

Right atrial cardioneuroablation of asystolic reflex syncope

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ABSTRACT

BACKGROUND Cardioneuroablation (CNA) should focus on the vagal ganglia located in the right atrium close to the sinoatrial and the atrioventricular nodes.

OBJECTIVE The study aimed to evaluate the efficacy and safety of right atrial CNA.

METHODS Patients with severe, asystolic reflex syncope identified by implantable loop recorder (ILR) or tilt testing underwent right atrial CNA and were subsequently monitored using ILR.

RESULTS The population included 28 patients with a mean age of 40.5 ± 13.4 years, of whom 71% were men. Over a median follow-up period of 12.5 months, 8 patients experienced 44 episodes of asystole lasting longer than 3 seconds, as recorded by an ILR. The burden of asystolic episodes significantly reduced from 0.89 episodes per month before CNA (145 over 163 patient-months) to 0.11 episodes per month after CNA (44 over 397 patient-months), with a relative risk reduction of 0.12, $P = .0001$. Similarly, the burden of syncopal episodes decreased from 0.23 episodes per month before CNA to 0.06 episodes per month after CNA, resulting in a relative risk reduction of 0.24, $P = .0001$. Median heart rate increased from 75 bpm (interquartile range: 72–79) before ablation to 83 bpm (interquartile range: 78–85) after ablation, lasting up to 9 months post-procedure. No patients experienced complications during the procedure. During follow-up, 2 patients received pacemakers, 1 underwent a redo procedure, and 4 experienced mild transient symptoms: 3 had palpitations and 1 had dyspnea, none requiring therapy.

CONCLUSION Right atrial CNA reduced asystolic episodes by 88% and syncopal episodes by 76% during the mid-term follow-up. Adverse events were infrequent and mild.

KEYWORDS Asystole; AV node; Catheter ablation; Implantable loop recorder; Neurally-mediated syncope; Reflex syncope; Sinoatrial node; Syncope; Tilt testing

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Introduction

Cardioneuroablation (CNA) therapy for reflex asystolic syncope is becoming more popular.¹ However, there is only 1 small randomized controlled trial² and a few meta-analyses of small to moderate observational studies available.^{3,4} As a result, strong recommendations on CNA could not be made in a recent expert scientific statement.⁵ Assessing CNA's clin-

ical efficacy is challenging because of symptom variability, intermittent presentation, complex pathophysiology, and diverse treatment options. More systematic research, including randomized studies and standardized procedures, is needed to determine best practices and outcomes.⁵

The mechanism of action of CNA is quite like that of cardiac pacing because they both counteract the vagal outflow

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to the sinoatrial node and the atrioventricular (AV) node.⁶ Both therapies fail to counteract the vasodepressor reflex in the splanchnic region and vessels. Cardiac pacing is more effective when the cardio-inhibitory response dominates but less effective or ineffective when the hypotensive component prevails.^{7,8}

Most cholinergic fibers reach the human heart via the posterior and anterior right atrium.⁹ CNA should focus on the vagal ganglia located close to the sinoatrial and the AV nodes: specifically, the superior paraseptal ganglionated plexus (SPSGP), at the intersection of the interatrial septum and the superior vena cava and the inferior paraseptal ganglionated plexus (IPSGP), near to the ostium of the proximal coronary sinus (and around its ostium).¹⁰ Considering the mechanisms underpinning cardio-inhibition in vasovagal syncope, parasympathetic fibers firing on the sinoatrial node should be the preferred target for CNA in patients with treatment-resistant vasovagal syncope of cardioinhibitory type. This is because sinus arrest represents the predominant form of bradycardia form in these individuals. Additionally, ablation of parasympathetic fibers firing on the AV node should be performed especially in patients who exhibit vagally induced AV block. Based on these considerations, the SPSGP and the IPSGP represent key anatomical targets for CNA.⁶ These ganglia can be accessed by ablating in the right atrium only^{11,12} even if a bi-atrial ablation procedure seems to be necessary to achieve a more complete effect.¹³

In view of these premises, the study aimed to assess the efficacy and safety of right atrial CNA using continuous electrocardiography (ECG) monitoring in patients with asystolic reflex syncope.

