Reevaluation of indications for permanent pacemaker implantation after cardioneuroablation

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DOI: 10.33963/v.kp. 97828

Received:
May 9, 2023

Accepted:
October 13, 2023

Early publication date:
October 20, 2023

INTRODUCTION

Cardioneuroablation (CNA) was shown to effectively treat functional bradycardia without the need for permanent pacemaker (PPM) implantation in a wide spectrum of bradyarrhythmias including sinus node dysfunction (SND), tachycardia-bradycardia syndrome, atrioventricular blocks (AVBs), cardioinhibitory or mixed vasovagal syncope (VVS), and cardioinhibitory carotid sinus syndrome or hypersensitivity. Pacemaker implantation is associated with costs, complications, and restrictions on daily activities [1–4]. However, although CNA is associated with a favorable risk-to-benefit ratio, low complication rates, and targeted modulation of cardiac autonomic innervation, currently, it is not recommended by guidelines [5, 6]. According to class I/IIa/IIb indications for PPM therapy, CNA has to be canceled or postponed in eligible patients following shared decision-making and informed consent [7]. We aimed to reassess indications for PPM implantation and discontinuation of PPM therapy after CNA in patients referred for an electrophysiological study and extracardiac vagal nerve stimulation (ECVS).

METHODS

Data were collected from the Rare-a-CaREgistry, a Polish prospective and retrospective multicenter ablation registry (2017–present) involving 10 centers (listed in Supplementary material, *Table S1*). Patients were recruited in the years 2017–2022. This study was planned to asses secondary outcomes, involving consecutive patients qualified for cardioneuroablation. Patients with various cardiovascular abnormalities were recruited, including structural heart disease, previous cardiac surgery, supraventricular or ventricular arrhythmia, prolonged corrected sinus node recovery time (>525 ms), previous ablation procedures, or PPM implantation. Patient demographics are presented in Supplementary material, *Table S2*. The management of patients before and after CNA encompassed comprehensive consultations, state-of-the-art cardiovascular autonomic testing, atropine tests, and electrographic (ECG) monitoring. Shared decision-making was used to explain possible treatment options and to provide patient-centered therapy in order to ascertain that the patient fulfilled indications for PPM therapy according to the European Society of Cardiology (ESC) guidelines and was aware that CNA was used as an alternative and experimental technique.

All patients had bradycardia-related symptoms documented by ECG. Patients were referred for CNA following a positive atropine test, defined as an increase in heart rate in sinus rhythm by at least 30% within 10 min-

utes after intravenous atropine administration at a dose of 0.02–0.04 mg/kg (maximum, 2 mg). Following atropine administration, patients were monitored for 30 minutes.

The primary endpoint of CNA was the resolution of ECVS-induced sinus arrest and AVB during proximal coronary sinus pacing. Anatomically guided biatrial and binodal CNA was performed, with fluoroscopic and ultrasonographic guidance for ECVS [8]. CNA was performed using three-dimensional electroanatomic systems (EnSite Velocity/Precision Mapping Systems, Abbott, US), as reported previously [8–10]. Six GPs were targeted: superior septal GP (left and right), inferior septal GP (left and right), vena cava superior/aortic root GP, and left superior GP. In patients with previous severe syncope, with high-risk professions, and with PPMs, reassessment with an electrophysiological study and ECVS was recommended before the decision to discontinue pacing and perform transvenous lead extraction was made [10]. In the subgroup of tachycardia-bradycardia with indications for PPM therapy, 26 of 100 (26%) patients underwent CNA and pulmonary vein isolation.

The study was approved by an appropriate institutional review board (Rare-a-CaREgistry, Rzeszow University, 6.04.2017; No. 5/4/2017), and written informed consent was obtained from all patients.

Statistical analysis

Numerical data were expressed by means with standard deviation. Categorical data were presented as absolute numbers with percentages. Variables before and after CNA were compared using McNemar's χ^2 and exact McNemar's χ^2 tests. Statistica v. 13 (Statsoft, Poland) was used for analysis. Statistical significance of the test was assumed at $P < 0.05$.

