

Cardioneuroablation: Catheter Vagal Denervation as a New Therapy for Cardioinhibitory Syncope

Cardioneuroablação: A Denervação Vagal por Cateter Como Nova Terapia para Síncope Cardioinibitória

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ABSTRACT

The vasovagal syncope is the most frequent cause of transient loss of consciousness, especially in young people without significant heart disease. Malignant cardioinhibitory form is caused by abrupt and intense vagal reflex with or without defined triggers. Refractory cases to preventive measures and pharmacological handling, has been treated with definitive pacemaker implantation. Besides showing questionable results, pacemaker implantation is highly rejected by young patients. In the late 1990s, we proposed a specific vagal denervation by catheter ablation and spectral mapping, for paroxysmal AF, functional bradyarrhythmias and severe cases of malignant cardioinhibitory syncope giving rise to cardioneuroablation. Recently, many authors worldwide have been reproducing the cardioneuroablation results where elimination or significant reduction of the vagal response were observed, which abolished symptoms in more than 75% of patients followed up to 14 years, without complications. Therefore, cardioneuroablation has shown to be a real therapeutic option in malignant syncope cardioinhibitory and in any exclusive vagal mediated bradyarrhythmia without the need of pacemaker implantation.

KEYWORDS: Vasovagal Syncope; Malignant Neurocardiogenic Syncope; Catheter Ablation; Vagus Nerve Stimulation.

RESUMO

A síncope vasovagal é a causa mais frequente de perda transitória de consciência, especialmente em jovens sem doença cardíaca significativa. A forma cardioinibitória maligna é causada por reflexo vagal abrupto e intenso com ou sem gatilhos definidos. Casos refratários a medidas preventivas e manuseio farmacológico foram tratados com implante definitivo de marcapasso. Além de apresentar resultados questionáveis, o implante de marcapasso é altamente rejeitado por pacientes jovens. No final dos anos 1990, propusemos uma denervação vagal específica por ablação do cateter e mapeamento espectral para FA paroxística, bradiarritmias funcionais e casos graves de síncope cardioinibitória maligna dando origem à cardioneuroablação. Recentemente, muitos autores em todo o mundo vêm reproduzindo os resultados da cardioneuroablação, onde se observou eliminação ou redução significativa da resposta vagal, o que aboliu sintomas em mais de 75% dos pacientes acompanhados por até 14 anos, sem complicações. Portanto a cardioneuroablação tem se mostrado uma verdadeira opção terapêutica na síncope cardioinibitória maligna e em qualquer bradiarritmia vagal exclusiva mediada sem a necessidade de implante de marcapasso.

PALAVRAS-CHAVE: Síncope Vasovagal; Síncope Neurocardiogênica; Ablação por cateter; Estimulação do Nervo Vago.

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INTRODUCTION

According to the 2015 Heart Rhythm Society Expert Consensus, syncope is defined as a transient loss of consciousness, associated with an inability to maintain postural tone, rapid and spontaneous recovery, and the absence of clinical features specific for another form of transient loss of consciousness such as epileptic seizure¹. Common causes of syncope are the vasovagal, orthostatic hypotension, and cardiac disorders. The vasovagal syncope, neurocardiogenic or reflex syncope is the most frequent, especially in the younger population with no apparent heart disease¹. It is a very frequent clinical problem that reduces the quality of life and may increase the risk of trauma. Usually, it is a transient loss of consciousness due to a reflex response, caused by intense bradycardia or asystole (cardioinhibitory type) associated to a greater or lesser vasodepression degree (mixed type). Infrequently, the vasovagal syncope is caused by lone vasodepression (vasodepressor type).

Despite controversial results and some degree of uncertainty, pacemaker has been considered the treatment of choice for severe cardioinhibitory syncope without response to clinical treatment^{1,2}. However, besides showing a questionable result, the pacemaker is associated with great rejection by these patients, usually young and without apparent heart disease. As the cardioinhibitory response is mediated by a huge vagal reflex, the first proposal for autonomic ablation, more specifically vagal denervation by using RF catheter ablation in atrial walls (Cardioneuroablation - CNA) was published in 2005, as a definitive treatment for the severe cardioinhibitory syncope, being the first patient ablated in 2002¹. The great advantage of this method was the possibility of treatment without pacemaker implantation.

Vasovagal syncope

Also known as reflex, neurocardiogenic or vasovagal syncope, it is caused by a reflex mechanism, through multiple triggers, ending with intense cardioinhibition and/or vasodilatation leading to severe and transient hypotension. The cardioinhibition can be enough to cause prolonged asystole. Typically, the patient recovers spontaneously within minutes. Depending on the physiopathology, it can be classified as cardioinhibitory, vasodepressor or mixed. The first is characterized by

asystole, severe bradycardia and/or transient total AV block caused by intense vagal action. In the vasodepressor form, severe hypotension without significant bradycardia usually occurs, mainly due to a sudden reduction in sympathetic tone². In the mixed form, there is the contribution more or less intense of the two mechanisms.

CARDIAC AUTONOMIC NERVOUS SYSTEM

Anatomy

The autonomic nervous system of the heart consists of three major divisions, one afferent – the sensory nervous system – and two efferent partitions, the parasympathetic and sympathetic branches. The medulla oblongata is the main center for integration of cardiac innervation whose activity is modulated by the hypothalamus and more superior centers. The sensory fibers are bipolar neurons whose cells bodies are in the medulla oblongata. The efferent fibers comprise essentially two main neurons, the pre and the post-postganglionic. The parasympathetic postganglionic fiber is very short because its body neuron is located in the heart, mainly in the atrial wall and in the ganglionated plexuses (paracardiac fat pads)³. The cell body of the parasympathetic preganglionic neuron placed is in the medulla oblongata, more specifically in the nucleus ambiguus and in the vagus dorsal motor nucleus⁴. Its axon is led to the heart by the vagus nerves. In contrast, the sympathetic postganglionic neuron is too long because their cell body is sited in the paravertebral sympathetic chain. The result of this distribution is that only the parasympathetic postganglionic body neuron is located in the heart and only this one is prone to be eliminated by the endocardial RF ablation.

Physiology

Despite being the heart a striated muscle, its activity does not depend on the innervation. Unlike the skeletal muscle that atrophies when denervated, the heart retains its normal metabolism, structure and activity independent on the innervation. This fact is easily observed in cardiac transplantation patients. However, the autonomic nervous system acts permanently modulating all cardiac properties, through an intense inhibitory

(parasympathetic) and excitatory (sympathetic) tone. This functional antagonism creates a balance mediated by the brain stem that determines the instantaneous heart rate. This balance is constantly restored by the autonomic nervous system by adjusting the cardiac physiology at every moment. Thereby, in the case of vagal denervation, a proportional reduction in the sympathetic tone determined by the reflex balance of the autonomic nervous system is usually observed, bringing down the cardiac rate back to baseline.

Rationale

The cardioinhibition of the reflex syncope is caused by a massive sudden vagal reflex that may be totally eliminated by vagal denervation. That is also elegantly proved by preventing the cardioinhibitory syncope by atropine⁵. Aiming a new definitive treatment for this condition, in the late nineties, we proposed a specific vagal denervation⁵, by endocardial ablation guided by spectral mapping, for treating paroxysmal AF, functional bradyarrhythmias and severe cardioinhibitory syncope, given rise to cardioneuroablation. Since then, we have been studying the possibility of abolishing or attenuating, permanently, the cardioinhibitory reflex by using RF endocardial ablation. Although a temporary denervation can be obtained with the elimination of neural fibers, long-term denervation needs the elimination of cells bodies of the neurons to prevent reinnervation. As previously mentioned, cardiac innervation is composed of parasympathetic, sympathetic and sensory systems (Fig. 1). Only the parasympathetic innervation contains most of the postganglionic neuron within the heart, more specifically inside the atrial wall, on the epicardium, in the endocardium or in the paracardiac ganglia (epicardial fat pads). In contrast, the cells bodies of postganglionic sympathetic and sensory neurons lie, respectively, in the paravertebral chain ganglia and in the central nervous system, away from the heart. These features favor more selective vagal denervation since the cell body of the postganglionic parasympathetic neuron is the only directly exposed to RF application in atrial walls. The sympathetic and sensory body neurons are preserved and their function is usually recovered because only fibers endings are temporarily eliminated by endocardial RF energy^{6,7}.

