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Durable Physiological Changes and Decreased Syncope Burden 12 Months After Unifocal Right-Sided Ablation Under Computed Tomographic Guidance in Patients with Neurally Mediated syncope or Functional Sinus Node Dysfunction

Running title: *Debruyne et al.; Clinical outcomes after cardio-neuromodulation*

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Abstract:

Background - Cardio-neuromodulation (CardNM) is a cardioneuroablative approach aiming to create adequate vagolysis of the sinoatrial node through partial ablation of the anterior right ganglionated plexus.

Methods - We performed an interventional study in patients with recurrent neurally mediated syncope (group A) or functional sinus node (SN) dysfunction (group B). Syncope burden, electrocardiogram, 24-h rhythm data, tilt table test, exercise test, and pharmacological challenge with atropine were assessed at baseline and at regular intervals to 12-months.

Results - Fifty patients (31 in group A, 19 in group B) underwent CardNM. Mean number of syncopes during the previous 12 months was 9.7±18.2. The procedure was associated with a lower rate of syncope (−95%) and presyncope (−95%) at 12 months versus baseline (P<0.001). Thirty-seven patients remained entirely free of syncope at 12 months, and the syncope-free survival curve remained stable between 12- and 30-month follow-up. After a mean ablation time of 8±4 min, P-P interval shortened by 247±146 ms (P<0.001). Basal heart rate (HR) increased by 18% (P<0.001) and remained stable between 6 and 12 months. At 12 months, mean HR increased by 12% in the entire cohort (P<0.001), reached 23% in patients with baseline mean HR <70 bpm (P<0.01), and did not increase in patients with baseline HR >70 bpm. Maximum HR during exercise decreased by 10 bpm at 1 month (P<0.001) and was restored at 12 months.

Conclusions - CardNM is a safe and fast treatment giving rise to a long-term partial SN vagolysis with no apparent short- or long-term safety concerns or undesirable persisting modifications of the intracardiac autonomous nervous system. The impact on vasoplegia is less clear. CardNM is associated with a good clinical outcome in most patients with neurally mediated syncope or functional SN dysfunction. These promising data require confirmation in a multicenter randomized trial.

Clinical Trial Registration - ClinicalTrials.gov; Unique ID: NCT02954666

Key words: syncope; ablation; autonomic nervous system; cardio-neuromodulation; cardioneuroablation; ganglionated plexi; ARGP; neurally mediated syncope

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Nonstandard Abbreviations and Acronyms:
ARGP, anterior right ganglionated plexus
AT, atropine
CardNM, cardio-neuromodulation
CardNMH2 study, second study on cardio-neuromodulation in humans
CNA, cardioneuroablation
ICANS, intrinsic cardiac autonomous nervous system
SN, sinus node
TL, target line
TTT, tilt table test

Introduction

Neurally mediated syncope (NMS) is often refractory to routine treatments.[1,2] There is, therefore, a need for a new treatment modality. In 2005, Pachon et al. proposed cardiac vagal denervation to treat NMS, sinus node (SN) dysfunction, and functional atrioventricular block.[3,4] Other research groups, using different multisite cardioneuroablation (CNA) approaches, published good clinical results for different clinical conditions caused by an inadequate high vagal tone.[5-12] While a (dual) pacemaker implantation is indicated in patients with a degenerative sick sinus syndrome having an intrinsic SN dysfunction, patients with a functional SN dysfunction (sinus bradycardia and/or sinoatrial pause) secondary to excessive high vagal tone could benefit from an intervention that can correct inadequate neural activity of their intrinsic cardiac autonomous nervous system (ICANS).

Cardio-neuromodulation (CardNM) is a cardioneuroablative approach aiming to create adequate vagolysis of the sinoatrial node through partial ablation of the anterior right ganglionated plexus (ARGP).[13-15] Ganglionated plexi contain large populations of colocalized sympathetic and parasympathetic neurons. Ablation of these plexi will, therefore, not only affect

parasympathetic neural bodies and axons, but will also interrupt sympathetic axons.[3,16]

In this manuscript, we report the 12-month results of the CardNMH2 study in patients with NMS or functional sinus node dysfunction with no significant impairment of their intrinsic sinus node activity. We provide innovative data on changes in the ICANS physiology associated with CardNM.

Methods

CardNMH2 (ClinicalTrials.gov ID NCT02954666) is an investigator-initiated, prospective, open-label, interventional, single-center cohort study designed to assess the safety and efficacy of CardNM in patients with neurally mediated syncope or functional SN dysfunction. The primary safety outcome was freedom from serious adverse events at 7 days and the primary efficacy outcome was freedom from syncope at 12 months. Syncope and presyncope burden and electrocardiographic data were compared before and after CardNM.

CardNMH2 was approved by the Ethical Committee of Imeldaziekenhuis, Bonheiden, Belgium and has been 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 data at regular intervals to safeguard the wellbeing of the participants.

The authors declare that all supporting data are available in the article.

Study Population

The study enrolment criteria have been published.[14] Patients with syncope were assigned to group A if they had recurrent NMS syncope with a positive tilt table test (TTT) (a VASIS 1 or 2 response) and to group B if they had a documented sinus pause ≥3 s.[15,17] A P-P interval

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shortening ≥20% and <1000 ms after intravenous administration of 2 mg atropine was required for both groups. Patients in group A must have had ≥2 episodes of syncope (≥3 in patients <18 years of age) in their lifetime unless the last syncope was complicated by an injury or an accident. The main exclusion criteria were age <14 years, unstable medical condition, life expectancy <12 months, antiarrhythmic drugs, atrial fibrillation, bi- or trifascicular block, permanent PR prolongation, and valvular or myocardial disorders causing syncope. Patient baseline characteristics are summarized in Table 1.

Clinical and Electrocardiographic Data Collection

All patients underwent a 24-h rhythm registration and a transthoracic echocardiography (TTE) at baseline. A TTT was performed in patients in group A, tilting to 70° for 45 minutes without any pharmacological provocation, and was repeated following the same protocol during follow-up.

Data on syncope burden, presence of prodromes, and occurrence of injuries and accidents were recorded before CardNM. An electrocardiogram (ECG) was performed according to a highly standardized protocol, to establish the basal heart rate (HR) and the HR after two sequential intravenous injections of 1 mg atropine. Initially, the second bolus was not administrated if the HR after 1 mg atropine was >100 bpm. After a protocol amendment, a total dose of 2 mg was systematically administered, and the atropine test was repeated on the day after the procedure. Basal HR and HR after atropine injection were derived from the mean P-P interval of five consecutive P waves without extrasystole.

Therapeutic anticoagulation with a non-vitamin K antagonist oral anticoagulant was started >2 h before CardNM and was continued for 1 month afterwards. Patients with a high bleeding risk were treated with clopidogrel. Use of medications with a chronotropic or dromotropic action was discouraged.

An in-hospital visit was planned at 1, 3, 6, and 12 months. All cases of recurrent syncope were tracked at each visit. The 24-h rhythm registration and the ECG registration in resting conditions and after atropine injection were repeated at 1, 6, and 12 months.

The TTT was repeated at 1 and 6 months in patients in group A using the same protocol used at baseline. A cycloergometry test was performed whenever feasible to evaluate sinus node chronotropic function. Cycloergometry was repeated at 1 and 12 months and TTE at 12 months.

The number of patients who underwent each test is shown in the Supplemental Table.