Method

The multicenter, investigator-initiated, “proof of concept” clinical trial aimed to assess the effect of CNA in suppressing asystolic reflex pauses documented using continuous ECG monitoring with an implantable loop recorder (ILR). The study was conducted in 7 Italian hospitals, sponsored by GIMSI (Italian Multidisciplinary Group for the Study of Syncope), a non-profit scientific association, www.gimsi.it. The Ethical Committee of the centers approved the study. The research reported in this paper adhered to the Declaration of Helsinki as revised in 2013 guidelines.

Abbreviations

CNA: cardioneuroablation

HAFE: high-amplitude fractionated electrograms

HR: heart rate

HRV: heart rate variability

ILR: implantable loop recorder

IPSGP: inferior paraseptal ganglionated plexus

SPSGP: superior paraseptal ganglionated plexus

Study design

Patients who met the inclusion criteria received ILR implantation, underwent right atrial CNA ablation, and were then monitored continuously by the ILR for at least 6 months until the study ended in December 2024.

Inclusion Criteria:

- Age 18 to 60 years.

- Clinical diagnosis of reflex syncope as per class I criteria of the European Society of Cardiology guidelines.
- History of recurrent severe syncope (≥ 2 in the last year or ≥ 3 in the last 2 years), significantly affecting the quality of life.
- Documentation of ≥ 2 asystolic pauses > 3 seconds documented by ILR, with or without syncope or an asystolic syncope induced during tilt testing.

Exclusion Criteria:

- Intrinsic sinus dysfunction or AV node disease.
- Overt structural heart disease.
- Alternative diagnoses of syncope.

End points

The primary end point was the frequency of asystolic episodes per month detected through ILR monitoring before and after ablation.

The secondary end points were as follows: (1) the of syncopal episodes before and after ablation; (2) freedom from ablation-related complications during the follow-up period; and (3) the pattern of heart rate (HR) detected by ILR before and after ablation.

Follow-up

Asystolic episodes were monitored continuously by ILR throughout the study. Syncopal recurrences and complications post-CNA were assessed quarterly. Adverse events were assessed by a formal questionnaire that used the same classification used by Kulakowski and colleagues¹⁴ HR recorded by ILR was monitored for a 1-month period in the months before and after ablation and subsequently at 3-month intervals. HR was calculated as the median (with its interquartile range [IQR]) of the HR of each patient during each 30-day period. The PlotDigitizer (plotdigitizer.com) software^{15,16} was used to extract data from the graph images in numerical format. This software was employed to extract HR values from ILR graphs.

Ablation procedure

An anatomically guided approach with electrogram analysis of high-amplitude fractionated electrograms (HAFE) was used. Radiofrequency energy targeted 2 main ganglionic plexuses in the right atrium: the SPSGP and the IPSGP. Mapping and ablation were done under mild sedation and local anesthesia using commercially available catheters. Three right femoral vein punctures were performed: a decapolar catheter in the coronary sinus, an electrophysiological mapping catheter for creating a 3D electroanatomic map, and a quadripolar irrigated tip ablation catheter were inserted. Basal cycle length, AH interval, Wenckebach cycle length, and atropine test (0.02 mg/Kg intravenous) were evaluated before and after ablation. The ablation procedure used radiofrequency energy (43°, 30–35 W for 30–60 s) at right atrial sites likely containing ganglia clusters: near the superior vena cava and posterior right atrium junction, and between the inferior vena cava, coronary sinus ostium, and AV groove. Anatomical targets were