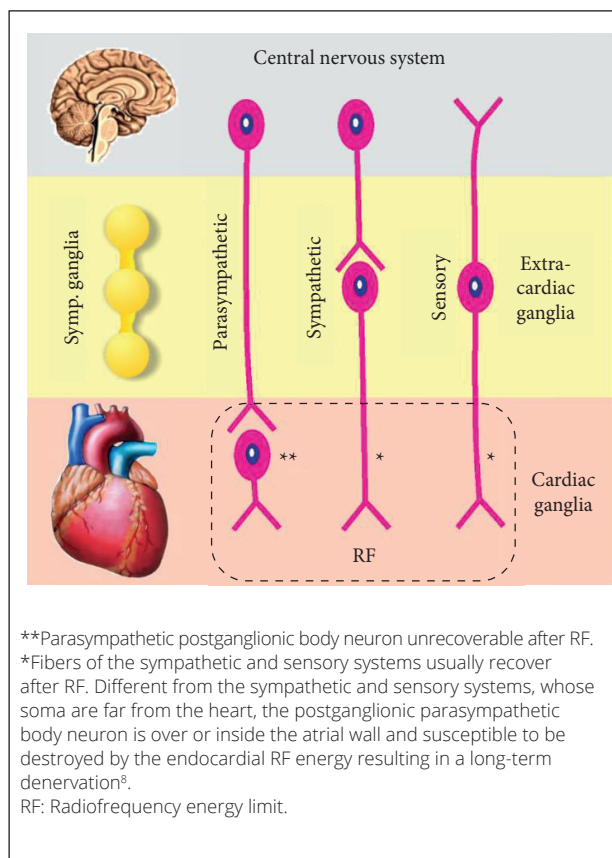


Figure 1. Sketch of the cardiac nervous system with the three main cardiac innervation partitions and the endocardial RF effect.

CARDIAC AUTONOMIC DENERVATION

Several attempts of cardiac denervation with purposes other than cardioinhibition treatment have been developed. Left stellectomy for the treatment of the Long QT Syndrome is a successful example by partially ablating the cardiac sympathetic nervous system⁹. More recently, surgical ablation of the epicardial ganglionated plexuses aiming treatment of atrial fibrillation has been tried^{10,11}. Unfortunately, this kind of denervation has not shown positive results¹². In contrast, the vagal denervation to treat vasovagal syncope appears to be highly efficient. The first study proposing this kind of denervation by endocardial ablation to eliminate cardioinhibition caused by vagal reflex was published in 2005⁵, and the first patient was treated in 2002. Since then, significant advances were obtained and many distinguished authors have been able to reproduce the results¹³⁻²¹.

RF catheter ablation for vagal denervation

The main purpose of the procedure is mapping and ablation of the vagal endings in the atrial wall. As the parasympathetic postganglionic neuron is sited inside or over the atrial wall and in the cardiac ganglionated plexuses, there is a great chance of getting their elimination by endocardial conventional RF. Nevertheless, the main challenge is the detection and mapping of endocardial innervation high-density areas in order to release the RF. The hypothesis was that endocardial RF could be able to eliminate the existing postganglionic parasympathetic neuron in the atrial wall (first neuron, Fig. 2), in the visceral epicardium and even part of neurons located in the ganglionated plexuses (second neuron, Fig. 2). The purpose was to obtain enough denervation to eliminate or attenuate the vagal tone and the cardioinhibition in long term, making the vasovagal cardioinhibitory reflex more resistant to triggers.

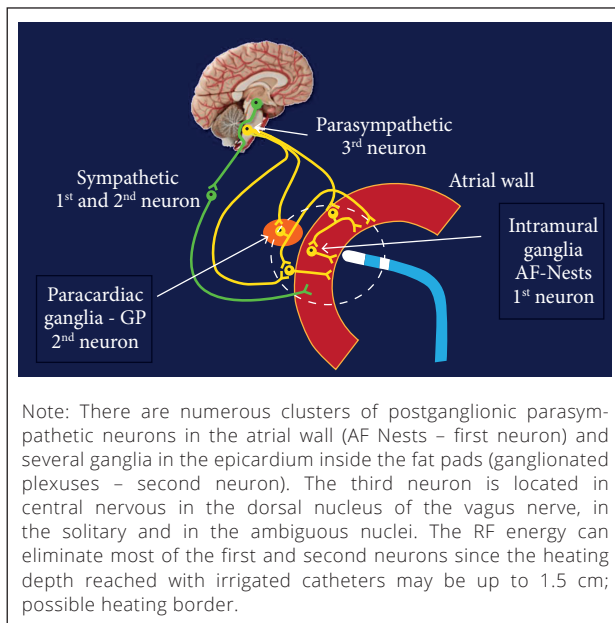


Figure 2. Scheme of the cardiac innervation and cardioneuroablation.

Mapping and ablating the cardiac innervation by endocardial approach

Unlike the skeletal muscle, the myocardium does not have a differentiate neuromuscular junction. In contrast, the nerve parasympathetic and sympathetic fibers directly penetrate the myocardium and interweave with the myocytes. Additionally, lots of microneurons (parasympathetic postganglionic neurons, first neuron in Fig. 2) colonize the atrial walls

(Figs. 4 and 5). This blend of cells changes some electrical properties of the atrial wall and may be identified by changes in the spectrum as “AF Nests”²²⁻²⁵ (this name resulted from its relation with the AF physiopathology as they present electrical resonance^{26,27} favoring the AF maintenance). Therefore, by using the spectral study during sinus rhythm, we have found two types of myocardium. The first one, the *compact myocardium*, is characterized by high amplitude, isotropic conduction and a smooth spectrum (Fig. 3a), whereas the second one, the *fibrillar myocardium*, has a low amplitude, anisotropic conduction and a segmented spectrum (Fig. 3b)^{26,28,31}.

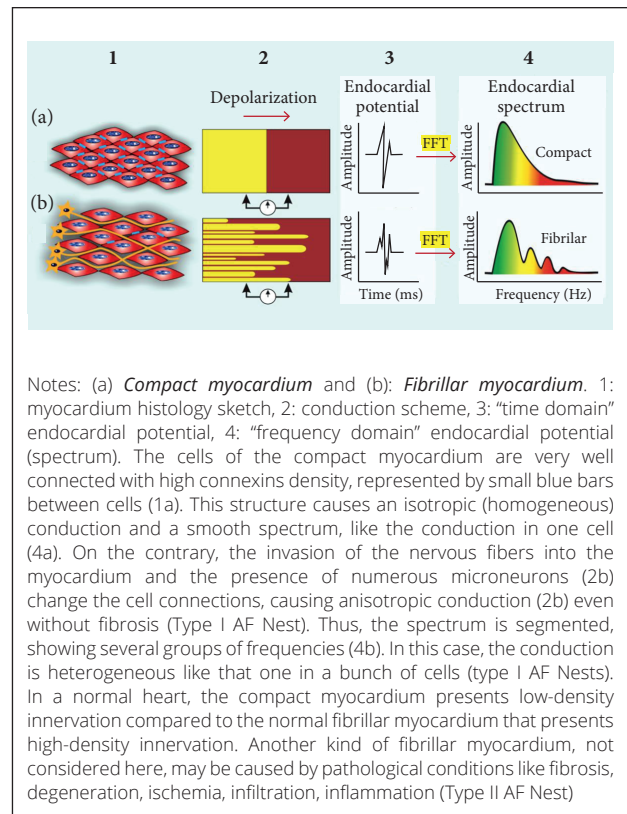
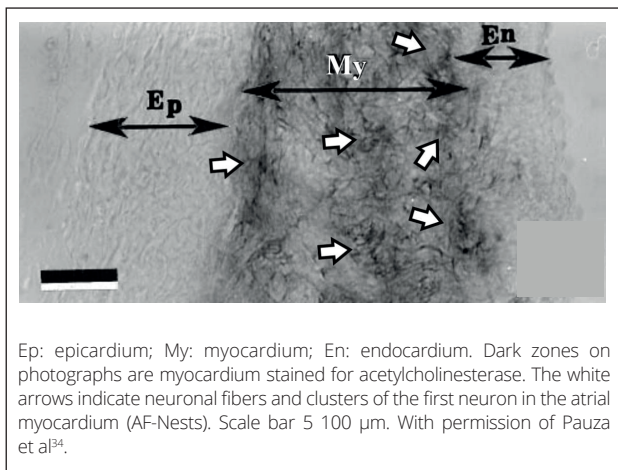


