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Cardioneuroablation as a strategy to prevent pacemaker implantation in young patients with vasovagal syncope

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ABSTRACT

Background: Cardioneuroablation (CNA) is an ablation technique that targets epicardial ganglionic plexi to reduce syncope burden and avoid pacemaker implantation in patients with cardioinhibitory vasovagal syncope (VVS). This study aims to demonstrate feasibility and safety of CNA in high-risk refractory VVS patients using continuous monitoring with an implantable loop recorder (ILR).

Methods: Data was collected prospectively for patients undergoing CNA. Patients were required to have recurrent syncope with documented asystole, refractory to conservative measures. Ganglionic plexi (GPs) were identified by fragmented signals and high frequency stimulation (HFS). Ablation was performed until loss of positive response to HFS, Wenckebach cycle shortening was achieved, or an increase in sinus rate of > 20 bpm. Follow-up was performed through remote and clinic follow-up of their ILRs.

Results: Between December 2020 and July 2023 six patients (mean age 29 $\pm$ 3, 67 % female) underwent CNA. The baseline heart rate and Wenckebach cycle length was 63.2 $\pm$ 15 bpm and 582 ms before and 91 $\pm$ 5 bpm and 358 ms after ablation respectively. During a median follow-up of 13.4 months, 3/5 patients had no further syncopal episodes, 1 had a recurrence, underwent repeat CNA with no further episodes at 1 year, and 1 had 5 syncopal events, which was a dramatic reduction from nearly daily episodes pre-CNA. There were no procedure related complications.

Conclusions: A dramatic reduction in documented pauses and syncope burden was noted post CNA. Appropriate patient selection with rigorous objective follow-up in an experienced center is necessary. Larger studies are required to confirm these findings.

1. Introduction

Although vasovagal syncope (VVS) is classically considered a benign disease, a proportion of patients with cardioinhibitory-type will have recurrent and often-times dramatic presentations [1]. In patients with documented asystole during head up tilt table testing (TT), up to 62.5 % will experience recurrent syncope despite avoidance of triggers, adequate hydration, and physical counterpressure maneuvers [2]. This is not surprising given that the vagal reflex is brief and transitory and any tonic intervention would not necessarily prevent an occasional autonomic destabilization [3]. No robust data indicate much benefit of these recommendations or any effective pharmacological approach beyond midodrine which has been found to reduce syncope in VVS, but not specific to the cardioinhibitory subtype [4].

The mechanism of spontaneous VVS documented by implantable loop recorder (ILR) is reproducible within patients [5,6], and was found to be asystole in approximately half of syncopal events in the International Study on Syncope of Uncertain /Etiology 2 (ISSUE 2) study [7]. There is clearly no rationale for pacing in patients without asystole in whom the likely mechanism for VVS syncope is a dominant hypotensive reflex, however in those with documented asystole, dual-chamber pacing has been shown to be effective in reducing syncope with an absolute risk reduction of 32 % [8]. Pacing in order to prevent asystole during VVS in those > 40 years of age is reflected within the guidelines as a class IIa (ESC) or IIb (ACC/AHA/HRS) indication [9,10]. This is primarily based on the results of the SPAIN study (Closed Loop Stimulation for

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Neuromediated Syncope) which confirmed a 72 % reduction in ≥ 50 % of patients during DDDR-closed loop stimulation (CLS) pacing as compared to 28 % in the placebo arm[11].

Certainly, a select population with recurrent and frequent episodes of syncope may benefit from pacing, however this therapy may be relatively aggressive in the presence of an alternative treatment particularly in a younger population. Lifelong implantable pacemaker therapy and required generator and lead revisions over the course of a lifetime must be considered. Cardioneural ablation (CNA) is a novel endocardial catheter-based technique that targets the parasympathetic ganglionic plexi surrounding the right and left atria to decrease vagal innervation to cardiac tissue. Previous studies examining the effect of cardioneural ablation have not had continuous long-term monitoring to document recurrent pauses [12,13]. There has also been no previous publication of redo ablations. Further, larger studies have evaluated ganglionic plexi ablation in patients with paroxysmal AV block, but in the context of concomitant atrial fibrillation (AF) where patients were already undergoing an AF ablation procedure [14].

