Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Unifocal Right-Sided Ablation Treatment for Neurally Mediated Syncope and Functional Sinus Node Dysfunction Under Computed Tomographic Guidance

Philippe Debruyne, MD
Tom Rossenbacker, MD, PhD
Christine Collienne, MD
John Roosen, MD
Bavo Ector, MD
Luc Janssens, MD
Filip Charlier, MD
Bart Vankelecom, MD
Willem Dewilde, MD, PhD
William Wijns, MD, PhD

BACKGROUND: Biatrial, extensive, and complex ablation strategies have been published for the treatment of neurally mediated syncope, sinus node dysfunction, and functional atrioventricular block. We have developed a less extensive and more specific approach compared with previously published cardioneuroablation strategies, called cardio-neuromodulation. It is based on tailored vagolysis of the sinoatrial node through partial ablation of the anterior right-ganglionated plexus, preferentially through a right-sided approach.

METHODS: Patients with syncope were enrolled between December 2016 and December 2017. They were assigned to group A if they had a positive head-up tilt test and to group B if they presented with a pause ≥3 seconds. The area to target during cardio-neuromodulation was designed offline on a computed tomographic scan. Slow heart rates and pauses were compared during 24-hour rhythm registration at baseline, at 1-month follow-up, and 6-month follow-up. Syncope burden was assessed before the procedure and at 3- and 6-month follow-up.

RESULTS: Twenty patients underwent cardio-neuromodulation through a right-sided approach (12 in group A, 8 in group B). The first application of radiofrequency energy led to a P-P interval shortening >120 ms in all 20 patients. After a mean±SD ablation time of 7±4 minutes and mean ablated surface area of 11±6 mm^2, the P-P interval shortened by 219±160 ms (P<0.001). The number of beats <50/min during 24-hour rhythm registration was reduced by a median of 100% at 6-month follow-up (P<0.001). Syncope burden was reduced by 95% at 6-month follow-up (P<0.001).

CONCLUSIONS: These data indicate that cardio-neuromodulation, through a right-sided and computed tomographic–guided procedure, is safe, fast, and highly reproducible in preventing inappropriate functional sinus bradycardia and syncope recurrence.

VISUAL OVERVIEW: An online visual overview is available for this article.

Key Words: atrioventricular block ■ autonomic nervous system ■ bradycardia ■ denervation ■ follow-up studies ■ syncope

https://www.ahajournals.org/journal/circep

WHAT IS KNOWN?

- Extensive biatrial ablation strategies have been published for the treatment of neurally mediated syncope.
- A pilot trial on cardio-neuromodulation, based on a vagolysis of the sinoatrial node through partial ablation of the anterior right ganglionated plexus, was able to prevent syncope recurrence at 1 year among 6 patients.

WHAT THE STUDY ADDS?

- Cardio-neuromodulation, through a right-sided and computed tomographic–guided procedure, may be a reproducible method to prevent inappropriate functional sinus bradycardia and syncope recurrence in patients affected by neurally mediated syncope or functional sinus node dysfunction.
- The anterior right-ganglionated plexus is the final common pathway of the sinus node vagal innervation.

Autonomic innervation of the heart has been studied in animals for >30 years.[1] The little brain of the heart was described a decade ago.[2] The first clinical study on cardiac denervation in humans was published in 2005.[3] Derived from this first method, different approaches to cardioneuroablation have been published to treat neurally mediated syncope, sinus node dysfunction, and functional atrioventricular block.[4–8] Such ablations are complex, biatrial, and extensive.

In 2014, we started to develop a less extensive and more specific approach to cardioneuroablation, called cardio-neuromodulation (CardNM).[9] This method is based on a tailored vagolysis of the sinoatrial node through partial ablation of the anterior right-ganglionated plexus (ARGP), preferentially through a right-sided approach. The results of a pilot trial (CardNMH1) demonstrated major clinical changes during CardNM, with an excellent clinical outcome at 1 year, which was maintained at 3.3 years of follow-up among 6 patients.[10] This second trial of CardNM (second study on CardNM in humans [CardNMH2]) was designed to assess the safety and the efficacy of CardNM in 2 well-defined patient groups and to gain additional insights in the physiological changes elicited by the procedure. We report on a prespecified interim analysis after the inclusion of 20 patients, for early safety and efficacy analyses.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Trial Design and Oversight

CardNMH2 (ClinicalTrials.gov ID NCT02954666) is an investigator-initiated phase IIA, prospective, open-label, interventional, single-center trial designed to assess the safety and the efficacy of CardNM in 2 well-defined groups of patients. Clinical and paraclinical end points were compared before and after CardNM in both groups, with each patient serving as their own control.

CardNMH2 was approved by the Ethical Committee of Imeldaziekenhuis, Bonheiden, Belgium. The trial is being conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent. An independent data and safety monitoring board reviewed cumulative safety data at regular intervals to safeguard the wellbeing of the participants.