Figure 3. Differences in electrical properties of the myocardium depending on the connection grade of the cells.

Clusters of fibrillar myocardium give rise to AF Nests. Several findings have demonstrated a close relation between the *fibrillar myocardium* and the cardiac innervation interface:

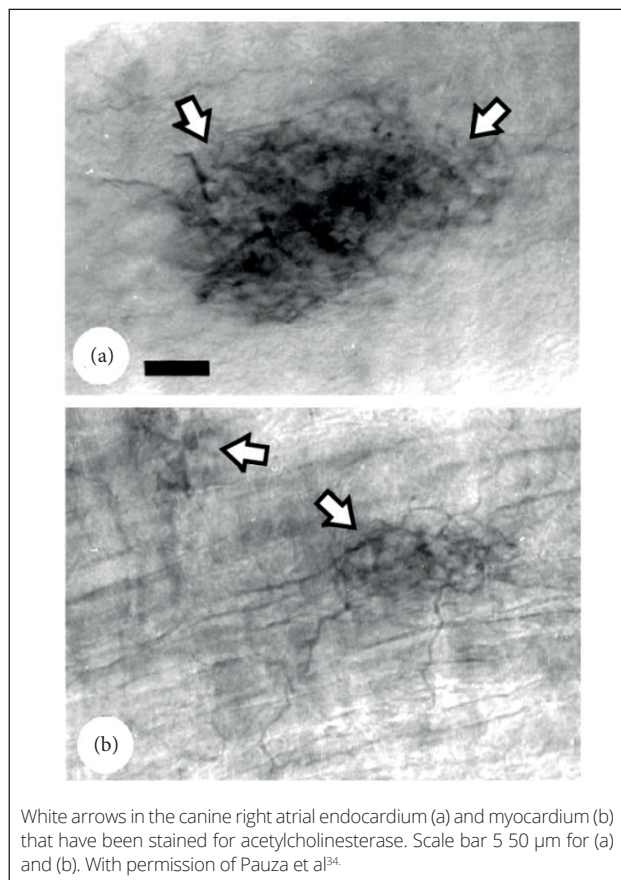
- RF delivery in the septal fibrillar myocardium usually causes immediate autonomic reactions, such as a significant heart rate and Wenckebach’s point increases^{29,30,8};

- Detailed studies based on neural staining have shown a high number of parasympathetic neurons and ganglia in the fibrillar myocardium areas³¹⁻³³;
- A large amount of fibrillar myocardium is found in the anatomical regions of the cardiac ganglionated plexuses^{26,27,31}.



Ep: epicardium; My: myocardium; En: endocardium. Dark zones on photographs are myocardium stained for acetylcholinesterase. The white arrows indicate neuronal fibers and clusters of the first neuron in the atrial myocardium (AF-Nests). Scale bar 5 100 µm. With permission of Pauza et al³⁴.

Figure 4. Photomicrographs of cross-sections through an adult canine right atrial wall.



White arrows in the canine right atrial endocardium (a) and myocardium (b) that have been stained for acetylcholinesterase. Scale bar 5 50 µm for (a) and (b). With permission of Pauza et al³⁴.

Figure 5. Examples of clusters of the first neuron in the atrial wall (AF Nests).

Through the on-line real-time spectral mapping, it is possible to disclose the fibrillar myocardium (AF Nests)

to guide the ablation (Fig. 3Bb4) of the first neuron. Consequently, most of the postganglionic parasympathetic neurons may be abolished and do not recover, whereas the sympathetic and sensory terminal fibers usually recover from weeks to months (Fig, 2). Preganglionic vagal fibers may provide some grade of reinnervation but it is reduced as they have lost the postganglionic link replaced by some post-RF fibrosis.

CARDIONEUROABLATION METHOD

Inclusion criteria

The success of the procedure depends on a strict inclusion criterion. The main one is the presence of a reflex and / or functional bradyarrhythmia in a symptomatic patient, without response or without the possibility of clinical treatment³⁵ in an apparently normal heart or having rationally excluded a significant cardiopathy³⁶. Likewise, pharmacological test to confirm the reversibility of the condition, as a positive response to the atropine, are decisive, Table 1.

Table 1. Cardioneuroablation inclusion criteria. During the atropine test, the heart rate must twofold or must reach more than 100 bpm at least by 15 min.

Reflex or functional symptomatic bradyarrhythmia
• Severe cardioinhibitory syncope
• Severe vasovagal syncope with a very important
• Cardioinhibitory component
• Symptomatic sinus node dysfunction or Brady-Tachy syndrome
• Symptomatic functional AV block
Absence of significant cardiopathy
Normal response to atropine (0.04 mg/kg = 2 × HR or HR > 100 bpm/15')
Impossibility or nonresponse to clinical treatment

Method

Since the patient has signed the consent form, the procedure is performed under general anesthesia. An important concern is that, inadvertently, the anesthesiologist may use atropine at the beginning of the procedure and that would make cardiologists miss the autonomic tone parameter; so, it is essential to warn the anesthesiologist team to discuss before they use any autonomic drug. The vital signs (heart rate, oximetry, blood pressure, plethysmography, peripheral

perfusion, capnography and respiratory gases) are strictly monitored. Skin adhesives of the 3D NavX™ or Velocity™ Electroanatomic Mapping System are applied and the esophageal echocardiography transducer is inserted. Brain function is monitored by spectral (BIS Aspect A-1000) keeping the consciousness level between 40 and 50 bi-spectral indexes. Conventional EP leads are placed and a routine EP study is carried out. Interatrial septum puncture is performed under transesophageal echocardiography guidance. Heparin (100 IU/kg) is used to keep the activated coagulation time around 300 s. Mapping is performed with a spectrometer or by setting the EP conventional recorder filters.

RF guided by spectral mapping or by endocardial potentials

The patient must be in sinus rhythm and the right and left atrial endocardium are scanned with conventional irrigated catheter with the thermocontrolled RF generator. RF is applied in all places featured as AF Nest (fibrillar myocardium) (Fig. 6) aiming the elimination of the first neuron. Scanning may be guided by spectral mapping (Fig. 7) or by conventional recordings with some filtering settings (Fig. 8).