This study examines the outcomes of a cohort of high-risk young patients admitted with traumatic syncope from documented prolonged pauses in whom CNA was chosen in an effort to avoid pacemaker implantation, and in which objective follow-up was performed by ILR.

2. Methods

2.1. Study population

The study population included all patients under the age of 40 who underwent cardioneural ablation between December 2020 to the present, and who met specific criteria: i) patients were required to have experienced at least 2 traumatic syncopal events that occurred with little or no prodrome; ii) a documented prolonged sinus pause, or day-time complete heart block with prolonged pauses correlating with symptoms; iii) pacemaker implantation was otherwise indicated after electrophysiological consult; iv) a complete work-up including physical exam, neurological assessment, cardiac and brain imaging, and monitoring was required in all patients to rule out secondary or reversible causes of syncope; and v) failure of non-invasive strategies in the management of VVS. Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the McGill University Health Center's human research committee.

2.2. Cardioneural Ablation: Procedural details

The risks, benefits, and alternatives to the procedure were outlined, and consent was obtained. Prior to anesthesia, all patients were given 2 mg of atropine, where the heart rate response was noted. The procedure was performed under general anesthesia, whereafter right femoral venous access was obtained. All baseline electrocardiographic measurements were taken prior and after anesthetic induction. A duodecapolar catheter was advanced with its tip at the distal coronary sinus. Intracardiac echo was used to guide transeptal puncture, create an anatomic shell, and visualize intracardiac structures and mapping/ablation catheters. Heparin was initiated for a target ACT of 350–400, and transseptal puncture performed using a small-curve steerable catheter and Baylis needle. An electroanatomic map of the left and right atrium were created using a multi-electrode mapping catheter, evaluating the voltage throughout (>1.5 mV indicating healthy voltage), and indicating any regions of fractionation (CARTO; Biosense Webster Inc). As per Aksu et al., the presence of fractionation was divided into low-amplitude fractionated electrograms (LAFE) demonstrating deflections ≥ 4 and amplitude < 0.7 mV, and high-amplitude fractionated electrograms (HAFE) demonstrating deflections ≥ 4 and an amplitude ≥ 0.7 mV [15,16]. An irrigated ablation catheter with a 3.5 mm tip (SmartTouch; Surroundflow-Biosense Webster Inc.) was then advanced into the left atrium (LA) for pacing and ablation.

The left superior pulmonary vein (LSPV) GP, located anteriorly and superiorly to the left superior PV was targeted first. High frequency stimulation (HFS) from the ablation catheter (60 ms delivered for 4 s at 20 mA and 2 ms pulse width) was delivered at a site of increased fractionation within the GP region. A GP location was identified if a prolongation of the R-R interval was observed upon termination of pacing. If the HFS did not result in a vagal response, further HFS was performed in the vicinity. If no HFS was noted, then ablation was performed guided by the presence of fractionation.

Radiofrequency energy was delivered with a power of 40–45 Watts targeting an ablation index (AI) of 400–420 on the roof, 450–500 on the ridge or left atrial septum, and 350 on the posterior wall. Vagal response during ablation was noted. Consolidation lesions were given at the immediate surrounding region and HFS was repeated post ablation to determine if the vagal response could still be elicited in that particular GP region. This method of HFS, ablation, and re-HFS was repeated at each of the known GP sites in the following order (see Figure 1): Left superior pulmonary vein (LSPV-GP) located anteriorly and superior to the LSPV, Marshal tract GP located at the Marshal ridge, and the left inferior PV (LIPV-GP) located 2–4 cm inferior to the left inferior PV. The catheter was then withdrawn into the right atrium where an electroanatomic and sinus activation map were created. HFS, localization of fractionation, and ablation were then performed at the posteromedial GP (located posterior to the coronary sinus os extending in the direction of the lower aspect of the LA), superior-vena cava (SVC)-aortic GP moving down to the septal GP region (right sided extension of the SVC-aortic GP), then proceeding back to the LA at the interatrial septum (anterior to the right superior and inferior PV), and right inferior GP (2–4 cm inferior to the posterior right inferior PV) were targeted.