The atropine test was not repeated in patients with poor tolerance during a previous test. During 24-h rhythm registration, the mean HR and the number of P-P intervals >1200 ms and >1000 ms were determined, and data on HR variability (HRV) were collected. The presence of a pause or an atrioventricular block was tracked. Data on HRV were, specifically: the mean of the standard deviations of all the NN intervals for each 5 min segment of the recording (SDNN-i), the percentage of successive RR intervals that differed by >50 ms (pNN50), and the integral of the density of the RR interval histogram divided by its height (HRV index). The QT interval was measured manually and the QTc was derived using Sagie's formula.

Cardiac Imaging and Invasive Procedure

CardNM was performed according to a right-sided ablation strategy under computed tomographic guidance.[15] The endocardial site to target during ablation was annotated by a target line 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 tomography image of the heart imported into the CARTO system (Biosense Webster, Diamond Bar, CA, USA) before the procedure (Figure 1). Each procedure was performed with the patient under general anesthesia with sevoflurane in a steady state,

favoring a high vagal tone.[14] Electroanatomical mapping of the right atrium, the superior and inferior vena cava, and the coronary sinus was performed and merged with the computed tomography image. A right atrium activation map was performed at baseline and repeated after CardNM. The crista terminalis was divided into four geometrical zones (cranial, midsuperior, midinferior, and caudal). The distance between the target line and right phrenic nerve and the shortest distance between the target line and the earliest endocardial activation area in sinus rhythm was provided (Table 2).

Radiofrequency applications were delivered along the target line with an irrigated tip catheter (Smart Touch catheter, Biosense Webster, Diamond Bar, CA, USA) with a power of 40 W and a contact force >8 g.[15] They were interrupted if no significant shortening of the P-P interval was observed after 30 s or were prolonged when P-P interval shortened without exceeding 90 s. The ablation procedure was considered complete if the P-P interval shortened by >30%, if the P-P interval was <600 ms after 5 min of waiting, if 10 radiofrequency applications were delivered, or if the total ablation time reached 900 s. ECG registrations were obtained >30 min after the last ablation before and after an intravenous injection of 2 mg atropine.

Statistical Analysis

The Wilcoxon rank-sum test was used for comparison of syncope and presyncope episodes. Proportions at baseline, 1 month, and 6 months were compared using the Mid-P adjustment to McNemar exact test. TTT results were compared using the McNemar test with Bonferroni correction. To assess the correlation between TTT response at baseline and the probability of syncope recurrence, Fisher's exact test was used. P-P interval and corrected SN recovery time were compared using the Wilcoxon rank-sum test. The Wilcoxon rank-sum test was used to compare P-P interval shortening between group A and group B, and for comparison of other

ablation data. The Bhapkar test was used for comparison of activation maps. ECG, exercise tests, and 24-h rhythm registrations were compared using a paired Student's *t*-test or the ANOVA test with Bonferroni correction when multiple samples were compared. Data on HRV were compared using the Wilcoxon signed-rank test with Bonferroni correction. QT and QTc intervals were compared using the linear mixed-effect modeling. Time to first recurrence of syncope was provided by the Kaplan-Meier survival analysis. Continuous data are presented as mean±standard deviation (SD). All 2-tailed *P*-values <0.05 were considered statistically significant. The statistical analysis was performed using the SPSS (IBM, New York, NY, USA) and the Stata (StataCorp, College Station, Texas, USA) software.

Results

Baseline Characteristics

Fifty patients were enrolled in the CardNMH2 study (Imeldaziekenhuis, Bonheiden, Belgium) between December 2016 and March 2019, 31 in group A and 19 in group B. All of the patients were in New York Heart Association (NYHA) class I and there were no noteworthy abnormalities on TTE. Patient characteristics and syncope presentation are provided in Table 1. Mean syncope burden in the previous 12 months was 9.7±18.2 (13.3±22.3 in group A and 3.8±3.3 in group B). Syncope was always preceded by long prodromes in 9 patients and never preceded by prodromes in 11 patients (3 in group A, of whom 2 had a documented pause ≥3 s during a spontaneous episode, and 8 in group B). In 22 patients (6 in group A and 16 in group B), a pause ≥3 s was documented during a spontaneous syncopal episode. Thirty-three patients had a history of complicated syncope. Among the patients with cerebral complications, 1 patient had a traumatic intracerebral hemorrhage, 1 patient had syncope complicated by urinary

incontinence, and 6 patients had *commotio cerebri*. Five patients had an internal loop recorder (3 in group A and 2 in group B); among these, 2 (group B) had a documented pause ≥3 s. Over the 12 months preceding CardNM, 2028 presyncope episodes were reported, corresponding to a mean of 56.2±107.6 in group A and 15.11±45.63 in group B.

According to the VASIS classification, the response in patients (group A) during the TTT was type 1 (mixed) in 20 patients, type 2A (cardioinhibition without asystole) in 3 patients, and type 2B (cardioinhibition with asystole) in 8 patients of whom 1 had atrioventricular block. Second-degree atrioventricular block was documented during 24-h rhythm registration in 2 patients. One patient in group A had idiopathic ventricular tachycardia. Seven patients were treated for arterial hypertension with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, combined with a diuretic in 2 patients and a calcium antagonist in 1 patient. Three patients were treated with beta-blockers, 2 for intermittent inappropriate SN tachycardia and 1 for migraine. One patient was treated with midodrine, 1 with fludrocortisone, and 1 with etilefrine. Two patients in group B were dependent on intravenous isoprenaline before the procedure. The patients did not take any other noteworthy medications.

Procedural Data

Procedural data are summarized in Table 2. After 6.1±2.9 applications of radiofrequency energy and a mean ablation time of 8±4 min, baseline procedural P-P interval shortened by a mean of 248±146 ms (P<0.001), resulting in an increase in the basal HR of 22±13 bpm. AH (73±17 ms) and HV (45±9 ms) intervals were normal. The Wenckebach point seemed similar before and after ablation (392±80 vs 395±70 ms, respectively; P=0.58). The earliest SN activation zone was found in the cranial zone in 18 patients before CardNM and in 24 patients after CardNM (P=0.21). The proportion of patients with a shift in the earliest activation zone toward the cranial

zone after CardNM did not appear to differ significantly in patients with and without syncope recurrence (61.5% vs 57.1%, respectively; *P*=1.00).

Whereas the HR after CardNM was higher in patients with versus without syncope recurrence (90±8.1 vs 80.1±17.0 bpm, respectively; *P*=0.007), the absolute increase in HR (25.8±9.2 vs 20.5±14.6 bpm; *P*=0.22) did not differ significantly. The HR increase following atropine injection was not significantly higher in patients with versus without syncope recurrence (3.5±4.3 vs 2.9±4.5 bpm, respectively; *P*=0.68). The HR before CardNM (64.5±5.9 vs 59.7 bpm; *P*=0.78), the endocardial distance between the RA/SVC junction and LA/RSPV at the target line (2.83±1.23 vs 3.60±2.18 mm; *P*=0.16) and the other procedural data, were not statistically different in patients with or without syncope recurrence.

Clinical Follow-Up

One patient developed a pseudoaneurysm >1 week after the procedure. No other adverse events were reported during follow-up. No patients were excluded or lost to 6-month follow-up.

Four patients were considered to have a treatment failure: 1 patient (age 17 years) in group A, reluctant to pacemaker implantation, who underwent an additional ablation procedure motivated by atrioventricular block and prolonged asystole during TTT at 6 months; and 3 patients in group B (age 29, 70 and 75 years) with syncope recurrence and documentation of a sinus pause who underwent pacemaker implantation after 6 months.