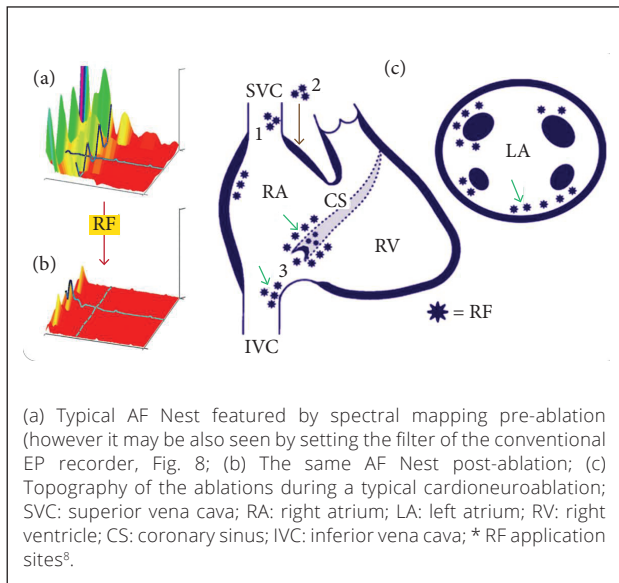


Figure 6. AF Nest main locations.

RF guided by anatomical landmarks

After ablation of all fibrillar scanned myocardium, endocardial anatomical ablation is also performed (at least 2 min in each place), in the areas related to the

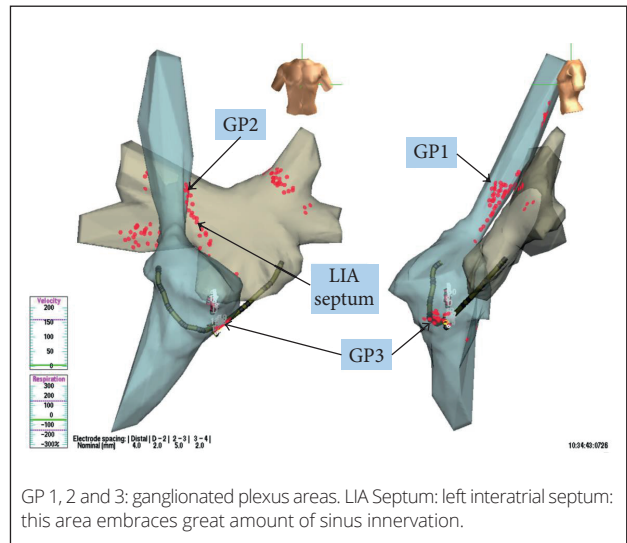


Figure 7. Typical electroanatomic mapping at the end of a regular CNA (not edited).

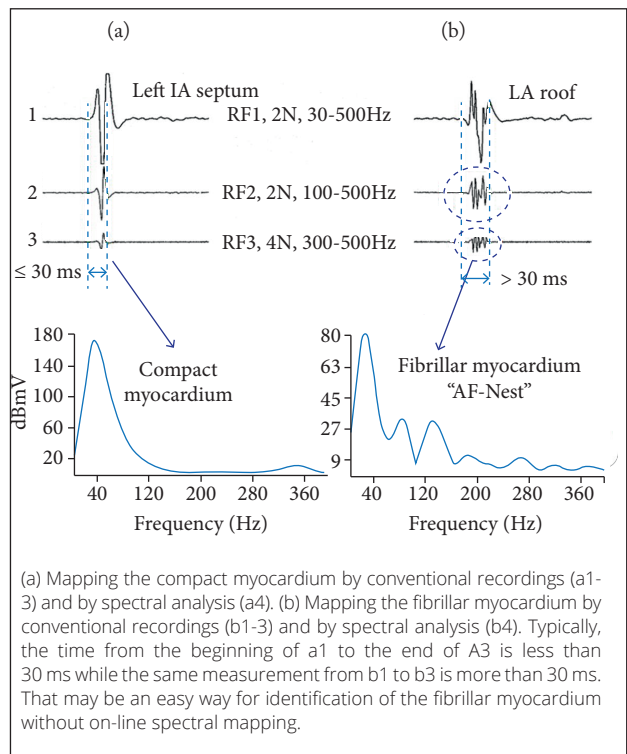


Figure 8. Conventional and Spectral recording

epicardial ganglionated plexuses (GP)³⁷. These areas typically present a high number of AF Nests and allow the elimination or depopulation of the second neuron. The RF in these areas should be extended for getting deep heating:

1. GP1: In the superior vena cava, medial and just above the vena cava atrial insertion (Figures 6c, 7 and 9-1);

2. GP2: In the left interatrial septum, between the right pulmonary veins and the fossa ovalis (ablated through the LA) and from the fossa ovalis to the Waterston's groove (ablated through RA) (Figs. 6c, 7 and 9);
3. GP3: The roof of the coronary sinus (ablated through the LA) and by the inferior vena cava, medial and just under the tricuspid valve and the coronary sinus ostium (Figs. 6c, 7 and 9);
4. GPn: There are several other GPs even related to the pulmonary vein insertion³⁴. Ancillary ablation of these sources may be obtained to a greater or lesser extent during pulmonary vein isolation (Fig. 7).

Methodology for controlling and confirm the vagal denervation

In this procedure, it is absolutely essential to have the demonstration of the vagal innervation effect, the stepwise control of denervation during the procedure

and finally the confirmation of vagal denervation at the end of the proceedings, as an immediate endpoint for success criterion. For this purpose, we have developed the extracardiac vagal stimulation, which is a very easy neural stimulation to meet all these steps. The procedure begins with the advancement of an electrophysiology catheter within the right or left internal jugular veins up to the level of the jugular foramen (Figs. 10 and 11).

The vagal stimulator releases square wave pulses of 50 microseconds width, frequency of 30 Hz and amplitude from 10 to 70 V, adjusted per patient weight (1 V/kg up to 70 V). An extremely short pulse duration with current limitation is employed for preventing tissue lesion. A timer function allows the application of pulse trains with predefined timing, usually between 5 to 10 s.

A new vagal stimulation is repeated at the end of CNA and compared with the first one. The procedure is finished if confirmed total elimination of the vagal response (Fig. 12b). Additional vagal stimulations during the procedure are used to show the vagal denervation progress.