2.3. Endpoints

After each GP region ablation set, a Wenckebach cycle length was performed. If the indication for cardioneural ablation was AV block, then a 1:1 AV conduction result at < 350 ms during general anesthesia was acceptable for procedure termination. In this circumstance, no further ablation was performed in the GPs innervating the AV node, however further ablation at the SVC-aortic GP was targeted if the sinus rate remained < 60 bpm. At the end of the procedure, all intervals were collected. Atropine 2 mg was given. A lack of heart rate increase was consistent with a positive response.

2.4. Follow-up

Baseline demographic and imaging data was collected at time of CNA. All patients underwent insertion of an ILR for long-term monitoring. The ILR was set to identify any pauses > 3 s or bradycardia < 40 bpm. All patients were followed remotely in addition to routine in-clinic visits at 1–2 weeks post insertion and every 6 months thereafter. All syncopal events were recorded, in addition to any correlating or non-correlating bradycardias, pauses, and tachyarrhythmias. Intra- and post-procedural complications were collected including vascular site complications, heart block, pericardial effusion/tamponade, stroke/TIA, esophageal fistula, and pericarditis in addition to the presence of inappropriate sinus tachycardia during follow-up.

2.5. Statistical analysis

Categorical variables were presented as frequencies and percentages, and continuous variables as the mean and standard deviation (SD), as well as median and inter-quartile range (IQR).

3. Results

A total of 6 patients underwent urgent CNA between December 2020

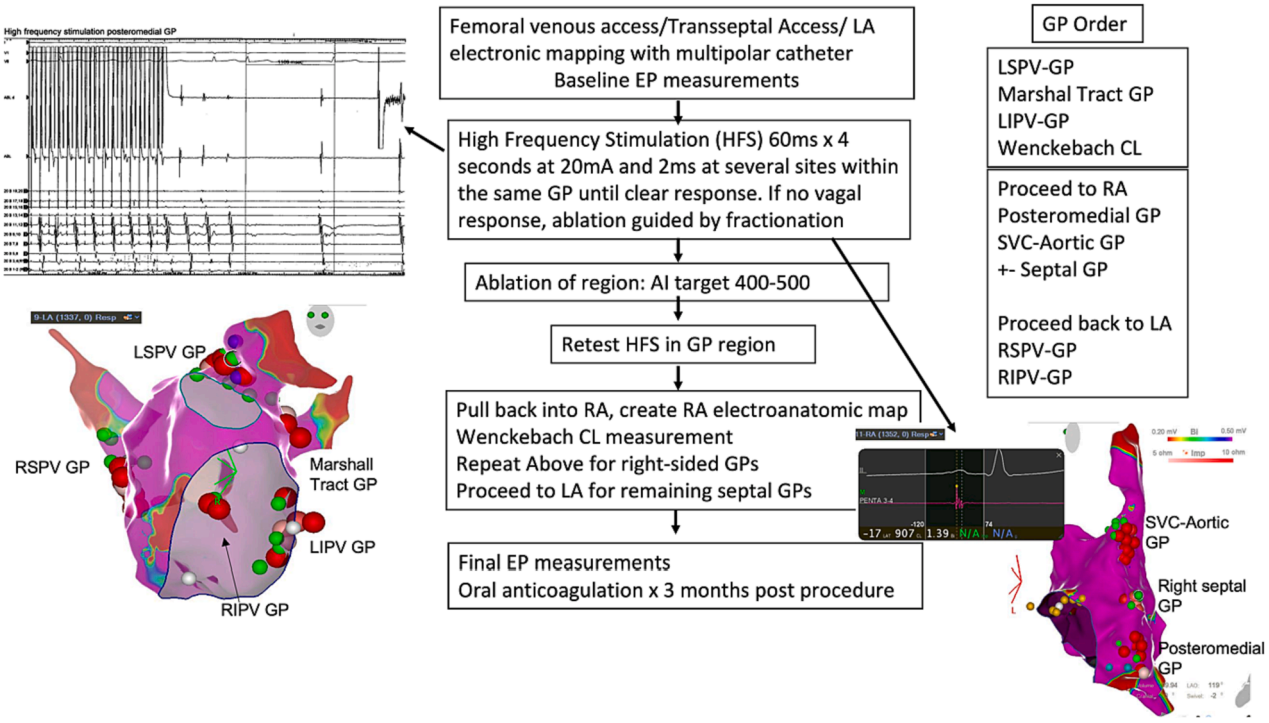

Fig. 1. Workflow of the CNA procedure.