Beta-blockers were initiated in 3 patients: for idiopathic fast ventricular tachycardia present before CardNM in 1 patient (beta-blockers had worsened the NMS episodes before CardNM); for palpitations without arrhythmia documentation in 1 patient; and for headache in 1 patient. Flecainide was initiated in 2 patients for supraventricular extrasystoles and ventricular extrasystoles. Midodrine, fludrocortisone, and etilefrine were interrupted after CardNM. No

other relevant medication changes occurred during follow-up.

Two patients underwent internal loop recorder implantation after CardNM. Of the 7 patients with an internal loop recorder, 5 had syncope recurrence but no cases of bradyarrhythmia were documented.

One patient in group A without syncope recurrence failed to attend 12-month follow-up. All patients remained in NYHA class I and none presented significant changes on TTE. Thirty-seven patients remained free of syncope at 12 months (P<0.001). Additional follow-up data beyond the 12-month final evaluation were obtained in 47 patients: 34 patients had 18-month data, 23 had 24-month data, and 18 had 30-month data. The syncope-free survival rate did not change between 12- and 30-month follow-up (Figure 2).

Syncope burden was lower (−95%) at 12-month follow-up compared with baseline (P<0.001) (Figure 3). No cases of complicated syncope occurred during the 96 patient-years of follow-up in the study. The 9 patients in group A with syncope recurrence cumulated 17 episodes during the 12 months after the procedure compared with 254 episodes at baseline (−93%, P=0.008). Eight of these patients had exclusively syncope with long prodromes compared with 2 at baseline. The procedure was associated with a lower presyncope burden during follow-up compared with baseline (−95%; P<0.001). With the exception of the patient with atrioventricular block during TTT at baseline, no patients developed atrioventricular block during follow-up.

Tilt Table Test

The results of the TTT were negative in 24 patients at both 1- and 6-month follow-up (P<0.001). Seven patients had a positive TTT result at 1 month (VASIS 1 in 2, VASIS 2A in 1, VASIS 2B in 1, and VASIS 3 in 3). Three patients with a VASIS 1 response at baseline had a positive test at 6 months (VASIS 1 in 1 patient and VASIS 3 in 2 patients) and 3 with a cardioinhibitory

response at baseline had a positive test (VASIS 1 in 1 patient and 2B in 2 patients). Eighty-two percent of the patients with syncope recurrence in group A had a VASIS 1 response during the TTT at baseline and 18% had a VASIS 2 response (P=0.11). One patient with an atrioventricular block at baseline presented an atrioventricular block at 6 months.

Electrocardiographic Data

The basal HR data and the HR data after atropine injection are shown in Figure 4 and Table 3. During CardNM, the basal HR was reset to 73±13 bpm, corresponding to a 20% mean increase in basal HR (P<0.001). In the patients who underwent pacemaker implantation after 6 months of follow-up, the basal HR was reset to 74 ± 14 bpm.

Compared with this post-procedural reset of basal HR, basal HR remained similar the day after the procedure (75±10 bpm; P=0.92), increased significantly at 1 month (82±12 bpm; P<0.001), and was identical at 12 months (73±11 bpm; P=0.93). The basal HR at baseline, the day after the procedure, and at 12-month follow-up was similar in patients with and without syncope recurrence.

At baseline, basal HR increased from 61±11 to 97±15 bpm after atropine injection (P<0.001). Twenty-one patients (15 in group A, 6 in group B) had a HR >100 bpm and 16 had a HR >90 bpm (10 in group A, 6 in group B). In 13 patients (6 in group A, 7 in group B) HR remained <90 bpm. After atropine, basal HR increased minimally after ablation (from 73±13 to 77±14 bpm; P<0.001) and modestly the day after the procedure (from 75±10 to 85±12 bpm; P<0.001). In the patients who underwent pacemaker implantation after 6 months of follow-up, HR increased by 2 ± 5 bpm after atropine injection after CardNM.

In the 39 patients who also underwent an atropine test at 12 months, HR post atropine was 99±15 bpm at baseline, tended to be lower at 1 month (94±15 bpm; P=0.24), and was

significantly lower at 6 months (93±12 bpm; *P*=0.027) and 12 months (92±12 bpm; *P*<0.004). The mean HR after atropine administration at 12-month follow-up was identical when using the HR value corresponding to a total dose of 2 mg in all patients or using the HR corresponding to the dose of atropine administered at baseline in all patients. There was no statistical difference between the HR post atropine at 6- and 12-month follow-up compared with baseline (*P*=1.00). The basal HR at baseline (61.1±14.1 vs 60.8±9.8 bpm; *P*=1.00), the day after the procedure (78.9±9.7 vs 73.7±9.7 bpm; *P*=0.71), and at 12-month follow-up (74.7±13.4 vs 72.5±10.9 bpm; *P*=1.00) did not differ significantly in patients with and without syncope recurrence. At baseline, the basal heart rate in the patients who underwent pacemaker implantation after 6 months of follow-up was 44 ± 11 bpm.

HRs after atropine administration at baseline (103.4±12.4 vs 94.4±15.4 bpm; *P*=0.28) and on the day after the procedure (88.7±9.4 vs 82.0±13.1 bpm; *P*=0.69) did not differ significantly in patients with and without syncope recurrence and tended to be higher in patients with syncope recurrence at 12 months (98.4±10.6 vs 89.6±12.21 bpm; *P*=0.07). At baseline, the HR after atropine in the patients who underwent pacemaker implantation after 6 months of follow-up was 83 ± 12 bpm (74 and 78 bpm in patients aged 70 and 75 years, respectively).

Twenty-Four Hour Rhythm Registration Data

Holter data are summarized in Table 3.

The number of PP intervals ≥1000 ms during 24-h rhythm registration decreased from 23 646±17 015 beats at baseline to 11 523±13 684 beats at 12 months (*P*<0.001). Equivalent data for PP intervals ≥1200 ms decreased from 7094±10 874 beats at baseline to 2063±5691 beats at 12 months (*P*<0.003).

Changes in mean HR during 24-h rhythm registration are detailed in Figure 5. Mean HR of the whole cohort increased from 69±9 bpm at baseline to 77±10 bpm at 12 months, corresponding to mean HR accelerations of 12% (P<0.001). Patients with a mean HR <70 bpm at baseline increased their mean HR from 61±6 to 75±12 bpm at 12 months (P<0.001), whereas patients with a mean HR ≥70 bpm at baseline did not increase their HR significantly (P=0.14).

SDNN-i decreased from 80.7 ± 29.2 ms at baseline to 59.4 ± 50.9 ms at 12 months, and the HRV index from 47.8 ± 15.1 at baseline to 35.4 ± 12.4 at 12 months. Mean HR and HRV data did not differ between patients with and without syncope recurrence.

The mean heart rate at baseline was 69 ± 9 bpm in patients without syncope recurrence and 56 ± 9 bpm in patients who underwent pacemaker implantation after 6 months. The mean heart rate at 1-month follow-up was 83 ± 11 vs 79 ± 6 bpm. At 6 months, Holter monitoring was performed in 2 patients who underwent later a pacemaker implantation and revealed a mean heart rate of 73 ± 9 bpm compared to 81 ± 11 in patients without a recurrence. The HRV data were in line with the ECG and Holter data.