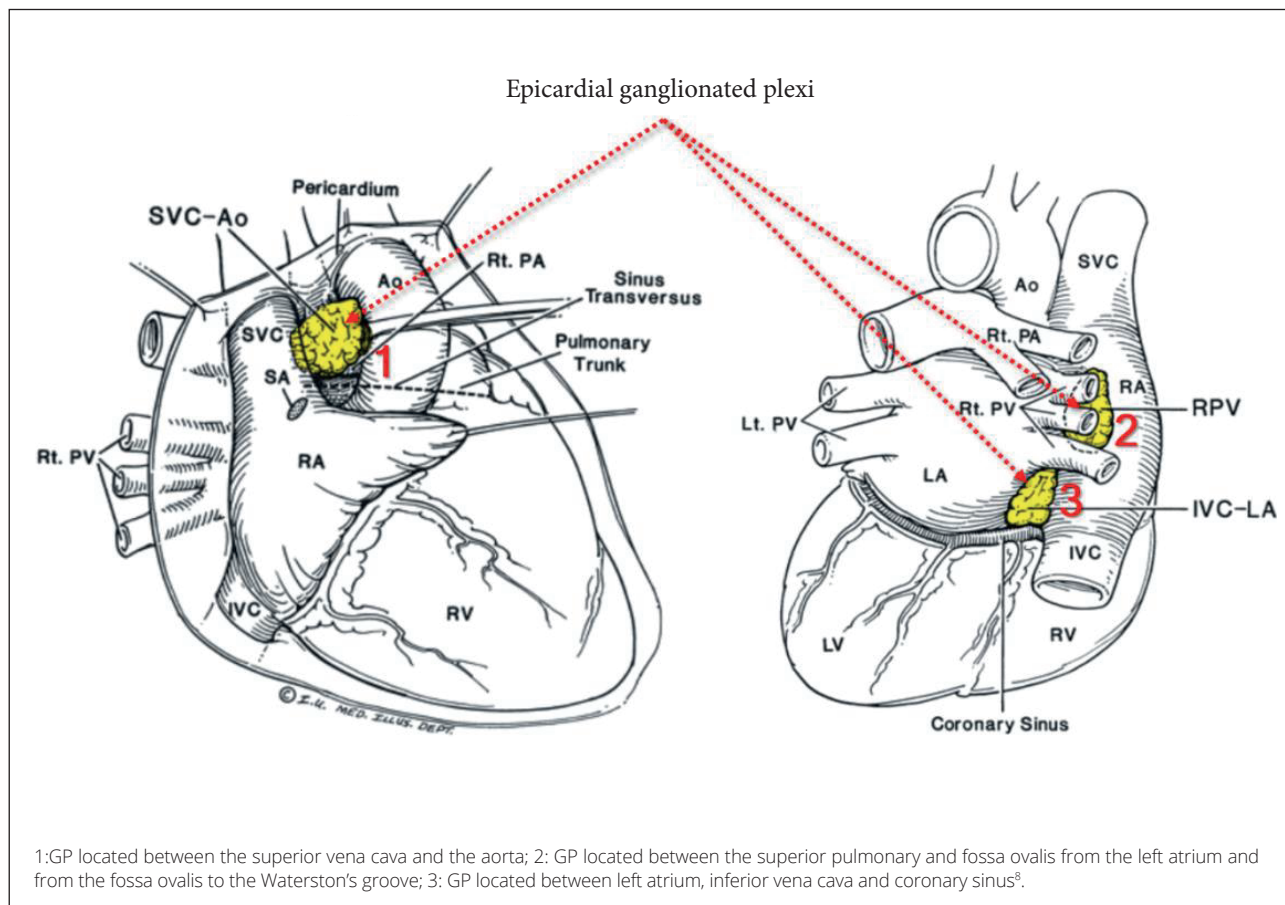


Figure 9. Topography of the main epicardial ganglionated plexus (GP)³⁸.

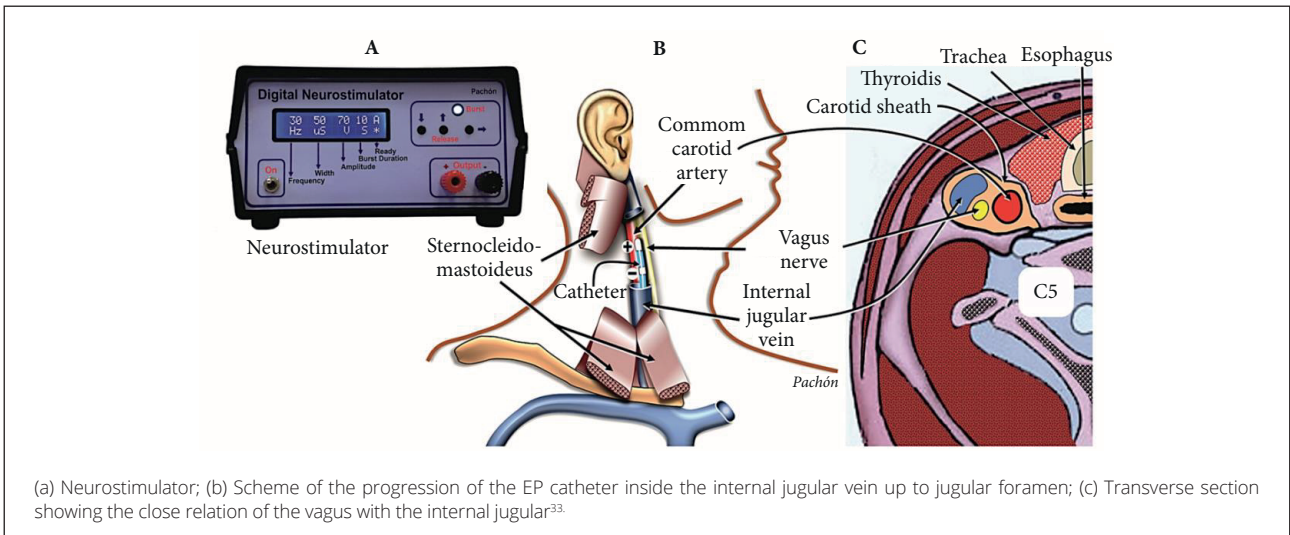


Figure 10. Methodology of vagal stimulation during cardioneuroablation.