identified by HAFE with > 4 deflections, amplitude > 0.7 mV, and duration > 40 ms. To prevent phrenic nerve injury, high-amplitude stimulation was used before radiofrequency delivery to the superior right atrial ganglia. Because of the uncertain borders of the ganglionated plexus, multiple radiofrequency applications formed a cloud-like ablation around the HAFE tags. Each ablation lasted 30 to 60 seconds, continuing until HAFE was significantly reduced (< 0.05 mV) and any vagal reflex disappeared. As per protocol, the procedure sought to increase the sinus rate by over 20% or shorten the AH interval by more than 25% and suppress HAFE in the anatomical sites of ablation within 10 minutes of the final radiofrequency delivery. However, the decision to stop the procedure was left to the investigator's judgment. The AV node Wenckebach point was also assessed but it was not considered as a procedural end point. The atropine test (0.02 mg/kg intravenous) was assessed the day prior to and was repeated at the end of the procedure. However, its outcome did not affect the ablation procedure.

Statistical analysis

ILR monitoring in a comparable group of untreated patients with likely asystolic reflex syncope revealed a monthly incidence of 0.82 ± 0.67 asystolic episodes lasting > 3 seconds.¹⁷ A 50% reduction in monthly asystole episodes (> 3 s) among 24 ablation patients would reject the null hypothesis of no difference in pre- or post-ablation episodes with 80% power on a bilateral t test ($\alpha = 0.05$).

Continuous data were presented as mean $\pm$ standard deviation or median (25th–75th percentile). Normality was checked using the Kolmogorov-Smirnov method. Categorical data were compared using absolute and relative frequencies. Continuous variables were compared with an unpaired Student t test or Wilcoxon test if not normally distributed. The Wilcoxon matched pairs test was used for non-normally distributed continuous variables. Proportions were compared using Fisher's exact test, and the Kaplan-Meier technique was used to build the survival curve.

Results

The study included 28 patients who underwent right atrial CNA ablation, monitored by ILR (Table 1). Of these, 22 had ILR monitoring before the procedure for a median of 5.3 (2.8–11.2) months, whereas the remaining 6 chose simultaneous ILR implantation and ablation. Tilt testing was performed on 21 patients, determining eligibility in 15 cases (eg, asystolic syncope). Eligibility was confirmed by both ILR and tilt testing in 8 patients, by ILR only in 13, and by tilt testing only in 7. The median follow-up duration post-CNA was 12.5 (7.6–19.4) months.

Primary end points

During the follow-up, 8 patients had 44 episodes of asystole > 3 seconds recorded by ILR: 28 (64%) were type 1A, and 16 (36%) were type 1. The burden of asystolic episodes decreased from 0.89 episodes per month in 22 patients

Table 1 Clinical characteristics of the study population at enrolment

Clinical characteristic	Population (n = 28)
Mean age, yrs	40.5 $\pm$ 13.4
Mean age at first syncope, yrs	30.5 $\pm$ 13.3
Men	20 (71)
Syncope, median number during life (IQR)	6 (5–10)
Syncope, median number last 2 years (IQR)	4 (3–5)
Syncope, median number last year (IQR)	3 (2–3)
History of pre-syncope	16 (57)
Hospitalization for syncope	18 (64)
Syncope, severe trauma	7 (25)
Syncope, mild trauma	20 (71)
Antihypertensive medications	5 (18%)
ECG abnormalities	4 (14)
Mild structural heart disease	1 (4)
Orthostatic hypotension	4 (14)
Tilt testing:	
- performed	21 (75)
- positive response	17/21 (81)
- asystolic response	15/21 (71)
- mean asystole duration, s	21.1 $\pm$ 19.9
Implantable loop recorder before CNA:	
- performed	22 (79)
- median duration of ILR monitoring, IQR	5.3 (2.8–11.2)
- asystolic episodes	21/22 (95)
- total number of asystole episodes	145
- type 1A	84 (58)
- type 1B	56 (39)
- type 1C	5 (3)
- mean number of asystolic episodes per patient	6.6 $\pm$ 6.1
- mean longest asystole duration, s	11.5 $\pm$ 7.4