Study Population

Patients with syncope or pause were required to have a P-P interval shortening of ≥20% and a PP interval <1000 ms after administration of 2 mg of atropine. They were assigned to 1 of the 2 study groups based on prespecified criteria and received a unique number before ablation. Patients were assigned to group A if they were affected by neurally mediated syncope and had a type 1–, type 2A- or type 2B–positive head-up tilt test (HUT) result according to the modified version of the classification of neurally mediated syncope proposed by the Vasovagal Syncope International Study group (VASIS).[11] They were assigned to group B if they were affected by sinus node dysfunction and had a documented pause ≥3 seconds during the 6 months preceding enrollment. Patients fulfilling the inclusion criteria for both groups were assigned to group A. Patients in both groups were required to have a positive P wave >0.5 mm in lead 2 of a resting ECG and have had at least 1 episode of syncope in the 6 months preceding enrollment. Patients in group A must have had ≥2 syncopes in their lifetime unless the last syncope was complicated by an injury or an accident. Patients <18 years of age had to have at least 3 syncopes, with an interval exceeding 1 month between the first and the last syncope unless 1 syncope was complicated by an injury or accident.

Exclusion criteria were age <14 years, intake of chronotropic negative medications (except in patients with a history of atrial fibrillation), 4 g amiodarone intake (total dose) during the 2 months preceding enrollment, bi- or trifascicular block, permanent PR prolongation >240 ms, permanent atrial fibrillation, paroxysmal atrial fibrillation or electrical cardioversion during the past 6 months, clinically relevant obstructive cardiac disease, any unstable medical condition, life expectancy <12 months, advanced neuropathy, pregnancy, or glaucoma. Patients with transient atrioventricular conduction disturbances and normal atrioventricular conduction during an exercise test and normal QRS complexes were eligible.

Clinical Data Collection

All patients underwent a 24-hour rhythm registration at baseline and an HUT, whenever feasible. The number of syncopes occurring in the 3, 6, and 12 months before CardNM was noted, and the presence or absence of prodromes, injuries, and accidents was recorded. An ECG was

performed according to a standardized protocol in resting conditions and after intravenous administration of atropine. Ambulatory ECG registrations and atropine tests were performed according to a standardized and stepwise protocol. Importantly, venous access was performed at the hospitalization unit at least 30 minutes before the test. Patients lying in bed were moved to a dedicated room, the lights were dimmed, and 6 sequential ECG registrations of >1 minute were performed with our electrophysiological system by a single dedicated study nurse: 4 before atropine injection, 1 >3 minutes after injection of 1 mg atropine (step 5), and the last registration >3 minutes after a second bolus of 1 mg (step 6). The whole procedure typically took 30 minutes.

Therapeutic anticoagulation with a nonvitamin K antagonist oral anticoagulant was started >2 hours before CardNM and was continued for 1 month afterward. Patients with a high bleeding risk were treated with clopidogrel (75 mg daily for 1 month started <4 hours before the procedure). The use of medications with a chronotropic or dromotropic action was discouraged unless judged indispensable according to the patient's condition. After the procedure, patients were monitored in-hospital for 12 hours. A clinical evaluation, 12-lead ECG, laboratory test, and transthoracic echocardiogram were performed before discharge. Discharged patients were followed-up by telephone calls between 7 and 15 days after the ablation procedure to assess the occurrence of any adverse events. An office visit was planned at 1-,3- and 6-month follow-up, and the 24-hour rhythm registration was repeated at 1- and 6-month follow-up.

Cardiac Imaging and Invasive Procedure

Visualizing both left and right atrial structures on the computed tomographic scan is important for this anatomically guided approach. Conceptually, the right atrium, the vena cava superior, the right superior pulmonary vein antrum, and the coronary sinus need to be well visualized to trace the target line offline and perform the fusion with the electroanatomical map during the procedure. The endocardial site to target during ablation was determined by the interactions between the antrum of the right superior pulmonary vein and right heart cavities, as previously reported.[10] A target line was annotated at the posteroseptal side of the junction, between the right atrium and the superior vena cava, facing the mid and caudal parts of the right superior pulmonary vein antrum on the right heart cavities on a computed tomographic image of the heart imported into the CARTO system (Biosense Webster, Diamond Bar, CA) before the procedure (Figure 1A).

Each procedure was performed with the patient under general anesthesia in a steady state. The use of catecholamines, drugs, and gasses with direct or indirect sympathomimetic properties was avoided.