Exercise Test

The maximal HR decreased transiently by 10 bpm at 1 month (P<0.001). The maximal workload at baseline (202±64 W) and at 1 month (197±58 W) appeared similar (P=0.75). Maximal HR changes are detailed in Table 3.

Discussion

In this article, we report 12-month data from 50 patients with syncope included in the CardNMH2 study, 31 with NMS and 19 with a pause ≥3 s. These results confirm our intermediate analysis and show that CardNM is a reproducible and fast procedure and was

associated with a lower syncope and presyncope burden (−95%) compared to baseline and was without safety concerns in this patient cohort. The treatment was considered to have failed in 1 patient in group A and in 3 patients in group B. Of these 3 patients, 2 were ≥70 years old and hence were at higher risk of having intrinsic sinus node impairment. Of note, their heart rates accelerated moderately after atropine at baseline, possibly pointing to the beginnings of intrinsic sinus node dysfunction. Based on this, we believe that the criteria used for group B need to be more selective to improve our ability to identify with greater specificity patients with a functional sinus node dysfunction. The remaining 9 patients in group A who were not free of syncope had a lower rate of syncope during follow-up (−93%); in all except 1 patient, syncope recurred only after long prodromes. Limited medication changes occurred during the study and are unlikely to have affected the conclusions.

At baseline, the HR after atropine injection indicates to which level the basal HR could be reset by any procedure aiming at complete SN vagal denervation. Had long-term complete vagal denervation been achieved, the basal HR would have been >100 bpm in 21 patients and >90 bpm in 37 patients. We discuss further why this was not observed.

A marked shortening in the P-P interval was observed during CardNM. At 12 months, the basal HR and the mean HR were reset to a higher level compared with baseline. Interestingly, the HR acceleration was more pronounced in patients with a slow HR at baseline. Twenty-four−hour rhythm registration data confirmed the marked diminution in the number of beats <60 per min after CardNM.

The basal HR, maximum HR during exercise, and mean 24-h rhythm data showed dynamic changes during follow-up due to modifications in SN innervation. Whereas basal HR at 12 months was similar to post-procedural reset HR, HR after AT injection was lower at 12

months versus baseline. How do we explain this? HR increased significantly more after atropine injection at 12 months compared with post-procedure, probably due to vagal reinnervation. Despite this, basal HR at 12 months remained similar to post-procedural reset basal HR. This apparent paradox could be explained by a concomitant sympathetic reinnervation. As the sympathetic activity does affect the basal HR, we link the transient higher basal HR at 1 month versus the post-procedural basal HR to the fact that SN sympathetic reinnervation should have occurred faster than SN vagal reinnervation.[18] We assume that SN sympathetic reinnervation after CardNM is essentially due to axonal regrowth of neurons penetrating the ARGP, whereas SN vagal reinnervation after CardNM is due to axonal regrowth from nontargeted ganglionated plexi. As these ganglionated plexi are located further from the SN area, sympathetic and vagal SN reinnervation processes are not complete at the same moment. The average rate of axonal regeneration in the peripheral nervous system is 1 mm/day.[19] We have not found similar data in the literature concerning the ICANS, but axonal regeneration could be in the same range. Indeed, assuming that our data pointed to SN sympathetic reinnervation at 1 month, sympathetic axonal regeneration should be ≥0.8 mm/day as the distance between the target line and the SN area was 23±7 mm.

At 12 months, vagal and sympathetic reinnervations effects appeared to antagonize each other, resulting in a basal HR at 12 months similar to the post-procedural basal HR. As ganglionated plexi contain both vagal and sympathetic fibers, it is reasonable to assume that CardNM induced not only SN vagal denervation but also SN sympathetic innervation modifications. Although SN sympathetic reinnervation predominated at 1 month, sympathetic reinnervation was then not complete, as the maximal HR was lower than that at baseline and fortunately was restored at 6 months.

During CardNM, ARGP ablation reset the basal HR to a higher level. During follow-up, modified ICANS physiology resulted from dynamic modifications of both the vagal and the sympathetic SN innervation. Twelve months after ARGP ablation, the persisting effect corresponded to a partial SN vagolysis, which was the goal of the procedure.

Assuming the intrinsic SN function was unaffected by the CardNM procedure and remained unchanged during follow-up, the decrease in HR during the atropine test at 12 months versus baseline could be due to a higher catecholaminergic status at baseline despite the highly standardized ECG registration protocol. Alternatively, it may indicate a residual nonclinical impairment of SN sympathetic denervation. Regarding this, one should also note that, although not statistically significant (P=0.09), the maximal HR during exercise tended to be lower at 12 months (153±15 bpm) versus baseline (158±19 bpm).

Partial vagal reinnervation after any CNA procedure is desirable. Indeed, any ablation procedure achieving a persisting long-term complete SN vagal denervation will give rise to an inappropriate high basal HR in most patients, unless the procedure downgrades the intrinsic SN function or compromises the sympathetic SN innervation in the long-term. This should be kept in mind when assessing, developing, proposing, or performing any CNA approach.

The goal of CNA procedures is to modify the ICANS physiology to improve patient outcome. Ganglionated plexi have been proposed as complex integration centers modulating cardiac responses to autonomic input.[20] Changes in ICANS physiology induced by CNA procedures may differ greatly according to the sites being targeted, and hence have different short- and long-term consequences. Ganglionated plexi contain not only large populations of colocalized sympathetic and parasympathetic neurons but also afferent neurons, motor neurons, interconnecting local neurons, and, interestingly, some neurons expressing both cholinergic and

adrenergic activity.[15] Any CNA strategy will interfere specifically with this complex system. After CNA, the interactions of the different neurons of the ICANS can change substantially. This effect could partially explain the apparent efficacy of these approaches even in the long term when vagal reinnervation is thought to be complete. Although the global level of vagal reinnervation after a procedure can be assessed, the fine interactions between the different components of the ICANS will probably be difficult to assess in humans. Standardization of the lesion set is important, to be able to investigate the physiological changes associated with the different ablation strategies. Targeting a single ganglionated plexus selectively offered us a unique opportunity to describe the short- and long-term physiological changes associated with ARGP ablation and enabled us to demonstrate that the ARGP belonged to the final common pathway of SN vagal innervation.[14]

Our opinion is that total syncope burden and nonprodromic and complicated syncope-free survival curves are the most important clinical variables when assessing the efficacy of any CNA approach for syncope. Moreover, the effect on syncope should always be put into perspective with the collateral effects and risks. The ideal CNA approach for a specific clinical problem should be safe, fast, and reproducible, with minimal physiological changes, but still able to predict a good clinical outcome.[21] CardNM is a fast procedure, exposing patients to fewer procedural risks than left-sided or biatrial multiple-site ablation strategies. The long-term clinical results were good, with a persisting adequate partial SN vagolysis, while the chronotropic SN function seems only transiently and modestly affected by CardNM. Interestingly, Hu et al. pointed out that ARGP could be the cornerstone of CNA procedures.[9]

In this study, level of SN vagolysis achieved during CardNM was similar in patients with or without syncope recurrence. The 24-h rhythm registration data did not reveal a higher level of

vagal reinnervation at 12 months in patient with syncope recurrence compared to patients without recurrence.

While our data suggest that CardNM could be useful for most patients with NMS (having a VASIS 1 or 2 response during the TTT) and for patients with functional SN dysfunction, they do not suggest that CardNM could be useful for treating functional atrioventricular block. Additional ablation steps, or a 'panablation' strategy, could be of use for this particular clinical problem. Importantly, in this cohort of 50 patients, none of the patients without an atrioventricular block at baseline developed a block during follow-up (12−30 months). Vasoplegia could be the underlying mechanism of syncope recurrence in patients with NMS without documented bradycardia.

