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Permanent pacing extraction after successful cardioneuroablation in patients with cardioinhibitory reflex syncope

Short title: PM extraction after CNA in patients with cardioinhibitory RS

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INTRODUCTION

Reflex syncope (RS) is the most frequent cause of sudden and transient loss of consciousness due to parasympathetic overactivity, mainly affecting young patients [1]. Permanent cardiac pacing is one of the treatment options if the cardioinhibitory reflex is dominant [2]. Considering such therapy, particularly in young patients, we must be aware of long-term complications such as pacemaker (PM) system damage, infection including endocarditis, risk of tricuspid valve injury, and limitations on practicing certain sports or professional activities. Additionally, over a lifetime, the PM generator and potentially the leads will require multiple replacements [3]. Recently, catheter-based cardioneuroablation (CNA) has been implemented in clinical practice

as an alternative treatment option for cardioinhibitory RS [4]. The good long-term efficacy of CNA [5–7] eliminates the indication for permanent pacing and provides a rational basis for pacing, discontinuing, or refusing device re-implantation after pacing generator and/or lead extraction. Our case-series report presents patients with RS and permanent pacing who underwent successful CNA and discontinuation of PM therapy after shared decision-making process.

METHODS

Cardioneuroablation and transvenous lead extraction

A case-series study included patients under 40 years of age with cardioinhibitory or mixed RS, who had previously been implanted with a PM. Indications for pacing system extraction included patient preference, PM infection or damage. Patients with a history of cardiac surgery or a negative atropine test were excluded from the study. A negative response was defined as failing to achieve a 25% increase in sinus rate two minutes after injection. The test involved 0.04 mg/kg intravenous atropine sulfate for patients under 50 kg and 2 mg for those 50 kg or more [5]. Anatomical-based approach CNA was performed using the CARTO® 3 (Biosense Webster Inc., Diamond Bar, CA, US) electro-anatomical mapping system under conscious sedation (midazolam and fentanyl) or general anesthesia. In all cases, bi-atrial ganglionated plexi (GP) ablation was performed using a 3.5 mm irrigated-tip catheter with a contact force module (Navistar Thermocool SmartTouch, Biosense Webster Inc). CNA included the para-septal GPs (SPSPGP and IPSGP) ablation and ganglia in the LSPV area (LSGP) if necessary. The procedural effectiveness of the CNA was assessed based on changes in electrophysiological parameters of the sinoatrial node and atrioventricular node collected before and after CNA. In all cases, the atropine challenge was performed before and after the procedure. In one case, extracardiac vagal stimulation was used to confirm vagal denervation.

All extraction leads procedures were performed in the hybrid operating room with on-site cardiothoracic surgical standby, under general anesthesia or intravenous sedation. All patients were prepared for a possible emergency sternotomy with a heart-lung machine on standby. While extracting the leads, we used a stepwise approach. A description of the transvenous lead extraction procedure (TLE) was presented in our previous study [9]. All patients gave written, informed consent to undergo CNA and TLE.

The study was approved by an appropriate institutional review board or ethics committee (KBET/259/B/2011 and 118.0043.1.315.2024), and that patients provided written informed consent to participate in the study.

RESULTS AND DISCUSSION

We present a series of 3 patients without structural heart disease or neurological abnormalities who had undergone PM implantation due to very symptomatic cardioinhibitory (or mixed) RS followed by CNA and TLE (details are presented in Table 1). In case 1, the patient developed a local infection in the PM pocket, leading to TLE and a 2-week course of intravenous antibiotic therapy. Considering the patient's history of syncopal episodes and the complications related to the PM, an shared decision-making was made to proceed with CNA with discontinuation of PM therapy. After a successful CNA over an 18-month follow-up period, the patient did not experience any episodes of syncope or presyncope. In case 2, the decision to perform CNA and subsequently extracting the pacing system was made on a purely prophylactic basis after SMD, considering the patient's age, the risk of PM long-term complications, and the impact on quality of life. Before CNA, a tilt test (TT) was performed which showed an asystolic response with the PM set to OVO mode. After one year of follow-up with the pacemaker set in OVO mode, the pacing system extraction was done. In case 3, one year after PM implantation, a telemetric control revealed early signs of ventricular lead damage, indicating a forthcoming need for lead replacement. The patient was offered CNA followed by extraction of the pacing system after at least one year of follow-up. The patient consented to the treatment strategy, and CNA was performed. During the year and a half of follow-up with PM set on pacing 30/min, the patient remained symptom-free with 0 % pacing time. In all patients, CNA and TLE were made without complications. During follow-up control, Holter electrocardiography and TT showed no bradyarrhythmia.