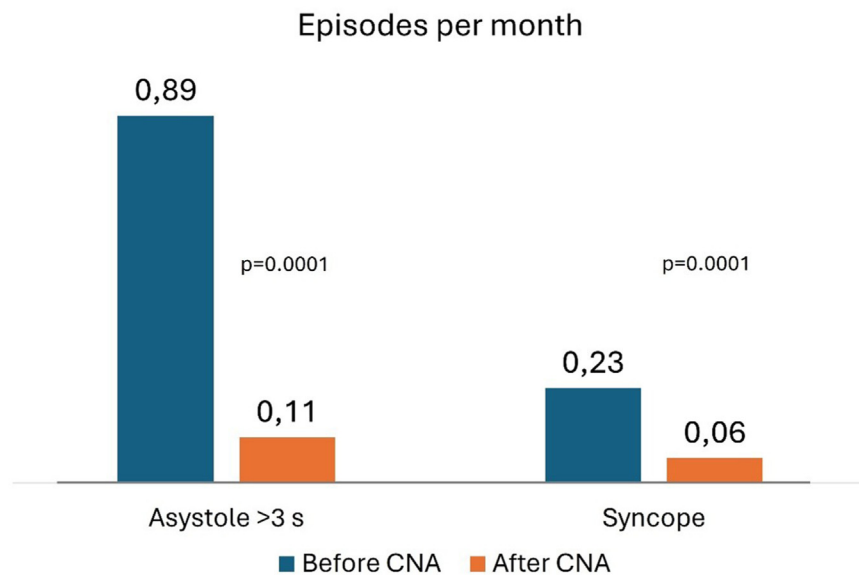
Values are n (%) and continuous variables are given as mean $\pm$ standard deviation.

CNA = cardioneuroablation; ECG = electrocardiogram; ILR = implantable loop recorder; IQR = interquartile range.

before CNA (145 episodes in total 163 patient-months of follow-up) to 0.11 episodes per month in 28 patients after CNA (44 episodes in total 397 months of follow-up), relative risk reduction (RRR) 0.12 (95% confidence interval [CI] 0.09–0.17), $P = .0001$ (Figure 1).

Two sensitivity analyses yielded similar results. In the intra-patient comparison, performed in the 22 patients who had ILR recording both before and after CNA, asystolic episodes > 3 seconds decreased from 0.89 episodes per month (145/163 patient-months) to 0.14 episodes per month (44/318 patient-months), RRR 0.16 (95% CI 0.12–0.21), $P = 0.0001$. In the intra-patient comparison of individual data, the median burden of asystolic episodes > 3 seconds decreased from 0.95 (IQR 0.53–1.39) per month before CNA to 0.0 (IQR 0.0–0.19) after CNA, $P = 0.0001$.

The burden of asystolic episodes decreased also in the 8 patients who had recurrences of asystolic episodes > 3 seconds after CNA from 0.92 episodes per month before (76/83 months) to 0.29 episodes per month (44/151

**Figure 1**

Monthly burden of asystolic and syncopal episodes before and after CNA procedure. CNA = cardioablation.

patient-months) after, RRR 0.32 (95% CI 0.25–0.41), $P = 0.0001$.

No clinical or electrophysiological variable was able to predict the recurrence of asystolic pauses (Supplemental data Tables S1 and S2).

Recurrence of syncope

During the follow-up, 9 patients had recurrence of 22 episodes of syncope, of whom 18 (82%) were associated with the ECG documentation of asystole > 3 seconds and 4 (18%) did not. One patient had only non-asystolic syncope (#3 episodes) and another had both asystolic and non-asystolic syncope. The burden of syncopal episodes decreased from 0.23 episodes per month in the year before CNA (78/336 patient-months) to 0.06 episodes per month

after CNA (22/397 patient-months), RRR 0.24 (95% CI 0.15–0.37), $P = 0.0001$ (Figure 1). The burden of syncopal episodes after ablation decreased also significantly when compared with that of the previous 2 years before ablation (0.18 episodes per month, 117/648 patient-months), RRR 0.31 (95% CI 0.20–0.48), $P = 0.0001$. In the intra-patient comparison of individual data, the median syncope burden was 0.25 (IQR 0.53–1.39) per month in the year before CNA and decreased to 0.0 (IQR 0.0–0.07) after CNA, $P = 0.0001$. The Kaplan-Meier survival curve is shown in Figure 2. The estimated recurrence rate of syncope was 15.6% (95% CI 7.6–23.6) at 1 year and 27.7% (95% CI 14.7–30.7) at 2 years.