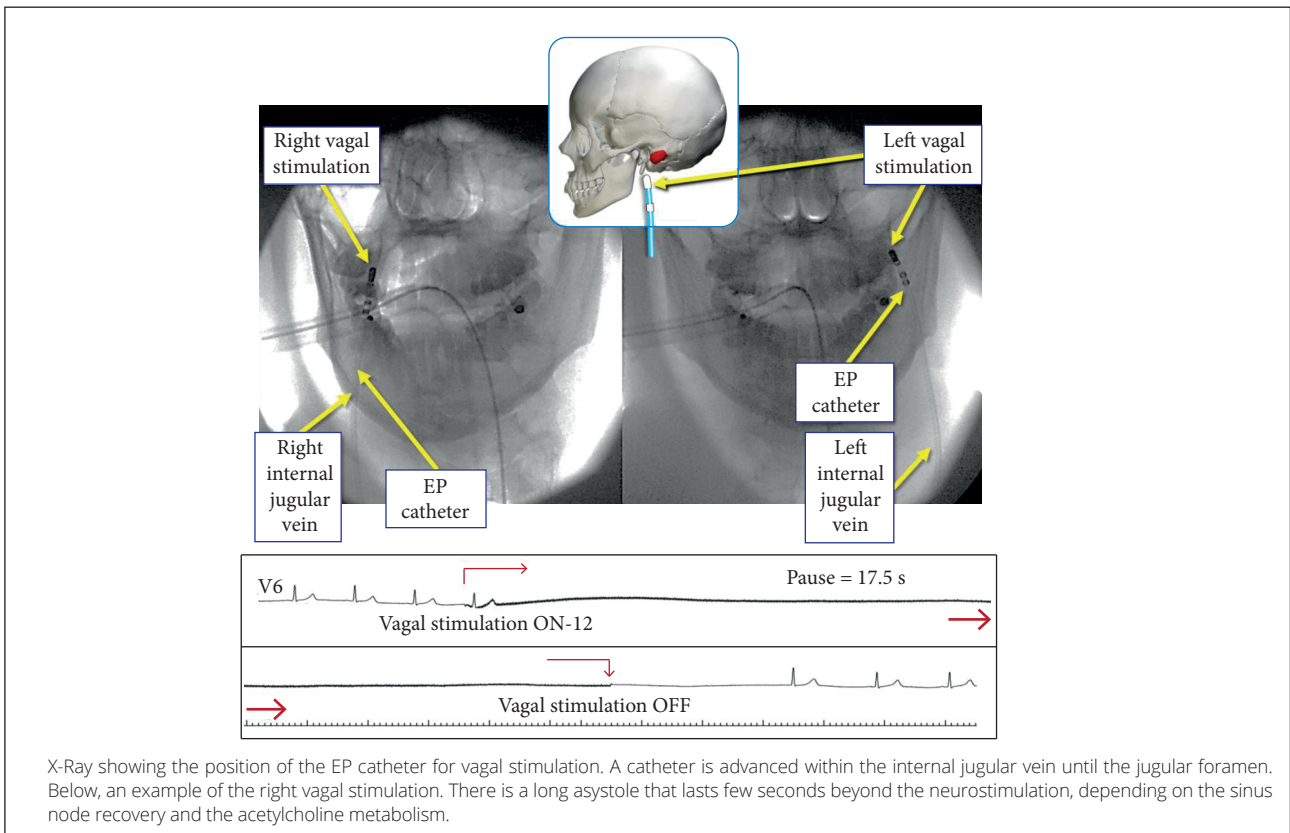


Figure 11. Site of vagal stimulation

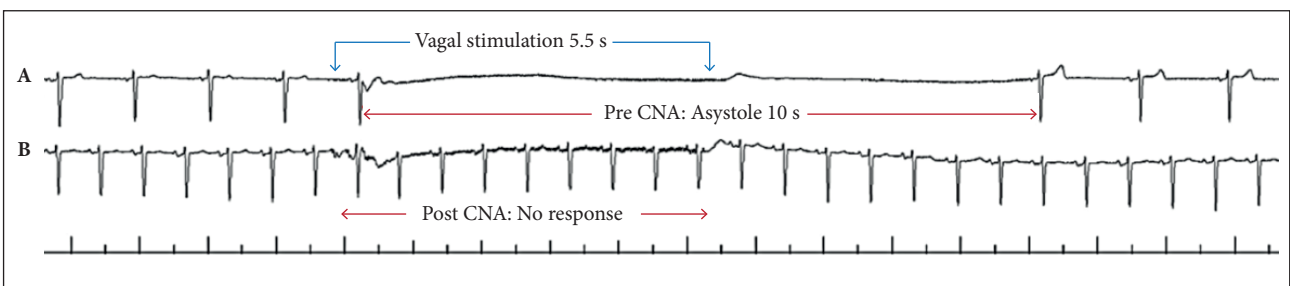


Figure 12. Vagal stimulation before (a) and at the end (b) of CNA demonstrating successful vagal denervation (complete abolition of vagal response).

Immediate cardioneuroablation endpoints

Several endpoints must be considered to enhance the results of CNA, as shown in Table 2.

Table 2. Main immediate cardioneuroablation endpoints.

Ablation of the most AF-Nests in left atrium and right atrium
Anatomical ablation of main ganglionated plexuses areas
Sustained increase of the heart rate and Wenckebach's point
Complete suppression of the vagal response by vagal stimulation
Total abolition of the atropine response

Esophageal protection during cardioneuroablation

The wider the AF Nests ablation the greater and more lasting will be the vagal denervation. In addition to the regions of GPs, large vagal innervation enters the atria by the pulmonary veins insertion. Therefore, it is highly desirable to eliminate the AF-Nests related to these areas like the atrial fibrillation ablation. In this sense, special care for the protection of the esophagus is necessary. For this purpose, we developed a method, applied to all patients included in this study, which is the mechanical displacement of the esophagus by using the transesophageal echocardiographic transducer³⁹. Usually, the displacement is enough to move the esophagus 4 to 8 cm in the opposite direction of the RF spot, expressively reducing the risk of esophageal heating and lesion (Fig. 13).

RESULTS OF CARDIONEUROABLATION

The immediate result at the end of CNA is the complete absence of vagal response indicating a successful vagal denervation (Fig. 12b). In fact, this is the main success criterion and if not achieved the ablation must be resumed and expanded until getting complete vagal response elimination.

The long-term outcome should be assessed primarily by the clinical follow-up, but it is required to be tried with the same assessment that demonstrated the most important cardioinhibitory response at the inclusion time, more often, the Tilt-test (Fig. 14). However, especially in cases of nonreflex functional bradyarrhythmias, the cardioinhibition may have been detected by stress-test or Holter recording. The Tilt-test is undoubtedly the most commonly used trial as an inclusion and control criterion. It is recommended to be repeated from 2 months post-CNA using the same protocol of the inclusion phase (Fig. 15).

In a long-term cohort study of 43 cardioinhibitory patients, with a FU of 45.1±22 - 11 to 91.4 months⁴¹, it was observed positive control Tilt-test only in 4 cases (9.3%), with the same degree of cardioinhibition but, all of them, having a significant vasodepressor response, Table 3.

These results show that the low number of patients presenting syncope after CNA appear to shift the vasovagal behavior from the severe cardioinhibition to a predominant less important vasodepressor response as the procedure significantly decreases the cardioinhibition response even in the long-term phase.