and June 2022. All 6 patients were referred for pacemaker implantation. The mean age of the patients was 29 ± 4 years and 67 % were female (see Table 1). Two of the six patients underwent CNA as inpatients given the severity of the trauma incurred during syncope in combination with a documented very prolonged pause (≥20 s) for which one underwent insertion of a temporary pacing wire. The four remaining patients underwent CNA as outpatients on a more urgent basis after demonstration of recurring prolonged pauses on ILR despite attempt at conservative measures. One patient had undergone tilt table testing with a negative result (no bradycardia or syncope was induced).

Table 1
Baseline patient and procedural characteristics.

	Patients (n = 6)
Mean age (years)	29 ± 4
% Female	67 %
Median time from first documented syncope (months)	6 (IQR 3.1,78)
Mean number of syncopal events pre-ablation	14 (±7.2)
Average longest documented pause (seconds)	15.8
Type of pause	
AV block	2
Sinus pause	2
Mixed: AV block and sinus pause	2
History of atrial fibrillation	0
Vagal slowing during HFS or ablation	
Left atrium	
-LSPV-GP	6/6
-Marshall Tract-GP	6/6
-LIPV-GP	5/6
-RSPV-GP	2/6
-RIPV-GP	2/6
Right atrium	
-Posteromedial GP	0/6
-Right interatrial septum-GP	0/6
-SVC-aortic GP	0/6
Mean number of ablation lesions	
Left atrium	
-LSPV-GP-Marshall Tract-GP	5.52.8
-LIPV-GP	3.6
-RSPV-GP	4
-RIPV-GP	2.2
-Posteromedial GP	5
-SVC-aortic GP	4.7
-Right interatrial septum-GP	2
Atrial fibrillation induced during procedure	4/6
Cardioversion required intra-procedure for sustained AF	2/4

Legend: CNA: cardioneural ablation; GP: ganglionic plexus; LSPV-GP: left superior pulmonary vein-GP; LIPV-GP: left inferior pulmonary vein-GP; SVC-aortic GP: superior vena cava-aortic GP; RSPV-GP: right superior pulmonary vein GP; RIPV-GP: right inferior pulmonary vein GP.

The indication for CNA was asystole due to sinus pause in 2, AV block with pause in 2, and both AV block and sinus pause in 2 others. The average length of the longest documented pause was 15.5 s (10–22 s). The mean number of syncopal events pre-CNA was 14 (±7.2) where 4/6 patients reported a very short prodrome prior to syncope and sustained a traumatic fall. The median time from the very first syncopal event experienced was 6 months (3.1, 78).

3.1. Procedural results

All patients underwent ablation under general anesthesia, and all patients underwent mapping and ablation of both right and left atria. The median procedure time was 92 min (IQR 86,99) with a mean number of ablation lesions of 28.8 (Table 1). The mean baseline heart rate pre-anesthesia was 62 ± 14 bpm and post CNA was 89 ± 6 bpm. The mean Wenckebach cycle length at baseline was 645 ± 97 msec, mid-procedure 496 ± 32 msec and post CNA 361 ± 47 msec. The mean corrected sinus node recovery time (cSNRT) was 2.5 ± 0.9 sec and post 0.7 ± 0.5 sec.

All patients demonstrated vagal slowing during HFS at the LSPV-GP, the Marshall Tract-GP, and 5 of 6 patients at the LIPV-GP. Only 2 patients (patient 5 and 6 with pure AV block pauses) were found to have a vagal response during ablation at the RSPV-GPs. Post CNA, atropine was given to all patients, where no patient had an increase in heart rate greater than 2–3 bpm.

3.2. Follow-up

The median follow-up post CNA was 12.7 months (IQR 7.2,16.9).