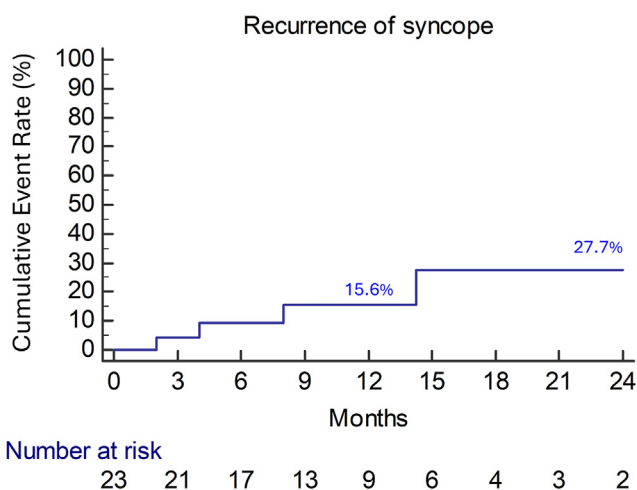
A 32-year-old patient with persistent sinus bradycardia and pre-ablation blunted atropine response experienced recurring symptoms after ablation with no HR increase. Three patients who underwent only superior paraseptal ganglia ablation had no recurrence during follow-up. Another patient, requiring additional left-side ablation because of unsatisfactory right-side results, also remained symptom-free during follow-up.

HR

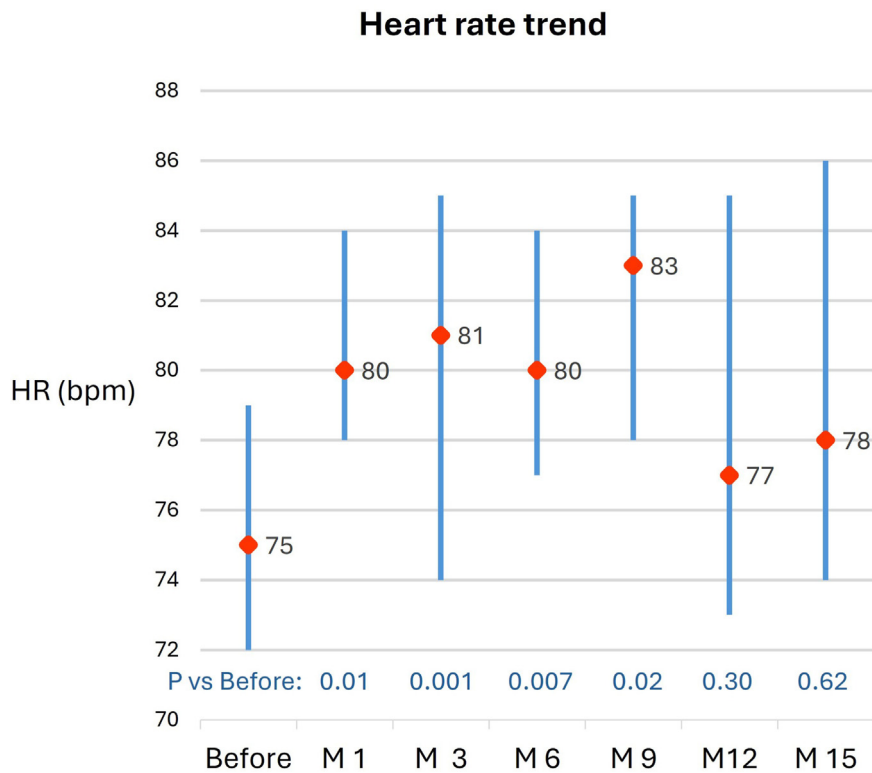
A monthly assessment of HR was conducted before and after ablation for up to 15 months (Figure 3 and Figure 4). Following ablation, there was a significant increase in HR from 75 bpm (IQR: 72–79) before ablation to 83 bpm (IQR: 78–85), which persisted up to 9 months before showing signs of attenuation. HR was unable to predict the recurrence of asystolic pauses (Supplemental data Table S2).