Limitations

As the atropine test the day after the procedure was not included in the first version of the protocol, the corresponding data are limited. The dose of atropine used has been adjusted at the beginning of the trial. Although this protocol amendment could be considered as a limitation, it apparently did not affect the results.

This is a single-center, nonrandomized, unblinded trial with no control arm (sham procedure) as with previous trials on cardioneuroablation. There was no other active arm such as a pacemaker with a dedicated algorithm or another ablation strategy targeting other parts of the ICANS or all the structures of the ICANS. Therefore, we cannot determine whether these therapeutic strategies would have given different results. All procedures were performed by the same operator. The current results need to be confirmed in a multicenter randomized trial.

Conclusions

CardNM is a safe and fast treatment that gives rise to a long-term partial SN vagolysis with no apparent short- or long-term safety concerns or undesirable persisting modifications of the intracardiac autonomous nervous system. The impact on vasoplegia is more questionable. It is associated with a good clinical outcome in most patients with NMS or functional SN dysfunction. These promising data require confirmation in a multicenter randomized trial.

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Supplemental Materials:
Supplemental Table I

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Table 1. Patient Baseline Characteristics and Syncope Presentation

Characteristic	All patients (n=50)	Group A (n=31)	Group B (n=19)
Age, y	42.4 ± 17	39.6 ± 16	46.9 ± 19
Female sex	21 (42)	16 (52)	5 (26)
Body weight, kg	71.4 ± 15.4	68.4 ± 14.5	76.3 ± 15.9
Syncope burden before ablation (n)			
≤3 months	255	189	66
≤6 months	361	292	69
≤12 months	484	412	72
Syncope presentation: type of prodromes			
Long prodromes exclusively	9	7	2
No prodromes exclusively	11	3	8
Very short prodromes exclusively	13	9	4
Very short and no prodromes	10	6	4
Long and very short or no prodromes	7	6	1
Complicated syncope*			
Motor vehicle accident	3	2	1
Bicycle accident	6	5	1
Fracture	7	3	4
Luxation	1	1	0
Cerebral complications	8	6	2
Large wounds	8	4	4
Large hematomas	13	13	1

Data are mean (SD), number (%), or n.
*Some patients had more than one type of complicated syncope.

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Table 2. Procedural Characteristics

Characteristic		All patients (n=50)	Group A (n=31)	Group B (n=19)
Anatomical data				
TL length, mm		12 ± 2	12 ± 2	12 ± 1
'd SVC/RA − RSPV endocardium at TL, mm'		3 ± 2	3 ± 2	4 ± 2
d TL-His bundle, mm		43 ± 8	43 ± 9	42 ± 6
d TL-phrenic nerve, mm		14 ± 4	14 ± 4	15 ± 5
d TL-SN, mm		23 ± 7	23 ± 7	23 ± 6
Ablation data				
Ablation time, min		8 ± 4	7 ± 4	9 ± 4
Number of RFA per patient, n		6.1 ± 2.3	5.7 ± 2.9	6.7 ± 2.9
Ablation surface, mm^2		10 ± 5	9 ± 5	11 ± 4
Patients with P-P shortening >120 ms after the first RFA		44 (88)	29 (94)	15 (68)
Functional data				
P-P interval, ms	Baseline	1000 ± 141	1007 ± 121	998 ± 172
	After CardNM	756 ± 173	740 ± 188	782 ± 147
	P value	<0.001	<0.001	<0.001
SNRTc, ms	Baseline	331 ± 384	271 ± 167	425 ± 577
	After CardNM	214 ± 173	203 ± 177	232 ± 170
	P value	0.010	0.14	0.014
Delta HR after AT, bpm		3 ± 3	3 ± 4	3 ± 3

Data are mean ± SD or number (%).
AT indicates atropine (2 mg after CardNM); bpm, beats per minute; CardNM, cardioneuromodulation; d, distance; HR, heart rate; P-P, P-P interval; RFA, radiofrequency application; RSPV, right superior pulmonary vein; SN, sinus node; SNRTc, corrected SN recovery time; SVC/RA, junction between the superior vena cava and the right atrium; and TL, target line.

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Table 3. Ambulatory Electrocardiographic Data

	Baseline	Month 1		Month 6		Month 12	
	Rate	Rate	*P* value*	Rate	*P* value*	Rate	*P* value*
HR during standardized ECG registrations							
Basal HR, bpm	61 ± 11	82 ± 12	<0.001	75 ± 12	<0.001	73 ± 11	<0.001
HR after AT, bpm	97 ± 15	94 ± 15	0.24	93 ± 13	0.027	92 ± 12	0.004
Maximal HR during exercise							
All patients, bpm	158±19	148±19	<0.001	−	−	153±15	0.09
Mean HR during 24-h rhythm registration							
All patients, bpm	69±9	83±11	<0.001	81±11	<0.001	77±10	<0.001
Mean HR of different subgroups based on the mean HR at baseline, bpm							
<60	55 ± 5	76 ± 6	<0.001	76 ± 10	0.008	71 ± 11	0.035
60 to 69	65 ± 3	84 ± 13	<0.001	78 ± 10	0.001	77 ± 12	0.003
≥70	76 ± 5	86 ± 9	<0.001	84 ± 10	0.002	79 ± 9	0.14
Number of P-P intervals ≥1000 ms during 24-h rhythm registration							
All patients, bpm	23646 ± 17015	4816 ± 9277	<0.001	6391 ± 10537	<0.001	11 523 ± 13,684	<0.001
Number of P-P intervals ≥1200 ms during 24-h rhythm registration							
All patients, bpm	7094 ± 10,874	545 ± 2308	<0.001	1191 ± 3572	<0.001	2063 ± 5691	<0.003
HRV data							
SDNN-i, ms	80.7 ± 29.2	35.0 ± 22.9	<0.001	45.2 ± 23.8	<0.001	59.4 ± 50.9	<0.001
pNN50 (total), %	20.31 ± 15.2	4.30 ± 8.0	<0.001	6.5 ± 9.3	<0.001	9.3 ± 10.5	<0.001
HRV Index	47.8 ± 15.1	26.6 ± 10.1	<0.001	30.7 ± 11.4	<0.001	35.4 ± 12.4	<0.001
QT and QTc intervals							
QT, ms	437.4 ± 34.6	404.4 ± 35.4		399.2 ± 41.5		414.2 ± 32.5	
QTc, ms	393.3 ± 41.4	407.9 ± 29.6		397.6 ± 31.4		404.1 ± 32.5	

AT indicates atropine; bpm, beats per minute; HR, heart rate; HRV, heart rate variability; pNN50, the percentage of successive RR intervals that differ by >50 ms; and SDNN-i, mean of the standard deviations of all the NN intervals for each 5 min segment of the recording;

*****The data during follow-up are compared with the corresponding data at baseline.

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Figure Legends:

Figure 1. Computed tomography scan images (A to E) and electroanatomical map (F) indicating the region targeted during CardNM. (A) Red line delineating the mid- and caudal parts of the right superior pulmonary vein antrum in an anteroposterior projection. (B, C) Target line guiding CardNM indicated by the white line facing the first design line at the SVC-RA junction in a modified left anterior oblique (B) and cranial (C) projection. (D) Transversal slice at the mid-portion of the target line showing the location and thickness of the fat pad containing the ARGP at this level (blue asterisk). (E, F) Ablation tags along the target line in a posteroanterior CT scan view (E) and on the electroanatomical map (F) in the same projection after merging the two images. The region of the ARGP ablated is indicated by two green arrows. Each individual ablation is indicated using a colored tag. The phrenic nerve is tagged with black dots. CS indicates coronary sinus; IVC, inferior vena cava; LA, left atrium; RA, right atrium; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; and SVC, superior vena cava.