Activated clotting time was maintained at >300 seconds. A decapolar catheter was placed in the coronary sinus. Electroanatomical mapping (using CARTO) of the right atrium, the superior and inferior vena cava, and the coronary sinus was performed and merged with the computed tomographic image. The corrected sinus node recovery time was determined before and after CardNM. Radiofrequency applications were delivered along the target line with an irrigated tip catheter (Smart Touch catheter, Biosense Webster, Diamond Bar, CA) using a power of 40 W and a contact force >8 g. The P-P interval was carefully monitored. The duration of each individual ablation was typically prolonged for 30 seconds after stabilization of the P-P interval but did not exceed 90 seconds at the same location. Radiofrequency applications were interrupted if no significant shortening of the P-P interval was observed after 30 seconds. Points acquired during ablation were annotated by 2-mm tags and differentiated using a color code. The ablation procedure was considered complete if the P-P interval was <70% of the baseline procedural P-P interval, was <600 ms after 5 minutes of waiting time, if 10 radiofrequency applications were delivered, if the total ablation time reached 900 seconds, or if the operator estimated that no additional P-P interval shortening would be obtained by additional radiofrequency applications. After procedure completion and catheter retrieval, and with the patient still under anesthesia in a steady state and without any external stimulation, atropine was administrated intravenously >30 minutes after the last ablation; ECG registrations were performed before and after atropine injection, as for steps 5 and 6 of the ambulatory protocol. The ablation area was determined by the CARTO system by surrounding the ablation tags.

Statistical Analysis

The number of syncopes and the number of beats for a 24-hour period were compared before and after CardNM for different P-P intervals (≥1000, ≥1100, ≥1200 ms) using a paired Wilcoxon signed-rank test. Continuous data are presented as mean±SD. All 2-tailed $P<0.05$ was considered statistically significant. The statistical analysis was performed using SPSS Statistics 20 Software (IBM, New York, NY).

RESULTS

Baseline Characteristics

Twenty patients were enrolled in the CardNMH2 study (Imeldaziekenhuis, Bonheiden, Belgium) between December 2016 and December 2017, 12 in group A and 8 in group B. Patients were not affected by other noteworthy health problems. None of the patients was lost to follow-up or withdrew early from the study during this first evaluation period. A total of 193 syncopes was reported during the previous 12 months, of which 128 occurred during the 3 months before inclusion.

Fifteen of 20 patients had at least 1 complicated syncope (Table 1). Four patients had an accident and 10 had at least a significant injury. Several patients had different types of complications. One patient was affected by recurrent loss of consciousness and short prodromes, complicated by urinary incontinency and a slow neurological recovery. She developed an asystole of 90 seconds during HUT. All symptoms resolved after CardNM. We observed second-degree atrioventricular block in 3 patients in group A.