Adverse events

No patients experienced periprocedural complications. Three patients had paroxysmal atrial fibrillation during the

**Figure 2**

Kaplan-Meier estimated recurrence rate of syncope after CNA. CNA = cardioablation.

**Figure 3**

Heart rate (HR) trend. HR is reported as the median (red bullets) and interquartile range (blue vertical lines) over 30-day periods: the month before ablation, the month immediately after ablation (M1), and months 3 (M3), 6 (M6), 9 (M9), and 12 (M12). Monthly HR is the median HR (with its interquartile range) of each patient over 30 days. The Wilcoxon matched-pair test compared intra-individual values.

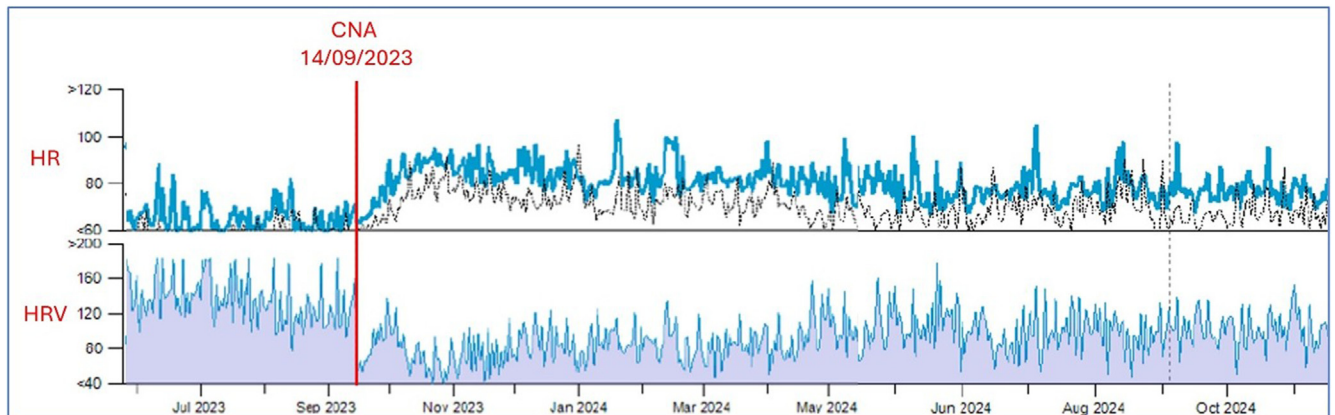
procedure. During the follow-up, 7 patients encountered adverse events related to CNA (Table 2).

Discussion

The study demonstrates that endocardial ablation in the right atrium, targeting areas near the sinoatrial and AV nodes, is effective in treating asystolic reflex syncope. This treatment reduced the burden of asystolic episodes by 88% during the

mid-term follow-up. Consequently, the burden of syncopal recurrences was reduced by 76% compared with the previous year and 69% compared with the 2 years before. Most patients remained symptom-free, with few mild adverse events. Right atrial CNA is a simple and safe procedure.

CNA reduced vagal activity, resulting in an immediate increase in HR, which lasted up to 9 months before gradually decreasing. This finding aligns with most studies in the literature.^{5,6} No correlation was found between changes in acute

**Figure 4**

A 47-year-old man with ILR-documented asystolic syncope of 6 seconds showed a rapid HR increase and heart rate variability (HRV) decrease after ablation. Peak variations were observed after 2 months, gradually reducing over the next year but still present after 14 months. CNA = cardioneuroablation; HR = heart rate; ILR = implantable loop recorder.