Figure 2. Syncope-free survival curves.

Figure 3. Syncope burden at 3, 6, and 12 months before and after cardio-neuromodulation Each patient is represented by a different color.

Figure 4. Basal HR and HR after atropine injection. Basal HRs are represented by red violin plots. Reset basal HR after ablation and 1 day later are represented by pale-red violin plots.

Corresponding HRs after atropine are shown by the blue and pale-blue violin plots. The median value is mentioned for each violon plot by a horizontal line. The number of patients involved ('X - X'), level of the median HR modification compared to baseline (%) are shown. HR acceleration (upward arrows) or deceleration (downward arrows) were all significant compared to baseline (P<0.001). The median basal HR at M6 and M12 was comparable with the post-procedural basal HR while the median basal HR at M1 was significantly higher (purple arrow; P<0.001). HR indicates heart rate; D, day; and M, month.

Figure 5. Mean HR during 24-h rhythm registration of patients with a mean HR at baseline under or above 70 bpm at baseline, M1, M6 and M12. The blue violin plots indicate patients with a mean HR at baseline <70 bpm and the light blue violin plots indicate these with a mean HR ≥70 bpm. The data are presented at baseline, M1, M6, and M12. The median values are indicated by the horizontal line in each violin plot. The level of HR acceleration compared to baseline is indicated in %. Significant values (P<0.001) compared to baseline are indicated by arrows. HR indicates heart rate; and M, month.

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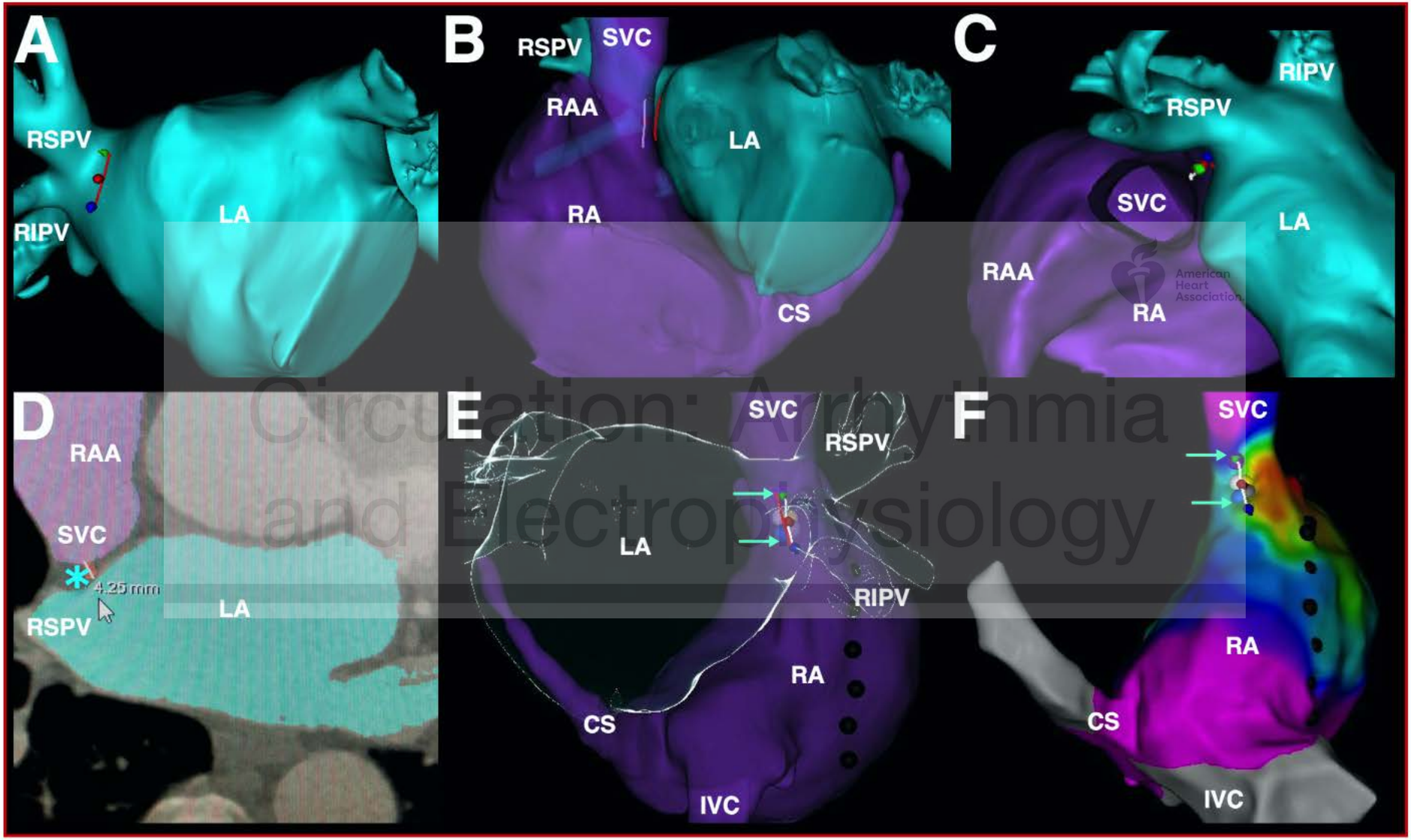
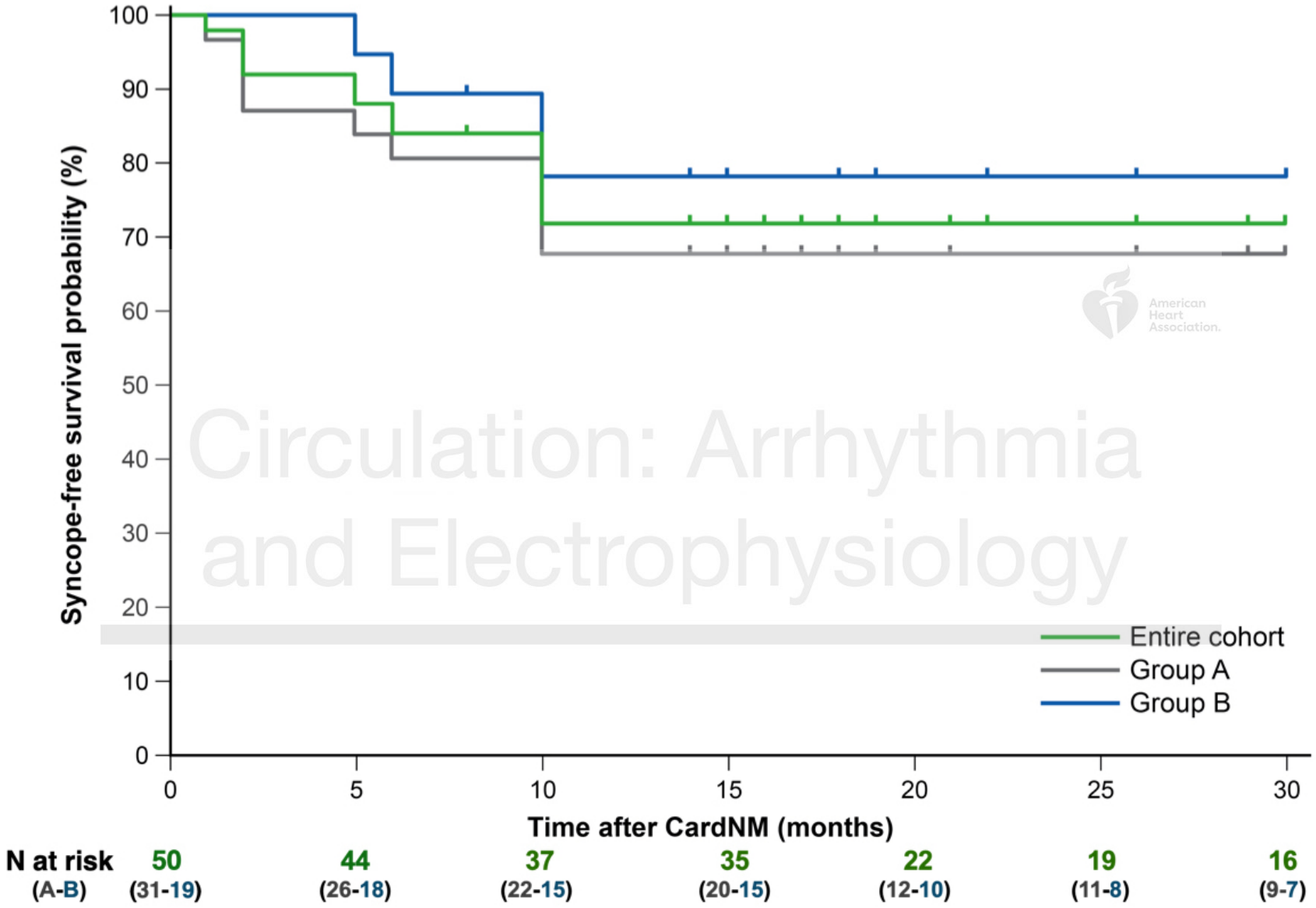
What Is Known?

