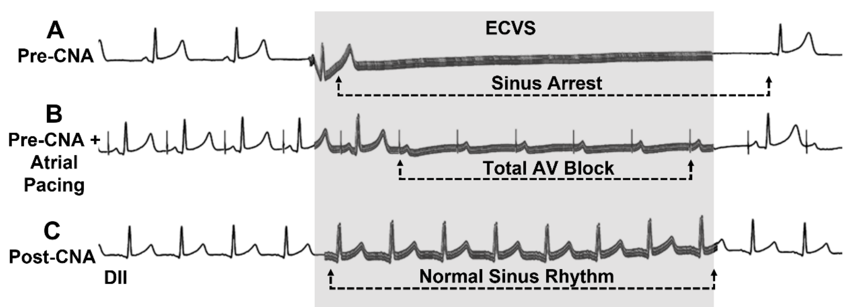


Figure 3

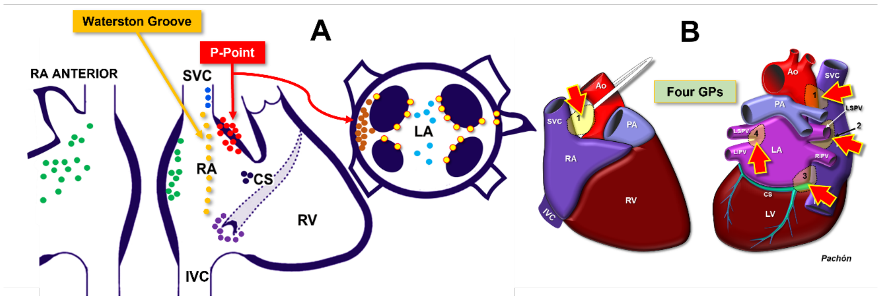


Figure 4

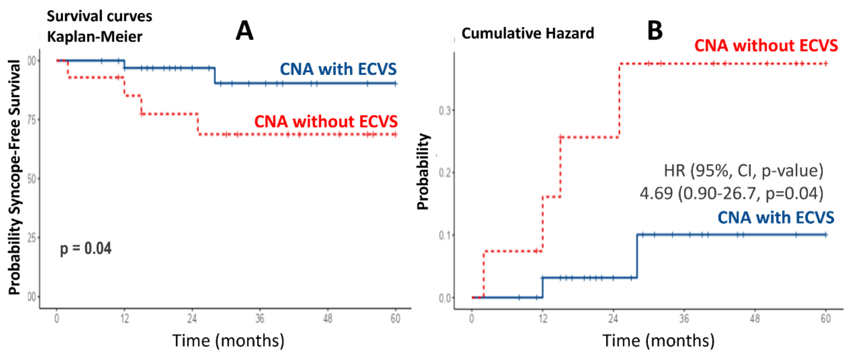


Figure 5

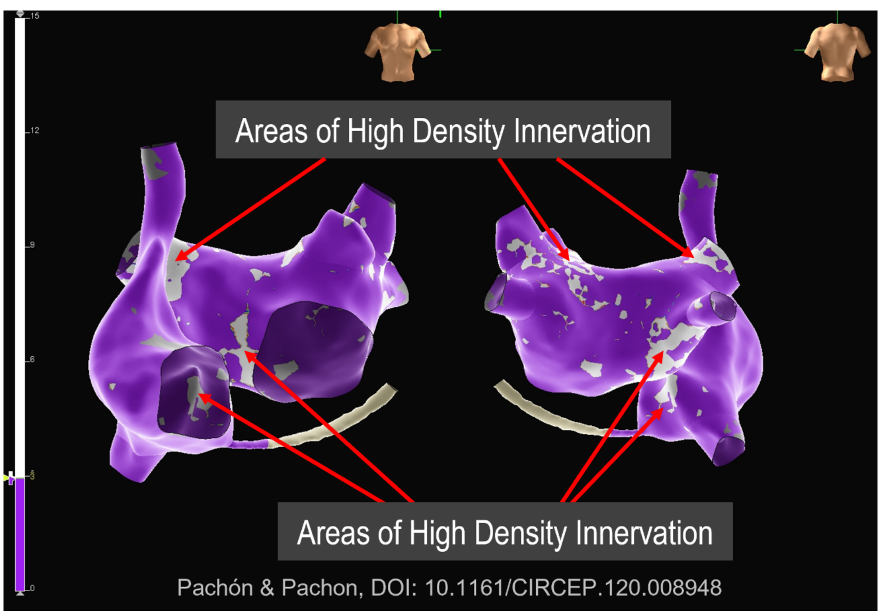


Figure Legends

Figure 1 - Extracardiac Vagal Stimulation Methodology: A: The ECVS is performed without direct contact with the vagus nerve through a specific Vagal Stimulator or a Neuro-Stimulator using pulses with an