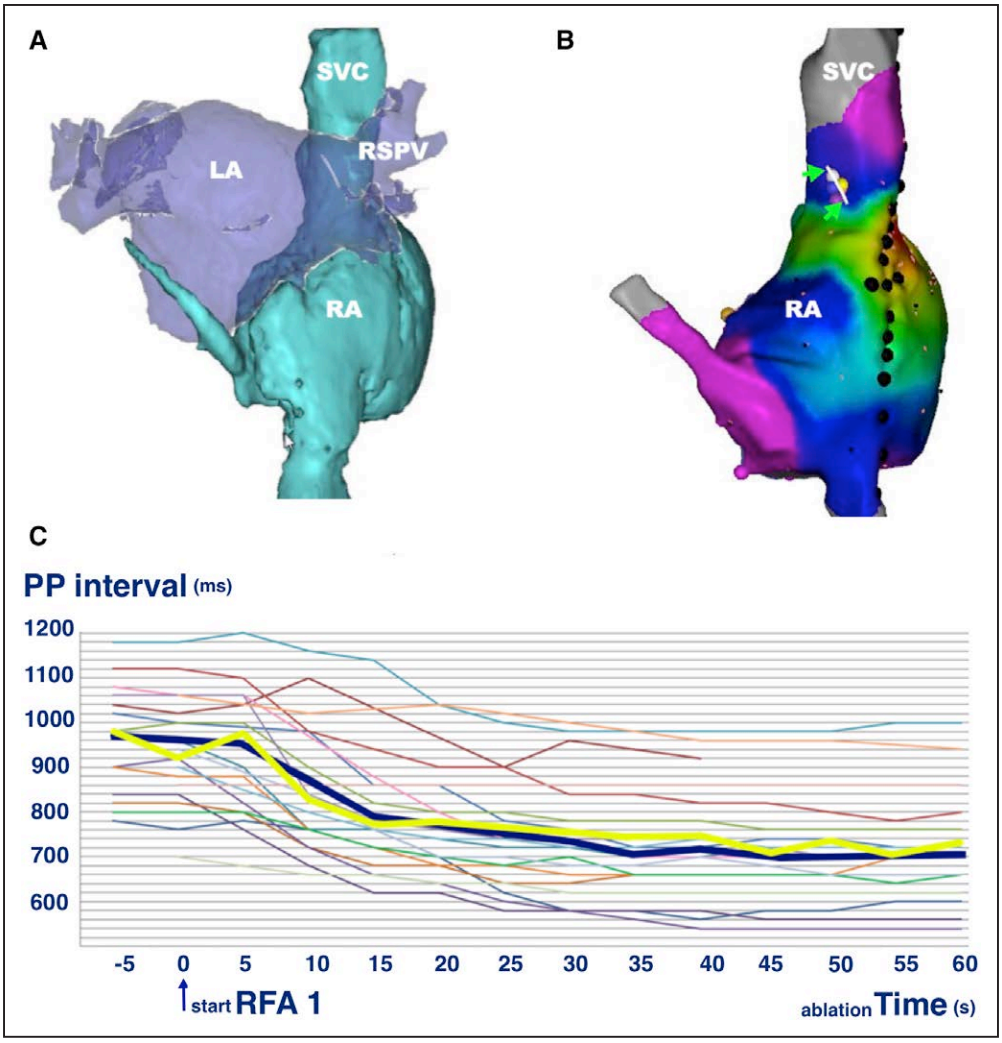

Figure 1. Target location and time-response curves during ablation.
A, Computed tomographic scan of the right atrium (RA) and outline of the left atrium (LA; glass view) of a patient having undergone cardio-neuromodulation in a posteroanterior projection. **B**, Activation map of the RA of the same patient in a posteroanterior projection. The target line, in white, is designed offline at the posteroseptal side of the junction, between the RA and the superior vena cava (SVC), facing the mid and caudal parts of the right superior pulmonary vein (RSPV) antrum on computed tomography and visualized during the procedure after merging the 2 images. The region of the anterior right-ganglionated ablated is indicated by 2 green arrows. Each individual ablation is indicated using a colored tag. The phrenic nerve is tagged with black dots. **C**, PP interval shortening as a function of time during the first radiofrequency ablation (RFA) for the entire cohort. The time–biological effect curve of each patient is represented by a different color. The dark blue line represents the mean value for group A and the yellow line for group B.

Nineteen patients underwent CardNM with a non-vitamin K antagonist oral anticoagulant and continued this medication for 1 month after the procedure. One patient was treated with clopidogrel for 1 month. Two patients in group B were treated for arterial hypertension (1 with perindopril and 1 with perindopril plus amlodipine). None of the patients took chronotropic or dromotropic medications before treatment or during follow-up. Two patients in group B were dependent on intravenous isoprenaline before the procedure; in one of these patients, isoprenaline could not be interrupted during 24-hour rhythm registration.

Procedural Data

CardNM was performed under general anesthesia with sevoflurane, except for the first 2 patients who underwent procedure under propofol. Procedural data are summarized in Table 2. The target line on the computed tomographic scan had a mean length of 11±2 mm. The mean distance between the right and left endocardium was 3±1 mm.

The first application of radiofrequency ablation led to a shortening of the PP interval >120 ms in all 20 patients. After a mean of 5.5±3.2 radiofrequency ablations, a mean ablation time of 7±4 minutes, and a mean ablation surface area of 11±6 mm^2, the baseline procedural P-P interval shortened by a mean of 219±160 ms: from 983±108 to 764±169 ms (P<0.001). The basal heart rate increased by a mean of 20±17 beats/min for group A (P=0.005) and 17±14 beats/min for group B (P=0.012). The corrected sinus node recovery time tended to decrease for the total cohort: from 232±176 to 132±107 ms (P=0.06).

Table 1. Baseline Characteristics of the Patients

Characteristic	All Patients (n=20)	Group A (n=12)	Group B (n=8)
Age, y	41.4±18.8	37.2±16.6	47.5±21.4
Female	9 (45%)	6 (50%)	3 (38%)
Syncope burden,* n			
Last 3 mo	128	107	21
Last 6 mo	152	128	24
Last 12 mo	193	167	26
Prodromes, n			
Long prodromes	4	4	0
Short prodromes	12	9	5
No prodromes	10	7	4
Patients with a complicated syncope,† n	15	10	5
Motor vehicle accident	2	2	0
Bicycle accident	2	2	0
Fracture	4	1	3
Open wounds	5	3	2
Large hematomas	5	5	0
Urinary incontinence	1	0	1

*Number of syncopes prior ablation.
†Some patients had >1 type of complicated syncope.

Table 2. Procedural Characteristics

Characteristic	All Patients (n=20)	Group A (n=12)	Group B (n=8)
Anatomic data, mm			
TL length	11±2	12±2	11±2
d RA-LA endocardium at TL	3±1	3±1	3±1
d TL-His bundle	42±10	42±11	42±8
d TL-phrenic nerve	14±4	14±4	15±5
Ablation data			
Ablation time, min	7±4	7±4	7±4
No. of radiofrequency ablations per patient, n	5.5±3.2	5.7±3.6	5.4±2.9
Ablation surface, mm^2	11±6	10±6	12±6
Patients with PP shortening >120 ms during the first radiofrequency ablation, n	20 (100)	12 (100)	8 (100)
Functional data			
PP interval			
Baseline, ms	983±108	1001±95	956±126
After CardNM, ms	764±169	790±209	726±79
P value	<0.001	0.002	0.012
Delta HR (bpm) after atropine*	3±3	3±4	3±3

CardNM indicates cardio-neuromodulation; d, distance; HR, heart rate; LA, left atrium; RA, right atrium; and TL, target line.
*Two milligram atropine after cardio-neuromodulation.