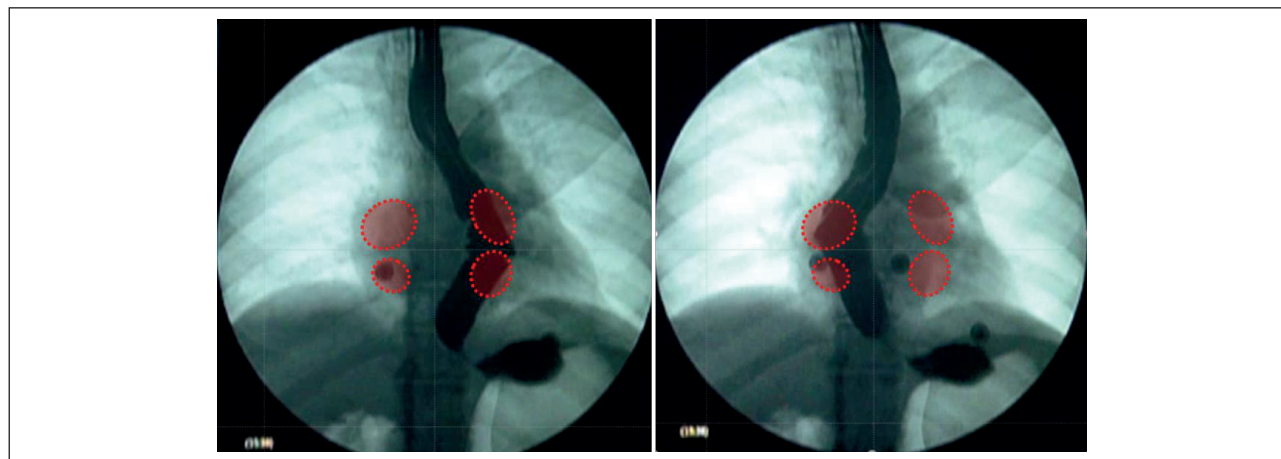
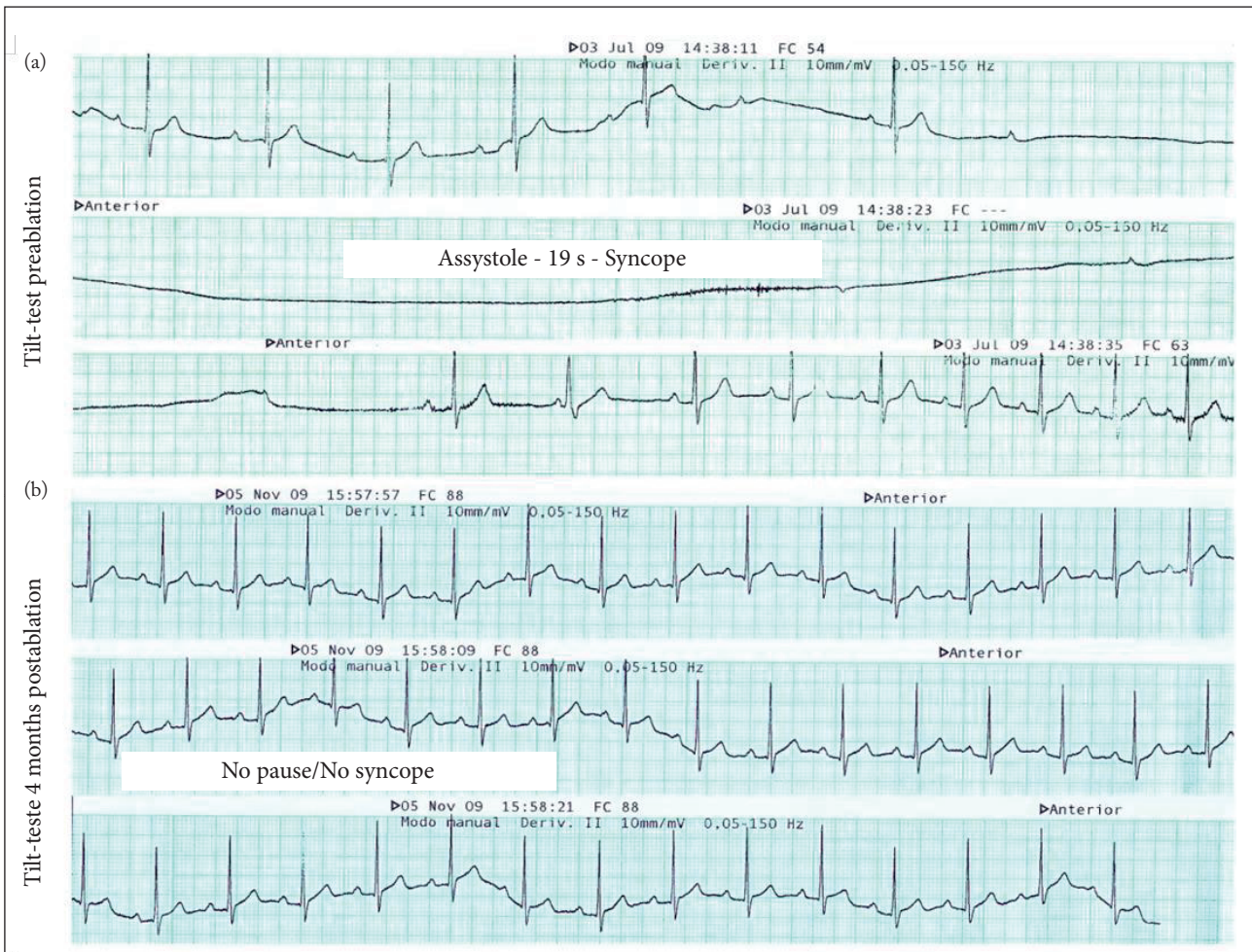
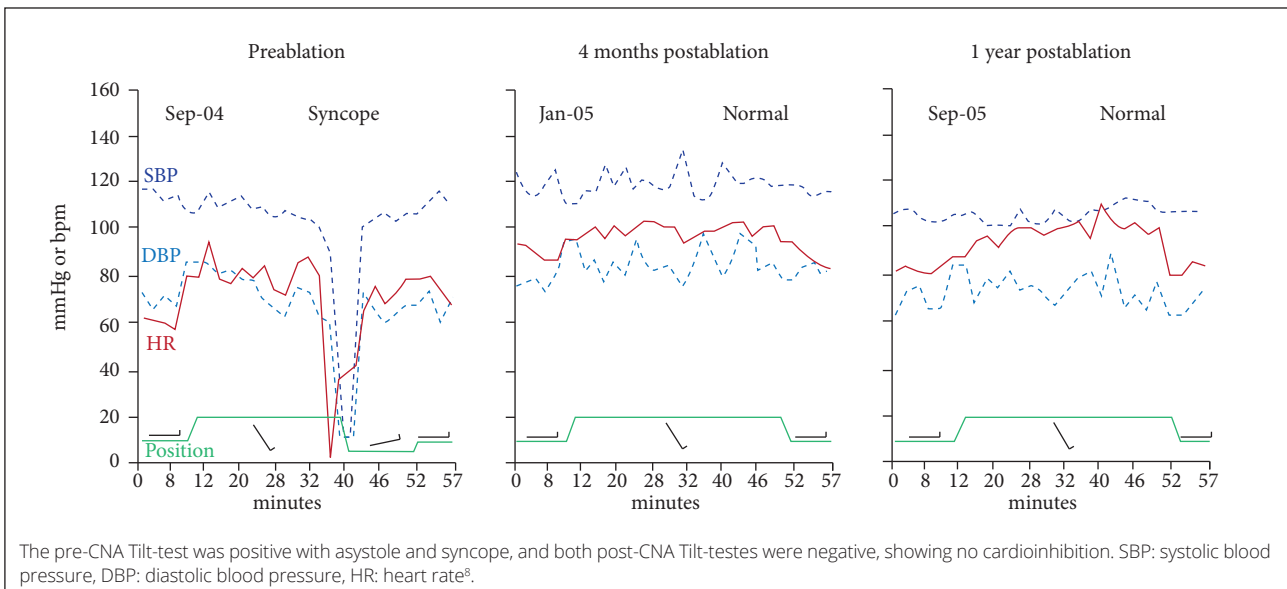


Figure 13. Contrast-enhanced radiography of the esophagus showing the displacement during RF ablation in the antrum of the pulmonary veins (red circles). The displacement extent is enough to allow a good protection of the esophagus in most patients⁴⁰.



(a) Pre-CNA Tilt-test showing a syncope caused by a severe cardio-inhibition (asystole of 19 s). (b) Tilt-Test 4 months post-CNA showing no cardioinhibition and no syncope. The asystole was replaced by sinus rate > 80 bpm. The Tilt-test pre-CNA showed asystole caused by inhibition of the sinus and AV nodes, both completely corrected by the CNA. Therefore, the Tilt-test 4 months post-CNA showed no cardioinhibition. This patient remains asymptomatic[®].

Figure 14. Tilt-Test for getting the long-term CNA outcome.



The pre-CNA Tilt-test was positive with asystole and syncope, and both post-CNA Tilt-tests were negative, showing no cardioinhibition. SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate[®].

Figure 15. Tilt-test in the long follow-up of CNA.

Table 3. Features of the cases with positive Tilt-test post-CNA in a cohort of 43 patients.

PIN	Age	Pre-CNA Tilt-test				Post-CNA Tilt-test				Outcome
		TTD	Response	Cardioinhibition	Pause (sec)	TTD	Response	Cardioinhibition	FU	
7	48	N	Positive/ Mixed	Junctional bradycardia	3.7	N	Positive/ Mixed	Sinus bradycardia	75	Asymptomatic
17	17	N	Positive/ Cardio- inhibitory	Asystole	12.0	Y	Positive/ Mixed	Sinus bradycardia	55	Dizziness (menstrual colic)
26	14	N	Positive/ Mixed	Sinus pause	3.0	Y (42)	Positive/ Mixed	Sinus bradycardia	43	Asymptomatic
37	51	Y	Positive/ Cardio- inhibitory	Asystole	6.0	Y	Positive/ Mixed	Junctional bradycardia	17	Asymptomatic

PIN: patient identification number; TTD: Tilt-Test Drug; FU: Follow-up in months. significant reduction of the cardioinhibition compared to pre-CNA Tilt-test⁸

Cardioneuroablation survival curves

The therapeutic value of the CNA⁸ may be evaluated by comparing the results with the clinical treatment⁴² and with pacemaker implantation in the ISSUE-3³ and SYNPACE³⁷ studies. In Figure 16, even considering longer follow-up than other studies, by using CNA only 6 of 75 patients had indeterminate syncope (8%) and the total of cases with

syncope indeterminate plus vasodepressor was 10 totaling 13.3% in a mean follow-up of 38 ± 28 months. However, if a shorter period of 24 months of follow-up is considered, as in the “*International Study on Syncope of Uncertain Etiology 3 - ISSUE 3*”, the incidence of syncope was 9% with CNA, 25% with a pacemaker on in the ISSUE 3 study, 28% with clinical treatment, 35% in the mixed syncope group of the Synpace study and 48% in the asystolic group of the same study, both with pacemakers ON. Thus, it may be concluded that the CNA in patients with vasovagal syncope with important cardioinhibitory component presents better result when compared to clinical treatment and pacemaker implantation, providing the clinician with a new option to treat difficult cases.