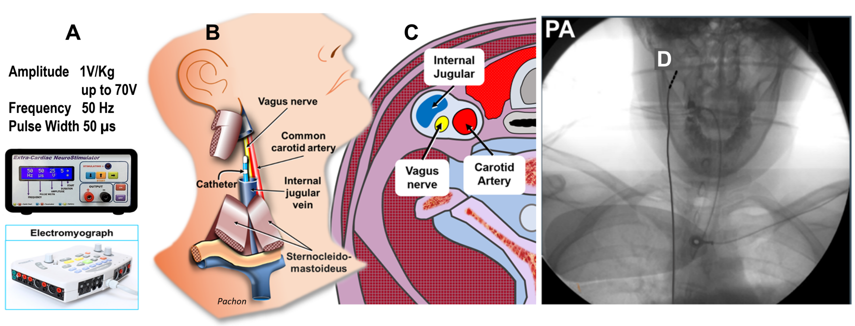
amplitude of 1V/Kg of body weight up to a maximum of 70V with 50microseconds and frequency of 50Hz; B: Schematic of the catheter inside the right or left internal jugular vein; C: Diagram of the anatomy of a section of the cervical region showing the close proximity of the vagus nerve and the internal jugular vein; D: anteroposterior radiological view of the position of the vagal stimulation catheter. The best stimulation site is usually from the lower limit of the orbit to the root of the wisdom tooth.

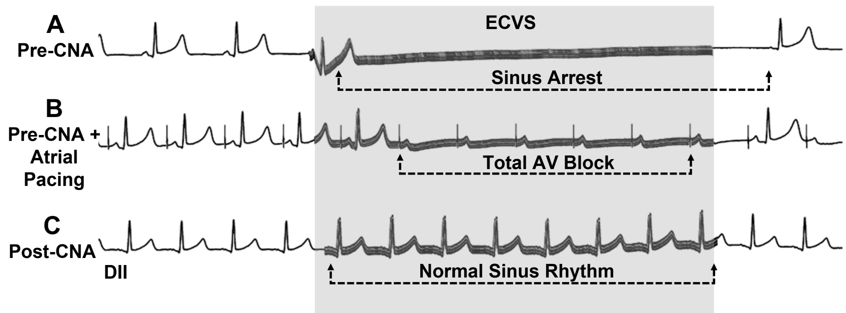
Figure 2 - ECVS Methodology. In the ECVS Group, the ECVS was used for gradual control of CNA and for the endpoint. A: before CNA, a sinus arrest is observed under ECVS. It is the usual response to ECVS in normal people due to sinus node suppression; B: When ECVS is performed with atrial pacing 10 to 20 ppm above the previous sinus rate before CNA, high-grade AV block is usually observed due to AV node suppression; C:ECVS applied after the CNA, obtaining a total absence of a vagal effect. There is no more sinus arrest, sinus pause, bradycardia or AV block. This was the expected endpoint in this group of patients.

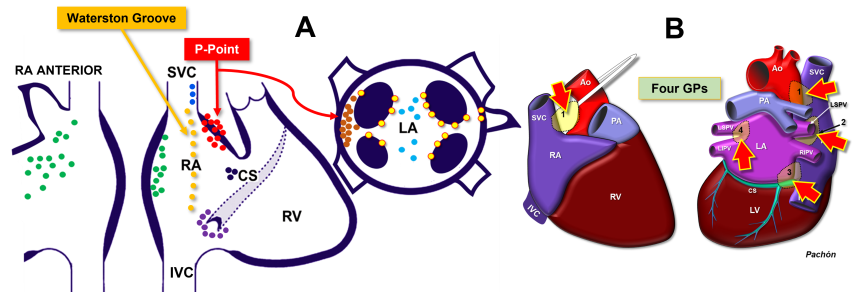
Figure 3 - A: Schematic of endocardial sites usually ablated during CNA. As the GPs are not visible, the sites of interest are assumed to be anatomically close and numbered from 1 to 4. In addition to the GP regions, the most important area for the CNA is the P Point located on the left side of the interatrial septum. In cases of more difficult denervation, additional areas are ablated such as the roof of the coronary sinus, the region of the Marshall's vein, superior vena cava, anterolateral wall of the right atrium, the Waterston groove and any other area indicated by the fractionation mapping; B: Schematic of the sites of the four main ganglionated plexuses. Site 1: between superior vena cava and aorta; Site 2: antrum of the right pulmonary veins; Site 3: Confluence of the coronary sinus ostium and the inferior vena cava; Site 4: Insertion of the left pulmonary veins.