After atropine injection, heart rate increased by a mean of 3±3 beats/min and was similar in both groups (Table 2). One patient developed a pseudoaneurysm during the first week after procedure, which required a thrombin injection. No other adverse events were reported.

Follow-Up

Three syncopes were reported at 3-month follow-up compared with 128 syncope episodes during the 3 months preceding the procedure (*P*<0.001). Eight syncope episodes were reported at 6-month follow-up compared with 152 episodes during the 6 months preceding the procedure (*P*<0.001). The reduction in syncope burden after treatment was statistically significant in both groups and is summarized in Figure 2. Sixteen patients remained free of syncope at 6-month follow-up. Of the remaining 4 patients, 3 in group A had a dramatic improvement in syncope burden and quality of life. One patient in group B had syncope recurrence with a sinus pause >3000 ms after 5 months and underwent a dual chamber pacemaker implantation; no Holter data are available for this patient at 6-month follow-up. Nine patients completed their 12-month follow-up, 8 of whom remained free of syncope during the last 6 months and 1 patient had 2 additional syncopes. During the 12 months after treatment, this patient reported 7 syncopes compared with 30 syncopes during the 12 months preceding treatment. Interestingly, she had no or short prodromes before treatment, and the syncopes were preceded by long prodromes after CardNM. This patient was considered to have a significant improvement in quality of life after CardNM.

The number of P-P intervals ≥1000 ms during 24-hour rhythm registration of the whole cohort decreased from 23 567±16 237 beats at baseline to 2570±6259 beats at 1-month follow-up, and to 3037±5577 beats at 6-month follow-up, corresponding to a 97% (*P*<0.001) and a 96% (*P*<0.001), respectively, median reduction compared with baseline (Figure 3). Equivalent data for P-P intervals ≥1200 ms decreased from 6050±7786 to 66±171 beats at 1-month follow-up and to 146±481 beats at 6-month follow-up, corresponding to a median 100% reduction compared with baseline at both 1-month (*P*<0.001) and 6-month follow-up (*P*<0.001; Figure 3).

The number of P-P intervals ≥1000 ms during 24-hour rhythm registration decreased by 27 535±14 001 beats in group A (*P*=0.002) and 11 228±12 621 beats in group B (*P*=0.012) at 1-month follow-up and by 25 745±13 259 beats in group A (*P*=0.002) and 8568±5499 beats in group B (*P*=0.018) at 6-month follow-up.

The longest mean P-P interval during the 3 months before the procedure decreased from 9850±20 928 to 1360±327 ms during the 3-month post-procedure (*P*<0.001). At 1-month follow-up, the mean value of the longest P-P interval decreased from 9418±26 333 to 1329±374 ms for patients in group A (*P*=0.002) and

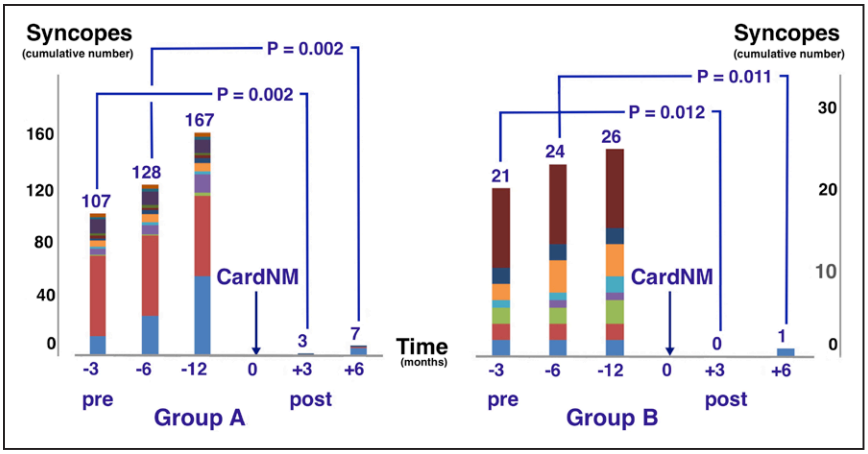

Figure 2. Cumulative number of syncope episodes before and after cardio-neuromodulation (CardNM) at 3- and 6-mo follow-up in group A and group B.
Each patient is represented by a different color.

from 10497±9917 to 1406±256 ms for patients in group B (*P*=0.012). At 6-month follow-up, the mean value of the longest P-P interval was 1307±330 ms for the 12 patients in group A (*P*=0.003) and 1756±965 ms for the 7 patients in group B having completed the 6-month follow-up (*P*=0.018).