The mean daytime HR at 0–3 months post CNA as derived from trends from the ILR was 81 ± 10 bpm, at 3–6 months it was 80 ± 8 bpm and at 6–12 months was 78 ± 9 bpm. The nighttime HR trend on ILR was 51 ± 2.9 bpm (in the only 3 patients who had an ILR capable of giving night-time trends and had an ILR pre-CNA). The night-time heart rate-trend in the 4 patients with an ILR capable of giving night-time trends post CNA was 68 ± 6 bpm, 75 ± 8 bpm, and 68 ± 10 bpm at 0–3 months post, 3–6 months post, and 6–12 months post CNA. No atrial fibrillation was identified on ILR.

Four of the six patients had no syncopal episodes post CNA with a combined median follow-up of 384 days (IQR 149,554) (Figure 2). One patient (patient 4) required a redo procedure at 8 months of follow-up. At 7-months post first CNA, the patient experienced a presyncopal episode correlating with a 5-second daytime pause, and a few weeks later, a subsequent 15-second pause with associated syncope with a near-absent prodrome. Given the success noted with the initial CNA and after discussion with the patient, the decision was made to take the patient to the EP lab where a modified CNA procedure was performed, targeting only the right atrium specifically at the posteromedial GP and the SVC-aortic GP. The heart rate increased from a baseline of 52 bpm to high 70′s, with an AV Wenckebach cycle length from 510 ms to 400 ms and sinus node recovery time from 3.2 to 1.1 s. The patient is reaching the 2-year follow-up post redo CNA and has not had any further pauses on ILR or symptoms of presyncope or syncope. The other recurrence was in patient 3 who had a syncope 1 month post CNA. The patient felt tired the day before and then had an early morning syncope associated with an 8-second sinus pause. No treatment other than conservative management was continued particularly given her substantial syncope burden of 5 syncopal episodes within 2 weeks pre-ablation. After a second episode several weeks later, associated with a 6-second pause, the patient was started on low-dose midodrine with significant improvement in her day-to-day symptoms. The midodrine dose was then optimized after a presyncopal episode several weeks later correlating with a 6-second pause. The patient was determined to have a mixed vasovagal picture. She had had such frequent episodes of syncope all correlating with very prolonged, 20-second pauses *pre*-CNA ablation that an attempt at midodrine with patient discharge was felt to be unsafe.

3.3. Complications

There were no intra-procedural or 30-day complications noted. Sustained atrial fibrillation (AF) was noted in 4/6 patients during high-frequency stimulation where one patient required cardioversion, but no clinical AF was observed on ILR during the follow-up. There were no cases of inappropriate sinus tachycardia among the group over follow-up.

4. Discussion

In this series of patients presenting with recurrent high-risk syncope and documented prolonged pauses, CNA was found to demonstrate safety and efficacy at a median follow-up of 1 year post ablation. Syncopal episodes and documented ILR pauses were completely eliminated in 4 of 6 patients. Of those that recurred, 1 patient required a redo CNA after which no further symptoms or pauses were identified at 1 year of follow-up, and 1 patient had a substantial reduction in symptoms and shorter documented pauses that improved with midodrine suggesting a mixed-type vasovagal syncope.

Given the interventional nature of the procedure in a relatively young patient population, patient selection for CNA is critical. At present given the relative naissance of CNA, patients should only be considered after having either exhausted conservative measures, or the severity of the syncopal event precludes the patient from returning home safely. Although there is no guideline for younger patients, pacing remains a class IIa indication for those > 40 years old who suffer from recurrent syncope with documented asystole [10]. Clearly young patients who would otherwise receive a pacemaker could stand to benefit from a CNA approach. But just as pacing is more effective when the cardioinhibitory response is dominant (and less or not effective if the hypotensive component is dominant [17]), so too is CNA. Therefore, it is important to consider that patients with a predominant hypotensive response are excluded. A clear documentation of asystole during spontaneous syncope is necessary, with a method of excluding hypotensive susceptibility with either inpatient blood pressure monitoring, or 24-hour ambulatory blood pressure monitoring [18,19]. However, despite all attempts to pre-select patients who are purely cardio-inhibitory,