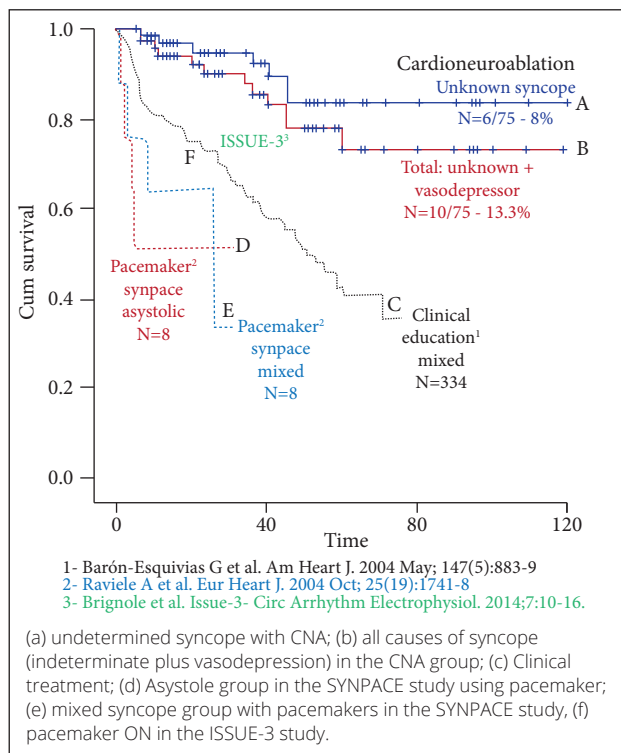


Figure 16. Survival curves free of syncope comparing the CNA with clinical treatment and with pacemaker implantation in the ISSUE-3 and SYNPACE studies.

The CNA can bring undesirable consequences?

Strictly follow-up of our patients over 14 years has shown no undesirable effect, even in the few cases in which the procedure was remade.

In the initial phase, there is a noteworthy change in the autonomic tone commonly observed as persistent sinus tachycardia. Because of this, it is customary to keep the patient with beta-blockers in the first 2 to 3 months. Clinically, there is a clear reduction or elimination of parasympathetic tone with a predominance of sympathetic one. However, gradually, there is a natural autonomic rebalancing with gradual reduction of the sympathetic drive bringing the

heart rate to normal values. In this sense, there is a beneficial result of a long-time natural reduction of the sympathetic tone (Fig. 17a).

The patient shown in Fig. 15 had a basal heart rate of 62 ppm in the pre-CNA tilt test, 85 ppm in the 4 months control and 80 ppm in tilt-test one-year post-CNA. However, due to the readjustment of the autonomic nervous system, the patients usually remain asymptomatic with normal life. Due to this autonomic plasticity, the chronotropic response and the exercise capacity is also fully preserved as can be seen in the study of the post-CNA exercise test, in which there was not observed additional chronotropic incompetence (Fig. 17b). One of the problems that must be questioned is if the reduction of RR variability may increase the cardiovascular risk. This effect was demonstrated after myocardial infarction and myocardial damage but there is no evidence that the primary RR variability reduction caused by vagal denervation with fully preserved myocardial has some consequence in this regard.

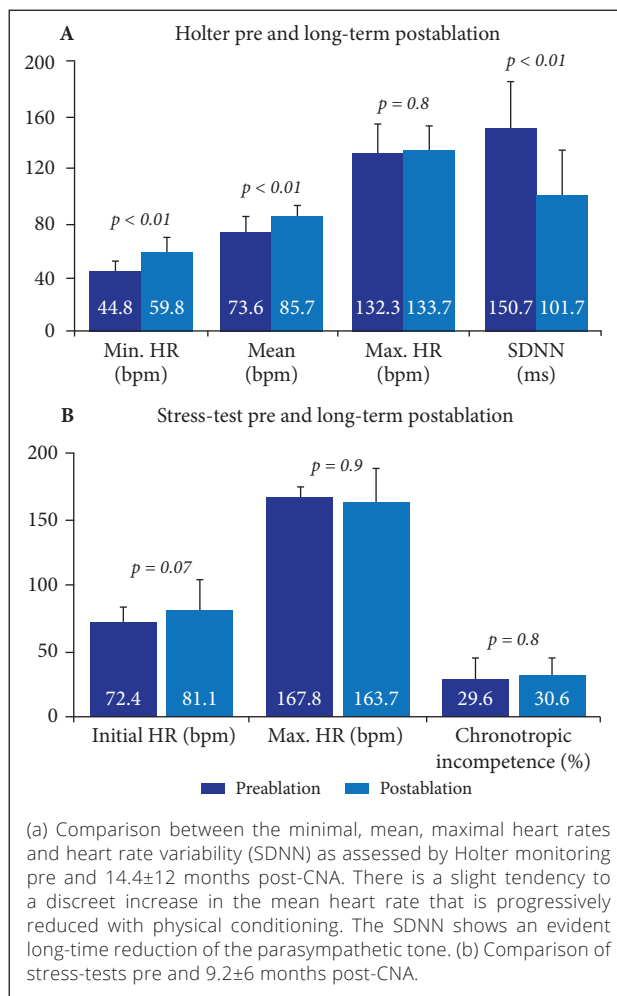


Figure 17. Holter pre- and post-RF.

COMPLICATIONS

With standard care, the CNA has been a very safe procedure. Its complication rate is equivalent to the ablation of paroxysmal AF in patients without heart disease. In a study of 44 CNA performed in 43 patients⁸, there were no major complications being observed, only two small groin hematomas solved clinically by compression. One patient had an episode of typical atrial flutter during the hospital stay, reverted by intravenous amiodarone requiring no long-term therapy. Ten patients (23.3%) were treated temporarily (1-3 months) with beta-blockers aiming the control of post-CNA mild sinus tachycardia. Physical conditioning was also indicated. No pacemaker implantation was needed. The patients were discharged after 2 days.

LIMITATIONS

The CNA is being reproduced by several investigators worldwide with similar good results. However, despite the positive results, randomized trials are required to further evaluate this therapeutic option. The application of RF anatomically guided over the GPs is not yet well defined and should be significantly improved in the future especially with the inclusion of imaging methods, such as magnetic resonance, and/or a ganglia marker, for example, a meta-iodobenzyl-guanidine scan, that accurately could indicate the position of the GPs that may exist in each case. Placebo effect is commonly observed in all treatment alternatives for neurally mediated reflex syncope, such as drugs, pacemaker implantation, education, and training. However, the significant and persistent autonomic changes observed after CNA, the abolishment of cardioinhibition in the control tilt-test and the undoubtedly long term better result, compared with other therapies, show that placebo effect plays an unimportant role in this therapy (Fig.15). One last limitation is that the CNA is an operator-dependent procedure with result highly related to the learning curve. Thus, controlled multicenter randomized trials should wait for the appropriate training of various services.

CONCLUSION

Treatment of severe syncope cardioinhibitory by ablation without requiring pacemaker is very attractive, especially in young patients in whom the prosthesis is highly undesirable. In the studied cohort, a pacemaker was not necessary in any case. Despite no prevention of the vasodepression the CNA seems to cause enough long-term vagal reflex attenuation, eliminating the cardioinhibition, and keeping most patients asymptomatic. By using the current atrial fibrillation ablation technology, the procedure is safe, feasible, and reproducible. The indication is simple and essentially based on clinical findings, in the presence of severe cardioinhibition unresponsive to medical treatment, and on the normal response to atropine. Vagal stimulation to control the extent of the denervation in addition to confirming the immediate

success seems to be decisive and indispensable. At last, as a rule for any new therapy, the results must be confirmed with experimental protocols and by randomized studies.

AUTHORS' CONTRIBUTION

Conceptualization, Mateos José CP; Methodology, Mateos José CP and Mateos EIP; Writing – First version, Mateos José CP; Writing – Review & Editing, Mateos José CP, Mateos EIP, Pachón CTC and Lobo TJ; Acquisition, Mateos José CP; Mateos EIP, Pachón CTC, Lobo TJ, Higuti C, Peña TGS, Mateos Juan CP, Acosta JCZ, Ortencio F and Amarante R; Resources, Mateos José CP and Mateos EIP; Supervision, Mateos José CP.

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