DISCUSSION

This report demonstrates that an effective vagolysis of the sinus node can be safely performed by a computed tomographic–guided, limited, right-sided ablation strategy that selectively targets the ARGP. There were no safety issues. We report data from the first 20 consecutive patients included in the ongoing CardNMH2 study. None of the patients was excluded, and we are not aware of any selection bias. The spectrum of clinical presentation of neurally mediated syncope was wide. Although the presence of prodromes is of value for diagnosing neurally mediated syncope, the reverse is not true. Prolonged hemodynamic impairment during severe neurally mediated syncope can lead to incontinence and transient cognitive dysfunction that persists after hemodynamic normalization.

The high reproducibility of the data concerning the biological effect during the first ablation point demonstrates the high accuracy of our anatomic strategy and strongly suggests that the ARGP has a precise location in humans. The distance between the left and the right endocardium surrounding the ARGP is only 3±1 mm. Hence, there is no anatomic factor potentially limiting the creation of a transmural ablation within the targeted structure through a right-sided irrigated endocardial ablation strategy. The absence of a significant increase in heart rate after postprocedural atropine injection in most of the patients demonstrates that a complete sinus node vagolysis can be obtained acutely during CardNM, suggesting that the ARGP is effectively the final common pathway of the sinus node vagal innervation.

We have previously introduced the concept of CardNM as a tailored vagolysis of the sinus node through a selective ARGP ablation.[9] Another group ablated the 4 ganglionated plexi during vagal denervation and

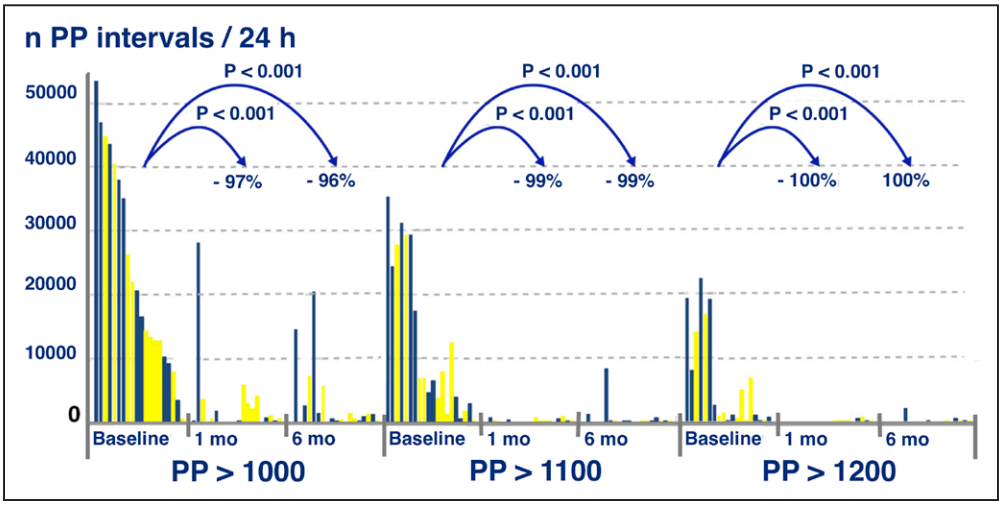

Figure 3. Twenty-four–hour rhythm registration data.
The histograms show the number of P-P intervals >1000, >1100, and >1200 ms for each patient at baseline, at 1-mo follow-up, and 6-mo follow-up. The histograms are colored blue for group A and yellow for group B. The median reduction of P-P intervals at follow-up and the *P* values are provided for the entire cohort.

proposed that the ARGP is a gateway for the cardiac autonomous nervous system to modulate sinus node activity. However, their data do not seem to support this statement as only one-third of their patients showed heart rate acceleration while targeting the ARGP area and because multiple ganglionated plexus ablations target not only the ganglionated plexi but also their interconnecting pathways.[12] It should be kept in mind that precise target localization and ablation parameters adapted to the epicardial location of the target are essential to ensure optimal thermal injury of epicardial structures during endocardial ablations.[13] We have previously reported that the anatomy of the right superior pulmonary vein antrum and the right/left interactions enabled us to identify a specific target.[10] To avoid entering the left atrium, we used computed tomography and fusion imaging to restrict the procedure to the right heart cavities. The importance of correct substrate localization before ablating has been documented for many different arrhythmias in the past because ablating in the vicinity of the ideal endocardial ablation site leads to edema formation and potentially precludes subsequent effective ablation. If this is true for an atrial substrate, it should be of even greater importance when targeting epicardial structures.

Our current study was designed to further investigate the concept of CardNM and not to determine the minimal energy transfer at the target line to maintain physiological changes and predict good clinical outcome.