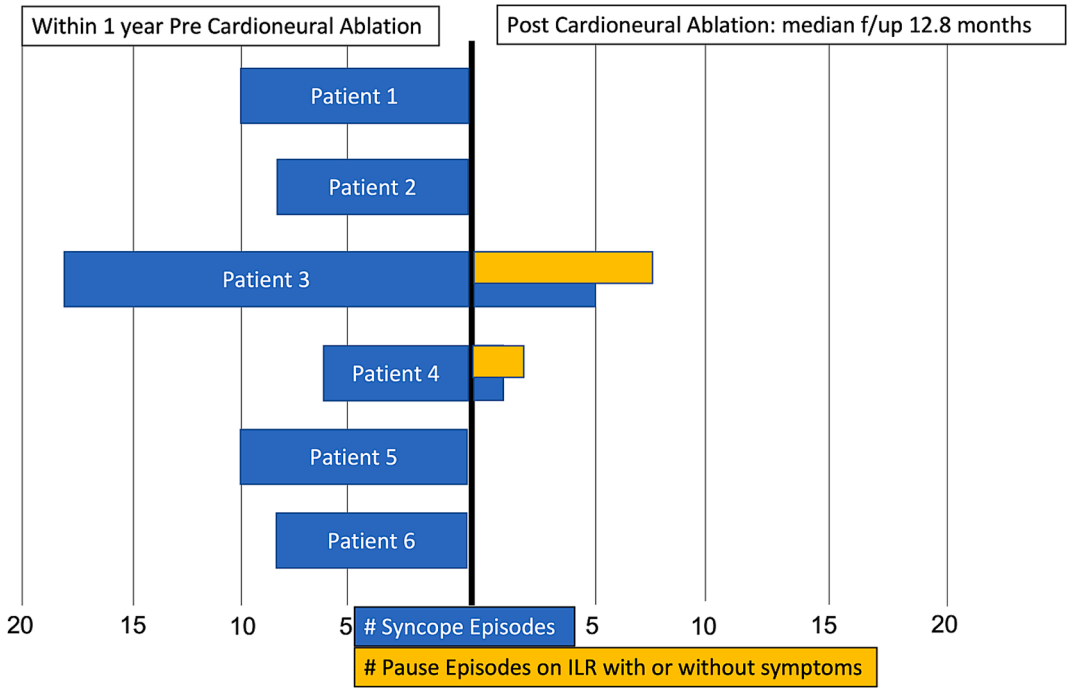

Fig. 2. Pre and post CNA syncopal recurrence and ILR-pause recurrence.

syncope recurrence will occur. In ISSUE-3 syncope recurrence occurred in 25 % of pacemakers implanted for documented asystole in spontaneous ILR recordings of vasovagal syncope [8], and hypotensive reflex syncope was present in up to 25 % of an older patient population with 3-years follow-up post pacemaker insertion [20]. Thus, CNA will also invariably include patients with a mixed VVS response as likely occurred in our patient (patient 3).

The only randomized controlled clinical trial investigating CNA for the treatment of refractory VVS showed a substantial decrease in syncope recurrence with CNA (54 % vs 8 %) over a 2-year follow-up [12]. In this study, a total of 48 patients (mean age 38 ± 10) were randomized to CNA vs optimal non-pharmacologic treatment. Most patients (35/48) had documentation of asystole during TT as opposed to 13 who had spontaneously documented asystole, but all had severe symptoms with failed nonpharmacologic measures. Most patients had asystole caused by sinus arrest. CNA was performed under conscious sedation by 1 operator where the ablation strategy was based on anatomical GP localization with ablation targets at sites with fragmented bipolar atrial EGMs. The endpoint was acceleration of the sinus rate by ≥ 25 % as compared to baseline and elimination of fractionated EGMs in ablated areas with lack of response to atropine at the end of the procedure. If this was not achieved, then additional applications targeted GPs at the left pulmonary veins, at the aorta-SVC junction or within the coronary sinus. No procedural complications were noted.

A recently published *meta*-analysis included mostly small observational cohorts and found a 92 % (75 %-100 %) overall freedom from syncope in 15 studies and 86 % (61 %-100 %) freedom from syncope prodromes in 8 studies [13]. The average age of patients was higher than in our study at 39.8 ± 4 years, with 66 % diagnosed with cardio-inhibitory syncope and 31 % having a mixed-type syncope. No difference was observed in subgroup analyses comparing different methods to identify targeted GPs. Procedure-related adverse events were reported in 13 % in the eleven studies that reported on complications. In 6 studies, there were 0 % reported complications [21,22,23,24,25] and in the other 5 studies, transient inappropriate sinus tachycardia was reported in a total of 3 patients [26,27], temporary initiation of beta blocker for transient mild sinus tachycardia during the first 3 months post ablation was noted in 23 % in a study by Pachon et al [28], and AF was reported in 22 % in a study by Hu et al [29]. There was 1 pseudoaneurysm [30], 2 groin hematomas [31], and 1 induced cavo-tricuspid isthmus flutter [31].