Pacemaker implantation can be an effective treatment for a subset of patients with severe, recurrent cardioinhibitory RS. According to the current ESC guidelines from 2021, a dual-chamber PM is recommended for patients over 40 years old with RS and evidence of symptomatic pauses lasting at least 3 seconds or asymptomatic pauses lasting at least 6 seconds in asystole and/or AV block mechanisms [10]. This recommendation also applies to patients with cardioinhibitory carotid sinus syndrome and those with an asystolic TT. There is no specific pacing recommendation for patients under 40 years old due to a lack of trial evidence, but a PM may be a rational solution in very symptomatic patients. While effective, pacemakers can lead to long-term complications, which remain significant, especially in young patients [11]. The lack of evidence and risk of PM long-term complications make CNA a noteworthy treatment method. Recently published data have shown CNA's good safety and effectiveness in preventing recurrent RS in long-term follow-up [5–7]. Piotrowski et al. [5], in the first prospective, randomized controlled trial comparing CNA and standard non-invasive treatment

of RS (cardioinhibitory and mixed forms), showed a significantly lower risk of syncopal episodes in the CNA group (8% vs. 54%) over a two-year follow-up [4]. Gopinathannair et al. [12], in a retrospective study, compared CNA (n = 61) and PM implantation with CLS/RDR algorithms (n=86 with standard leads, n = 24 with leadless) [12]. After one year of follow-up, the risk of syncope recurrence and the safety profile were similar in both groups, however, there was a trend toward better CNA efficacy. Currently, there is no recommendation for CNA in the recent ESC guidelines concerning RS, but it is important to note that many studies and expert consensus have been published since then.

Wileczek et al. [13] showed that PM therapy could be discontinued after CNA in 14 of 17 patients (82.3%). In contrast, our patient group is relatively small but homogeneous, focusing on patients younger than 40 years of age with highly symptomatic cardioinhibitory or mixed reflex syncope and previously implanted PM. This unique patient population, we believe, represents a critical target for CNA and PM extraction.

Our case series highlights two types of patients: Patients requiring device extraction due to infection or pacing system damage, where discontinuing permanent pacing after CNA may be a reasonable alternative treatment option to PM re-implantation. The second type is patients who accept shared decision-making for prophylactic extraction of the PM after CNA to avoid potential long-term complications and eliminate numerous limitations related to PM implantation. The decision should be based on confirmation of the long-term efficacy of CNA. To assess long-term efficacy, the following methods may be utilized: evaluation of clinical symptoms, heart rate variability analysis in electrocardiography Holter monitoring, TT, or electrophysiological study with extracardiac vagal stimulation [13, 14]. Currently, there is no clear strategy for managing both groups of patients, and further studies are needed.

Article information

Conflict of interest: GK is a lecturer working for Biosense Webster Inc., Diamond Bar, CA, US Johnson and Johnson company; MK is a lecturer and proctor working for Biosense Webster Inc., Diamond Bar, CA, US Johnson and Johnson company; other authors declared no conflict of interest.

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Table 1. Detail characteristic of 3 cases described in a publication

	Case 1	**Case 2**	**Case 3**
Age, years	38	30	19
Sex	Female	Male	Male
PM indication	Cardioinhibitory type RS	Mixed-type RS	Mixed-type RS
Bradyarrhythmia in TT	39 sec sinus bradycardia	20 sec sinus bradycardia	9 sec sinus bradycardia
Bradyarrhythmia in Holter ECG (min/avg/max) bpm	44/69/121 no bradyarrhythmia	38/58/105/16 sinus asystole during blood collection	47/73/118,second-degree AV block Mobitz II
PM type	Dual chamber	Dual chamber	Dual chamber
Indication to lead extraction	PM pocket infection	Patient preferences	Ventricle lead damage/patient preferences
Age of PM implantation, years	34	14	19

Time from PM implantation and CNA	1 year and 1 month	16 years	2,5 years
CNA date, month/year	04/2022	03/2023	12/2021
Time between CNA and PM extraction	CNA after PM extraction	13 months	18 months
GPs ablated	SPSGP/IPSGP/LSPG	SPSGP/IPSGP/LSGP	SPSGP/IPSG -ICE guidance
ECVS	Not performed	Not performed	Performed
CNA-HR change, bpm	75 to 110	70 to 105	65 to 90
CNA-AHI change, ms	110 to 85	115 to 80	90 to 80
CNA-WP change, ms	340 to 280	320 to 280	400 to 330
CNA-ERP AVN change, ms	320 to 220	270 to 210	280 to 230
Atropine test after CNA	no response	no response	no response
Holter ECG after CNA (min/avg/max), bpm	64/93/131 no bradyarrhythmia	77/84/107 no bradyarrhythmia	53/75/180 no bradyarrhythmia
TT after CAN	Not performed	Negative	Negative
Syncope after CNA	No	No	No
Presyncope after CNA	No	No	No
CNA complications	None	None	None
Lead extraction complications	None	None	None

Abbreviations : AHI, atrium-his interval; AVN, atrioventricle node; CNA, cardioneuroablation; ECVS, extracardiac vagal stimulation; ERP, effective refractory period; GPs, ganglionated plexus; HR, heart rate; ICE, intracardiac echocardiography; IPSGP, inferior paraseptal ganglionated plexus; LSPG, left superior ganglionated plexus; PM, pacemaker; RS, reflex syncope; SPSGP- superior paraseptal ganglionated plexus; TT, tilt test; WP, wenckebach point