Table 2 Adverse events during the follow-up (according to the Kulakowski classification¹¹)

Adverse event	Population (n = 28)
Redo CNA	1
Pacemaker implantation	2
Transient dyspnea	1
Chronic chest pain	0
Decreased exercise capacity	0
Transient palpitations (< 3 months)	3
Persistent palpitations	0

CNA = cardioneuroablation.

electrophysiological parameters or HR with syncopal recurrences. Therefore, the causal relationship between ECG, electrophysiological effects of ablation, and clinical efficacy remains unresolved.

Few studies on CNA that have been verified by an ILR. Quintal and colleagues¹⁸ performed ILR follow-ups in 15 patients who had received CNA of the right ganglia for various diseases. Among the 4 individuals with indications for vasovagal syncope, 1 experienced a recurrence of syncope accompanied by an asystolic pause of 10 seconds, while another had an asymptomatic pause of 3 seconds. Joza and colleagues¹⁹ extensively ablated the right and left ganglia in 6 vasovagal syncope patients with documented asystolic pauses and implanted an ILR post-ablation. Despite a significant reduction in syncope, 2 patients experienced syncopal recurrence with long pauses recorded by ILR. It is crucial to objectively monitor patients after interventions for asystolic syncope. Previous studies have been criticized for not objectively assessing syncopal events or detecting less symptomatic pauses post-CNA. In 2 meta-analyses of observational studies,³ that virtually cover all the existing literature, the recurrence rate of syncope widely ranged from 0% in some studies to up to 30% in others. Such variability indicates a lack of standardized follow-up assessment, beyond differences in expertise or technique. Certainly, the lack of a sham control group and the unblinded nature of the studies are important factors to consider.⁶ More objective monitoring with ILRs would be a potential compromise for these concerns in future studies.

The difficulty of obtaining precise follow-up data in patients with intermittent symptoms is well known. A reassessment of the CNA field has been suggested.²⁰ Some placebo effects and the spontaneous reduction of syncopal recurrences in untreated patients have been supposed.^{21–23} A metaanalysis of the 17 studies showed a 64.6% absence of syncopal recurrences within a year after the index visit.²³ Continuous ECG monitoring with ILR reduces the risk of expectation bias for both patients and physicians.

It is challenging to compare right atrial ablation with other ablation techniques targeting the left atrium because there are few ILR studies. In the small study of Joza and colleagues,¹⁹ who performed extensive ablation of right and left ganglia, asystolic events documented by ILR recurred in

33% after ablation despite a great reduction in syncope burden which was of similar magnitude to that found in the present study. In the surrogate analysis of syncopal recurrences, a bi-atrial ablation procedure may be required to achieve a more comprehensive effect.¹³ A greater efficacy of bi-atrial ablation is reported in the metaanalyses, but it may be misleading because of the substantial heterogeneity of the data.³ Syncopal recurrences rate higher than 15% were reported with both right^{11,12} and bi-atrial ablation.^{14,24,25}

Because the mechanism of action of CNA is quite similar to that of cardiac pacing⁶ we can expect similar clinical results. In a meta-analysis of 4 studies, the patients with similar characteristics to those of the present study who had documented asystolic syncope treated with dual-chamber rate-drop pacemakers had a 13% recurrence rate at 1 year and 21% at 2 years.^{6,7} Another study on tilt-positive asystolic forms reported 19% recurrence at 1 year and 22% at 2 years.²⁶ These figures are consistent with the 15.6% and the 27.7% rate observed in the present study (Figure 2). The present study and pacemaker studies show that while selecting patients with cardio-inhibitory syncope can reduce syncopal recurrences, it cannot completely prevent them because of the common occurrence of a hypotensive reflex in nearly all patients.^{26,27} Future studies should prioritize the syncope burden over the recurrence-free rate.

In controlled studies with untreated patients who had clinical characteristics similar to those in the present study, the normalized syncope recurrence rate at 1 year was 54% in the control arm of the ROMAN trial on CNA,¹³ 53% in the control arm of the benefit of dual-chamber pacing with closed loop stimulation trial on cardiac pacing,^{13,26} 60% in the SPAIN trial on cardiac pacing,²⁸ and 37% in the International study of syncope of unexplained origin trial on ILR.^{28,29} Thus, assuming a 50% syncope recurrence rate in untreated patients, right-sided CNA could reduce this rate to 15%, a 70% relative reduction.