To estimate the surface ablated at the epicardial site, we chose tags of 2-mm diameter for each individual ablation. The endocardial surface ablated is larger and should probably be better estimated using 3-mm ablation tags. Visualizing both left and right atrial structures is important for this anatomically guided approach. The ideal computed tomographic scan protocol will most likely vary from center to center depending on imaging possibilities and technical characteristics of the equipment and should be validated at each site. Our mean ablation time was markedly shorter than in most studies on cardioneuroablation and slightly shorter than in 2 previous studies.[6,14] The total ablation time was significantly prolonged in the first individuals enrolled in our study and reveals more about our initial doubts and our limited knowledge at that time than on a real clinical need. We think that the ablated surface area, the number of ablated sites, and whether the ablation is right-sided, left-sided, or bilateral are more relevant than ablation time when assessing the extensiveness of a procedure. By limiting the ablation to critical sites, we will expose patients to fewer risks and we will learn more about heart physiology. Taking anatomic characteristics, such as the interendocardial ablation distance, into account could help us to refine our current ablation strategy and further shorten total ablation time.

A marked reduction in syncope burden was reported at 3-month follow-up. The 24-hour rhythm registration data confirm the major effect of CardNM on slow heart rate and the absence of a residual pause at 1-month follow-up. These findings are not compatible with a placebo effect. These promising short-term clinical results are in agreement with the long-term data of previously reported patients.[10] Syncope recurrence after denervation procedures could be explained by axonal regeneration, but also by incomplete ablations, and probably by both. We think that the long-term results will depend more on efficient ablation of key targets than on number of sites targeted by ablation. We hypothesized that limiting the ablation to critical sites while maintaining efficacy is an important objective for several reasons, including safety. By doing this, we will expose patients to fewer risks, and we will learn more about heart physiology. In addition, we propose that the present approach is an important step toward therapy standardization.

The effector component of the reflex implicated in neurally mediated syncope combines some degree of bradycardia and vasodilatation in all of the patients. The predominance of one of those components during HUT forms the basis of the VASIS classification. Most patients in this study, as in routine clinical practice, have a mixed response; HUT has poor reproducibility, and the type of response during HUT and during spontaneous syncope can differ. There are several potential reasons why our approach is efficient for patients with a type 1– or type 2–positive HUT test. First, cardioneuroablation procedures are thought to interrupt not only efferent but also afferent pathways implicated in the mechanism of neurally mediated syncope. This is one of the potential explanations for the apparent higher efficacy of cardioneuroablation procedures for patients with neurally mediated syncope compared with pacemaker implantation. Second, during both CardNM and follow-up, we noticed a significant and consistent increase in blood pressure without creating arterial hypertension, probably essentially because of a higher cardiac output secondary to heart-rate acceleration. Finally, as mentioned in 2018 European Society of Cardiology guidelines for syncope, the decrease of cardiac output is essential and probably more important than the decrease in total peripheral resistance in the pathophysiology of neurally mediated syncope.[15]

Patients with a functional atrioventricular block were not excluded from the current cohort. CardNM creates an indirect nonpharmacological vagolysis of the atrioventricular node through the ARGP–inferior right-ganglionated plexus pathway, a major pathway of the little brain of the heart in animal models.[2] Nevertheless, we are aware that this atrioventricular node vagolysis is partial, and that this could be a potential limitation of CardNM for some patients we are yet to identify.

The ablation of other ganglionated plexi could be necessary in some patients with functional atrioventricular block.[14,15] As the clinical outcome in the limited number of patients with spontaneous atrioventricular block is favorable, we do not have any reason to expose them to a different ablation strategy and hence to additional ablation risks.

Limitations

This is a single-center, nonrandomized, unblinded trial. All procedures were performed by the same operator. The current results need to be confirmed in a larger number of patients with a longer follow-up. The minimal level of sinus node vagolysis that predicts a good clinical outcome is unknown.

Conclusions

Our data indicate that CardNM, through a right-sided and computed tomographic–guided procedure, is safe, fast, and highly reproducible in preventing inappropriate functional sinus bradycardia and syncope recurrence in patients affected by neurally mediated syncope or functional sinus node dysfunction. In most patients, an effective vagolysis of the sinus node can be reached by a computed tomographic–guided, limited, right-sided ablation strategy. We are concerned about the potential risks of extended and biatrial procedures proposed by other groups. Further studies and a randomized multicenter trial should be performed to confirm the promising results presented in this study.

ARTICLE INFORMATION

Received March 28, 2018; accepted July 20, 2018.

Correspondence

Philippe Debruyne, MD, Department of Cardiology, Imeldaziekenhuis, 2820 Bonheiden, Belgium. Email philippe.debruyne@skynet.be

Affiliations

Department of Cardiology, Imeldaziekenhuis, Bonheiden, Belgium (P.D., T.R., J.R., B.E., L.J., F.C., B.V., W.D.). Department of Intensive Care, Cliniques Universitaires Saint-Luc, Woluwe, Belgium (C.C.). The Lambe Institute for Translational Medicine and Curam, National University of Ireland, Galway and Saolta University Healthcare Group (W.W.).