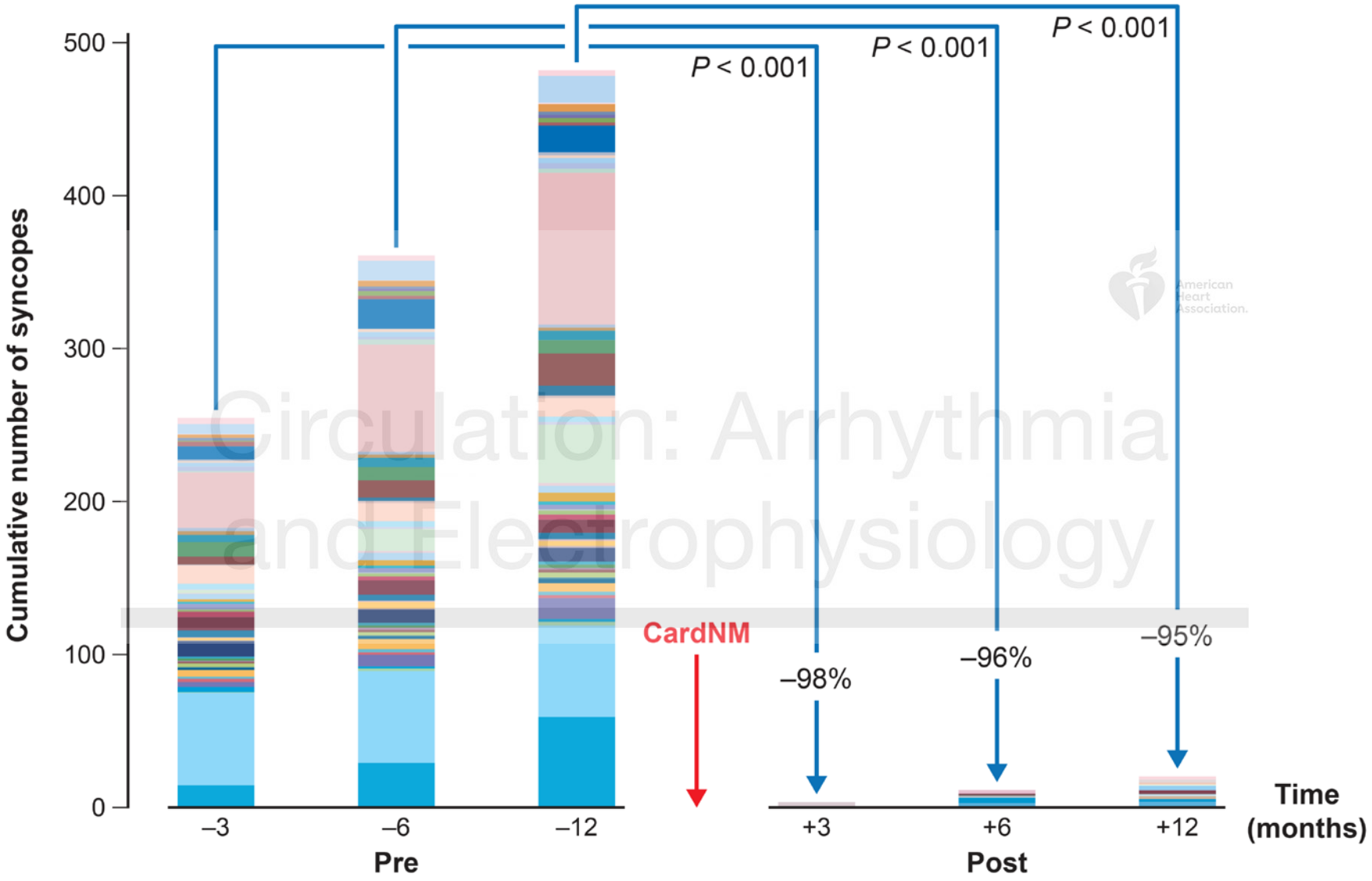
- In a prospective, open-label trial involving 50 patients with neurally mediated syncope or functional sinus node dysfunction, cardio-neuromodulation (CardNM) − through a right-sided and computed tomography-guided procedure – was safe and effective, giving rise to a long-term partial and adequate sinus node vagolysis.
- CardNM led to a good clinical outcome in most patients, with no apparent short- or long-term safety concerns or undesirable persisting modifications of the intrinsic cardiac autonomous nervous system.
- As the only ganglionated plexus targeted during CardNM is the anterior right ganglionated plexus, this particular type of cardioneuroablation has only a modest effect on atrioventricular node vagal innervation.