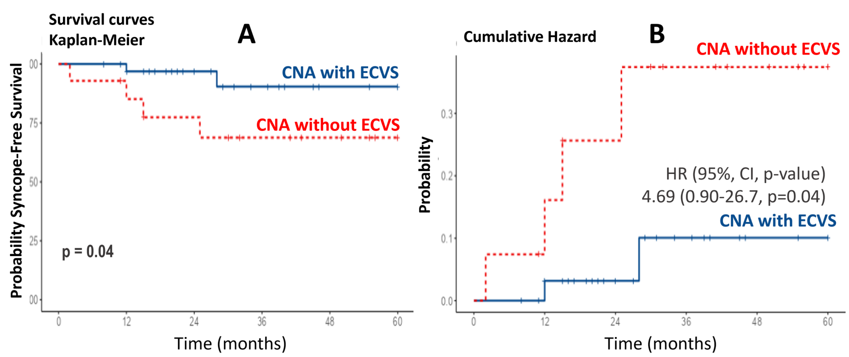
Figure 4 - A: Kaplan-Meier survival curves showing the free probability of syncope in the ECVS group (CNA controlled with ECVS) and in the NoECVS group (CNA without ECVS); B: Hazard cumulative risk curves for the possibility of recurrence comparing the CNA controlled with ECVS group with the CNA group without ECVS control.

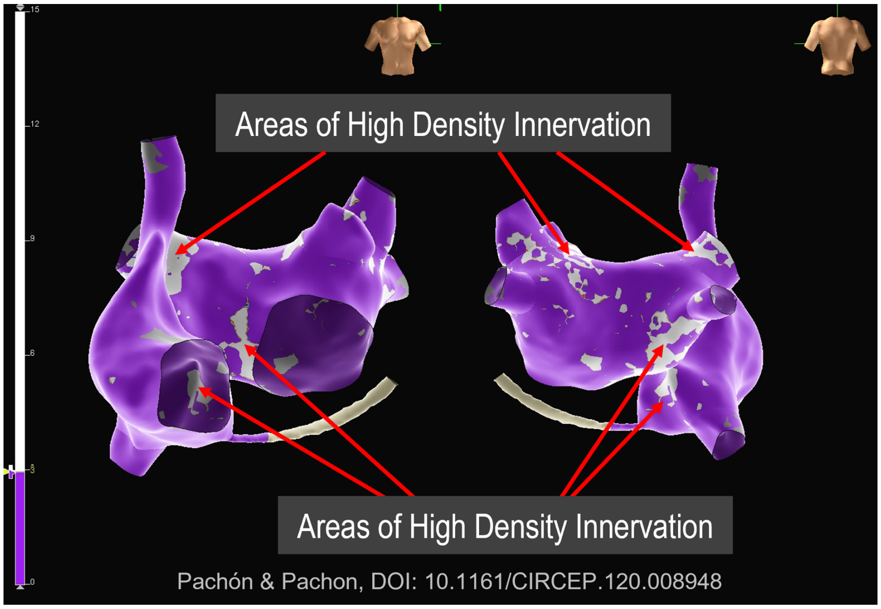
Figure 5 - Fractionation software. In the normal heart, vagal innervation can be indirectly identified through AF-Nests by spectral mapping. Based on this method, we developed the Fractionation software that allows the identification of AF-Nests in the electroanatomical model without the need for spectral analysis. Additionally, innervation can be approached by approximation by using the assumed position of the GPs. However, in many cases, due to anatomical variations, the fractionation map is necessary to complement the anatomical method and obtain complete denervation.




A
Pre-CNA
ECVS
Sinus Arrest
B
Pre-CNA +
Atrial
Pacing
Total AV Block
C
Post-CNA
DII
Normal Sinus Rhythm


Waterston Groove
P-Point
A
B
RA ANTERIOR
SVC
RA
CS
RV
IVC
LA
Four GPs
Ao
PA
SVC
RA
RV
IVC
LA
LV
CS
Pachón


Survival curves
Kaplan-Meier
A
CNA with ECVS
CNA without ECVS
Probability Syncope-Free Survival
p = 0.04
Time (months)
Cumulative Hazard
B
CNA without ECVS
HR (95%, CI, p-value)
4.69 (0.90-26.7, p=0.04)
CNA with ECVS
Probability
Time (months)


Areas of High Density Innervation
Areas of High Density Innervation
Pachón & Pachon, DOI: 10.1161/CIRCEP.120.008948