Acknowledgments

We thank Inge Benoy (Biosense Webster) for the professional support during procedures and Christine Bazelmans, PhD (Biotronik) for performing the statistical analysis. We thank Margareta Badts and Sofie Albertijn (study nurses of the cardiology department of Imeldaziekenhuis) for their enthusiastic support and for the data collection. Sophie Rushton-Smith, PhD (MedLink Healthcare Communications, London), provided editorial assistance for manuscript preparation under supervision of the author and was funded by Dr Debruyne.

Sources of Funding

The study is being supported by grants from Biosense Webster and Biotronik. The companies had no role in the design of the study or in the collection or management of the data or the writing of the manuscript. The funders performed the statistical analysis.

Disclosures

Dr Debruyne has applied for a patent related to this research. The other authors report no conflicts.

REFERENCES

1. Randall WC, Milosavljevic M, Wurster RD, Geis GS, Ardell JL. Selective vagal innervation of the heart. *Ann Clin Lab Sci*. 1986;16:198–208.
2. Hou Y, Scherlag BJ, Lin J, Zhang Y, Lu Z, Truong K, Patterson E, Lazzara R, Jackman WM, Po SS. Ganglionated plexi modulate extrinsic cardiac autonomic nerve input: effects on sinus rate, atrioventricular conduction, refractoriness, and inducibility of atrial fibrillation. *J Am Coll Cardiol*. 2007;50:61–68. doi: 10.1016/j.jacc.2007.02.066
3. Pachon JC, Pachon EI, Pachon JC, Lobo TJ, Pachon MZ, Vargas RN, Jatene AD. "Cardioneuroablation"–new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. *Europace*. 2005;7:1–13. doi: 10.1016/j.eupc.2004.10.003
4. Scanavacca M, Hachul D, Pisani C, Sosa E. Selective vagal denervation of the sinus and atrioventricular nodes, guided by vagal reflexes induced by high frequency stimulation, to treat refractory neurally mediated syncope. *J Cardiovasc Electrophysiol*. 2009;20:558–563. doi: 10.1111/j.1540-8167.2008.01385.x
5. Liang Z, Jiayou Z, Zonggui W, Dening L. Selective atrial vagal denervation guided by evoked vagal reflex to treat refractory vasovagal syncope. *Pacing Clin Electrophysiol*. 2012;35:e214–e218. doi: 10.1111/j.1540-8159.2011.03320.x
6. Yao Y, Shi R, Wong T, Zheng L, Chen W, Yang L, Huang W, Bao J, Zhang S. Endocardial autonomic denervation of the left atrium to treat vasovagal syncope: an early experience in humans. *Circ Arrhythm Electrophysiol*. 2012;5:279–286. doi: 10.1161/CIRCEP.111.966465
7. Zhao L, Jiang W, Zhou L, Wang Y, Zhang X, Wu S, Xu K, Liu X. Atrial autonomic denervation for the treatment of long-standing symptomatic sinus bradycardia in non-elderly patients. *J Interv Card Electrophysiol*. 2015;43:151–159. doi: 10.1007/s10840-015-9981-8
8. Aksu T, Golcuk E, Yalin K, Guler TE, Erden I. Simplified cardioneuroablation in the treatment of reflex syncope, functional AV block, and sinus node dysfunction. *Pacing Clin Electrophysiol*. 2016;39:42–53. doi: 10.1111/pace.12756
9. Debruyne P. "Cardio-neuromodulation" with a multielectrode irrigated catheter: a potential new approach for patients with cardio-inhibitory syncope. *J Cardiovasc Electrophysiol*. 2016;27:1110–1113. doi: 10.1111/jce.13031
10. Debruyne P, Wijns W. Cardio-neuromodulation: the right-sided approach. *JACC Clin Electrophysiol*. 2017;3:1056–1057. doi: 10.1016/j.jacep.2016.12.027
11. Brignole M, Menozzi C, Del Rosso A, Costa S, Gaggioli G, Bottoni N, Bartoli P, Sutton R. New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. Vasovagal Syncope International Study. *Europace*. 2000;2:66–76.
12. Qin M, Zhang Y, Liu X, Jiang WF, Wu SH, Po S. Atrial ganglionated plexus modification: a novel approach to treat symptomatic sinus bradycardia. *JACC Clin Electrophysiol*. 2017;3:950–959. doi: 10.1016/j.jacep.2017.01.022
13. Debruyne P. Letter by Debruyne regarding article, "Targets and end points in cardiac autonomic denervation procedures". *Circ Arrhythm Electrophysiol*. 2017;10:e005261. doi: 10.1161/CIRCEP.117.005261
14. Rivarola EW, Hachul D, Wu T, Pisani C, Hardy C, Raimundi F, Melo S, Darrieux F, Scanavacca M. Targets and end points in cardiac autonomic denervation procedures. *Circ Arrhythm Electrophysiol*. 2017;10:e004638. doi: 10.1161/CIRCEP.116.004638
15. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG; ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018;39:1883–1948. doi: 10.1093/eurheartj/ehy037