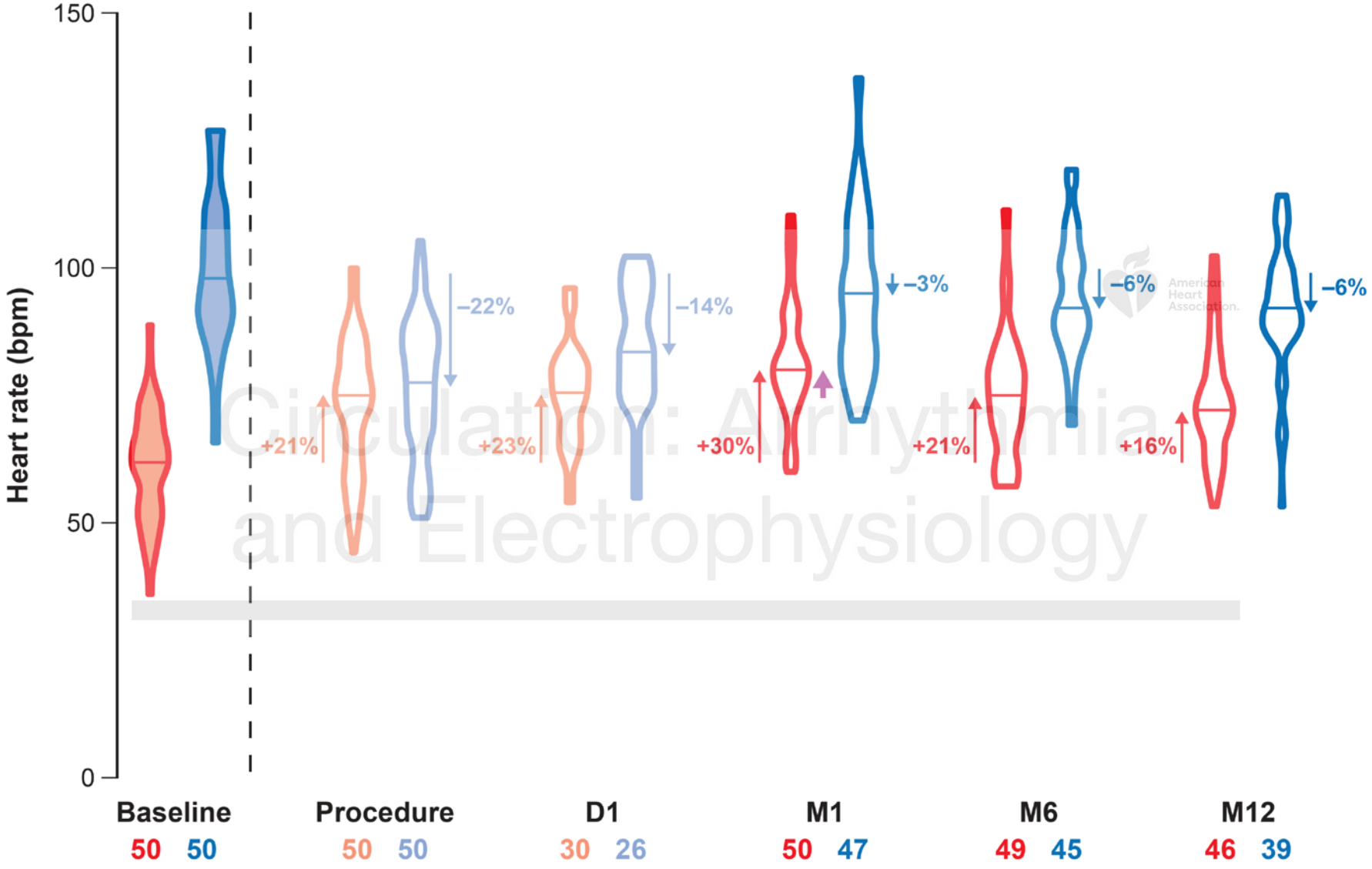
What the Study Adds?

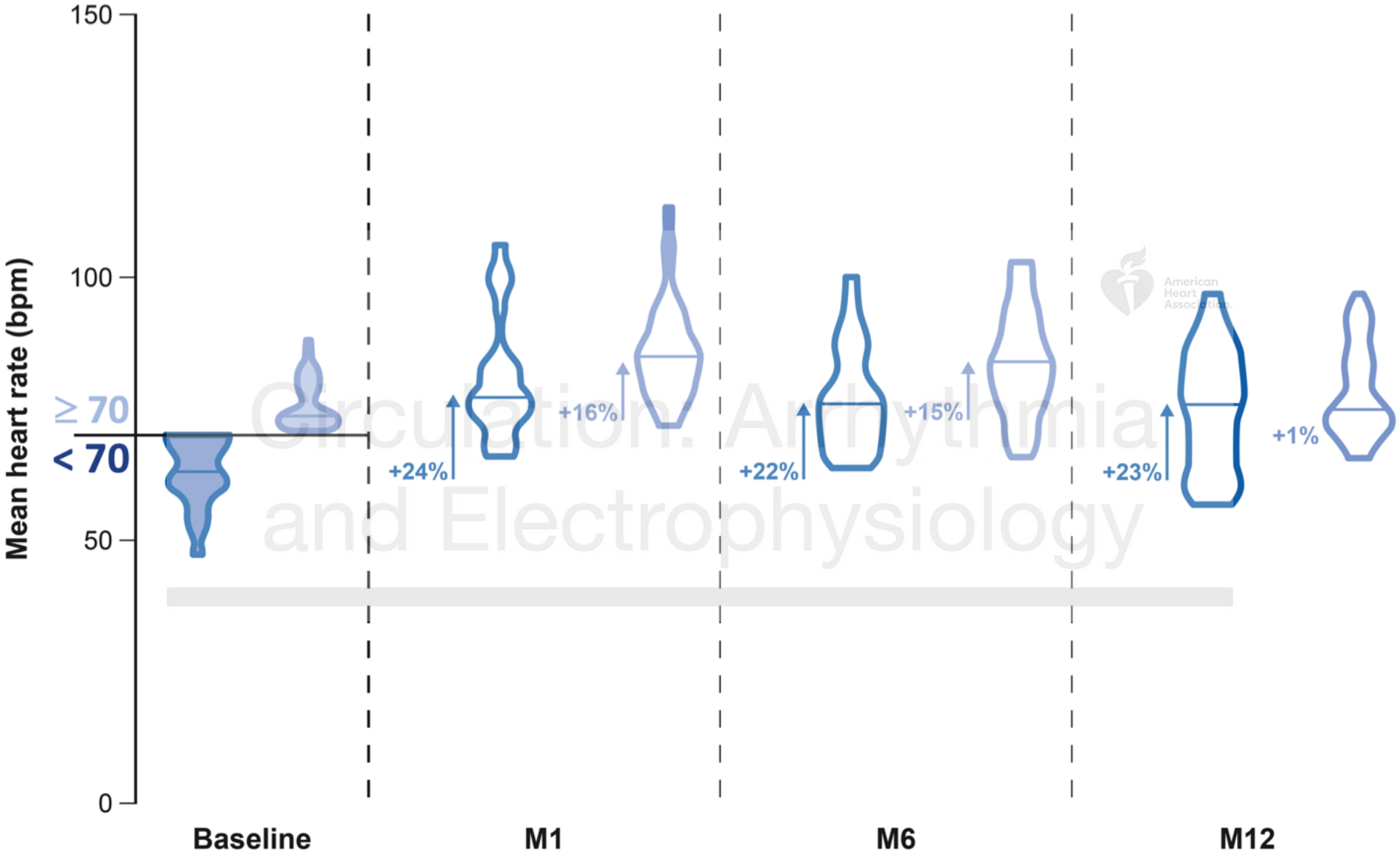
- CardNM is a fast procedure, exposing patients to fewer procedural risks than left-sided or biatrial multiple-site ablation strategies.
- Our data do not support the use of CardNM in patients with functional atrioventricular block.
- CardNM may offer a new, alternative treatment approach in patients with recurrent neurally mediated syncope with a VASIS type 1, 2A, or 2B response during the tilt table test.











Graphic Abstract