Adverse events were rare with no periprocedural complications. The lack of periprocedural complications is in contrast with the finding of Piotrowski and colleagues¹³ who observed some complications in 6 of 20 patients undergoing right atrial ablation: persistent nodal rhythm, phrenic nerve damage, earliest sinus node activation. One possible explanation, apart from the chance because of the small population, may be the more extensive method used for ablation by Piotrowski's study¹³ which was targeted to achieve complete vagal denervation guided by extra-cardiac vagal stimulation under general anesthesia.³⁰ Previous studies using a method like that of the present study reported no periprocedural complication.^{11,12,31} During follow-up, mild complications occurred in 4 patients (14%): 3 had transient palpitations requiring no therapy, and 1 had transient dyspnea. We used the same definition of side effects that were used by Kulakowsky and colleagues¹⁴ in 115 patients who had undergone bi-atrial ablation technique: 5% experienced dyspnea, 3% had chronic chest pain, 12% had decreased exercise capacity, 27% had

transient palpitations, and 7% required long-term drug therapy for persistent palpitations. Similarly, a high rate of transient and persistent symptomatic tachycardia requiring long-term rate-control drug therapy has been reported by others with bi-atrial ablation.³² In general, avoiding the complications of a left atrial approach makes right atrial ablation considered safer than bi-atrial ablation.⁵ Additionally, there is concern about potential long-term harm from extensive bi-atrial vagal denervation of cardiovascular function.^{5,6,21} Extensive CNA may potentially alter the autonomic balance to a state of sympathovagal imbalance with attenuation of cardiac parasympathetic activity. This condition is associated with adverse cardiovascular events and higher mortality in patients with cardiovascular autonomic neuropathy because of diabetes mellitus and in those with myocardial infarction and congestive heart failure.^{5,33–35} Chronic sympathovagal imbalance may also influence various cardiovascular disorders, including atrial and ventricular arrhythmias.^{5,21,36,37} Animal studies indicate that extensive CNA significantly reduces vagal tone, which protects against ventricular arrhythmias in structurally diseased hearts and increases the risk of sudden death.^{36,37} In an animal model of hearts with coronary artery disease, spinal cord stimulation is associated with a reduction in arrhythmia inducibility, because of decreased sympathetic activity and increased vagal activity.³⁸ From a prudential perspective, the partial vagal impairment achieved by right atrial ablation may attenuate these long-term risks by preserving some level of autonomic balance.³⁹

In summary, bi-atrial ablation may be more effective but increases adverse events. We gave preference to the simplicity and safety of the ablation procedure by avoiding the more complex and potentially harmful left atrial ablation and complex intra-procedural electrophysiological tests such as extra-cardiac vagal stimulation.^{5,30}

Limitation

The lack of a control group and small sample size limit result accuracy. The follow-up period was too short to demonstrate long-term efficacy and safety of CNA. A larger sample might show more consistent effects on HR. One patient required a redo procedure because of the recurrence of asystolic syncope. The effectiveness of redo procedures, similar to redo cases in patients with atrial fibrillation, should be evaluated in future studies. We could not identify clinical, ECG, or electrophysiological predictors of failure. A larger population might help identify some predictors.

Conclusion

Right atrial CNA was able to reduce by 88% the burden of asystolic episodes and by 76% the burden of syncopal episodes, thus proving the pathophysiological concept that endocardial ablation at the site of the right atrium, corresponding to the anatomical location of the epicardial vagal ganglia located close to the sinoatrial and AV nodes, is effective

in counteracting asystolic vagal reflexes. Right atrial CNA is a simple and safe procedure.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2025.05.038>.

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Data Availability: The datasets generated during and/or analyzed during the current study are available upon reasonable request.

Ethical Approval: Ethical approval was obtained from participating centers. Pre-registered Clinical Trial Number. [ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT05751330.

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