The importance of objective monitoring post any intervention for cardio-inhibitory syncope cannot be overstated. All patients in our study received an ILR prior to discharge if CNA was to be even considered as an outpatient, or at time of CNA in those who underwent intervention as an inpatient. One of the main criticisms of prior studies has been the lack of objective adjudication of syncopal events or the lack of ability to see less symptomatic pauses post CNA. No prior CNA study has used ILR monitoring for post-ablation monitoring and correlation of syncope [13]. The only RCT lacked adjudication for recurrent syncope where only 24-hour holter recordings were performed at 3, 12, and 24 months post CNA [12]. Certainly the lack of a sham control group and unblinded nature of the study are important factors to consider. More objective monitoring with ILRs would be a potential compromise for these concerns.

One patient in our study underwent a repeat ablation 8 months after an initial CNA for repeated traumatic syncope with asystole due to prolonged sinus pauses. At 2 years of follow-up after the repeat ablation, he remains syncope-free, and without pauses on his ILR. The patient's repeat ablation was limited to the right atrium given the consistent *sinus* pauses for which the sinoatrial GPs were targeted, the concern for over-ablation with the initial experience with heightened risk of inappropriate sinus tachycardia, and the avoidance of increased complication risk with a left-sided procedure.

Our second patient recurrence occurred 1 month after CNA. Given her substantial syncope burden as compared to pre-CNA, conservative management was continued. After a second episode midodrine was started and optimized over the following month. Her episodes were significantly more tolerable, with a longer prodrome and less post-syncope fatigue than pre-CNA. This suggested a mixed VVS picture with both cardio-inhibitory and hypotensive components. Patients with mixed VVS have been included in prior studies [12,13], although no differences in outcome from pure cardio-inhibitory indications were evaluated. In a recent *meta*-analysis evaluating midodrine in VVS, midodrine was found to be effective, but primarily in controlled settings where the endpoint of recurrence was evaluated by a repeat TT [32]. The benefit was much more modest in clinical settings suggesting lack of test reproducibility and reliability in predicting patient response to therapy. The studies generally lasted no longer than 1 year, so long-term benefits are unknown, and the potential for placebo effect and significant expectation bias were introduced with the results of three open-label clinical studies. Only two robust double-blind clinical trials (n = 180) offer insight into the true effect in clinical practice, and these studies had opposing results [4,33].

5. Limitations

The current study was small and only included 6 patients. Although the follow-up was performed with an ILR, longer follow-up times are necessary to improve our understanding of syncope and pause recurrence, as well as long-term effects post CNA. TTs were not performed in most of our patients, however as discussed, the TT is plagued by false positives and cannot play a role in guiding treatment.

6. Conclusion

CNA may be considered as a treatment option for recurrent high-risk syncope and documented prolonged pauses. The risks of the procedure may be acceptable in appropriately selected patients, particularly in younger patients where pacemaker implantation remains the only other option. In this small cohort of patients, we demonstrate safety and efficacy at nearly 1 year of follow-up. Larger studies are required to confirm these findings.

CRediT authorship contribution statement

Jacqueline Joza: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Luiz Gustavo Bravosi da Rosa:** . **Ahmed Alturki:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Valeria Anglesio:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Paula Sanchez-Somonte:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Vladimir Poletaev:** Writing – review & editing, Formal analysis, Data curation. **Martin Bernier:** Writing – review & editing, Visualization, Supervision, Formal analysis, Data curation. **Atul Verma:** Writing – review & editing, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Vidal Essebag:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [**Dr. Jacqueline Joza** reports investigator-initiated external grant support from Medtronic Inc. and consulting fees from Boston Scientific (Modest)and honoraria from Biosense Webster Canada (Modest). **Dr.**

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