RESULTS AND DISCUSSION

Cardioneuroablation was performed in 195 consecutive adult patients (mean age 55.6 [14.3] years; women, 107 [54%]) (Figure 1). Of the 195 patients, 17 (8.2%) previously underwent PPM implantation.

As per the ESC guidelines [6], 100 of the 178 patients (56.1%) had *de novo* indications for PPM therapy before CNA: SND was reported in 88 patients (45%); AVB in 21 (10%); tachycardia-bradycardia syndrome in 26 (13%); cardioinhibitory VVS in 41 (21%); and cardioinhibitory carotid sinus syndrome or carotid sinus hypersensitivity in 3 patients (1.5%). Complex indications (≥2) were reported in 45 patients (23%). In 78 patients, the indication for CNA was symptomatic bradycardia, which is not a class I, IIa, and IIb indication for PPM therapy. According to the 2021 ESC guidelines, pacing therapy is not recommended in patients with cardioinhibitory vasovagal reflex diagnosed during the head-up tilt test and aged below 40 years. Therefore, such patients were not considered candidates for PPM therapy in our study. Several patients did not fulfill the criteria for severe recurrent syncopal episodes.

Indications for *de novo* PPM therapy were present in 32 of the 86 patients (37%) aged 60 years or older. During follow-up (mean, 23.7 [10.3] months) after successful CNA procedures (226 procedures in 195 patients; mean, 1.1 [0.2] procedures), no deaths were reported, and only 10 of the 195 patients (5%) experienced recurrent syncopal episodes. Of the 10 patients, 8 were diagnosed with orthostatic/vasodepressive syncope with a clear prodromal phase. Despite positive atropine tests before the procedure and CNA, 4 of the 100 patients (4%) with indications for pacing before CNA still demonstrated those indications at follow-up due to an intrinsic substrate. Finally, 6 of the 178 patients (3.4%) met *de novo* criteria for pacing after CNA ($P < 0.01$). These criteria included coexisting functional and structural bradycardia (n = 3), recurrent bradycardia after CNA with syncope and presyncope and refusal to undergo the second CNA procedure (n = 2), and late development of severe sinus chronotropic incompetence (n = 1) after successful CNA for prolonged functional AVB with syncope. Of the 195 patients, 7 (3.5%) developed major complications associated with CNA, including cardiac tamponade (2 patients), pericarditis (2 patients), pericardial effusion (1 patient), femoral aneurysm (1 patient), and pneumothorax, also in 1 patient. All complications were treated non-surgically and had no late consequences.

The discontinuation of PPM therapy and transvenous lead extraction after CNA were recommended and performed in 14 of the 17 patients (82.3%) with previous PPM implantation ($P < 0.01$). At the last follow-up visit, patients were asked about recurrence of bradycardia symptoms, and indications for bradycardia treatment were reconsidered. Of the 186 patients without PPM after CNA, 81% gave consent to another CNA procedure instead of PPM implantation and 10% accepted the management strategy of the physician's choice. In 4 of 100 patients after cardioneuroablation, PPM therapy was continued or initiated (Supplementary material, Table S2).

In our study, 56.1% of patients referred for CNA had *de novo* indications for permanent pacing. At middle-term follow-up, the number of patients with indications for pacing significantly decreased. Our findings suggest that CNA is an effective therapeutic approach in a wide range of patients with functional bradycardia. However, if needed, coexisting intrinsic and extrinsic substrates should be considered for further assessment and permanent pacing. Complex bradyarrhythmic substrates before and after CNA require ongoing comprehensive management including multidisciplinary consultations, cardiovascular autonomic testing, ECG monitoring, and shared decision-making. There is currently no clearly defined strategy in European or American guidelines for the management of SND/AVB secondary to persistent and/or paroxysmal vagal tone hyperactivity [5, 6, 11]. The superiority of CNA in patients with cardioinhibitory or mixed VVS was confirmed only in the ROMAN-1 study

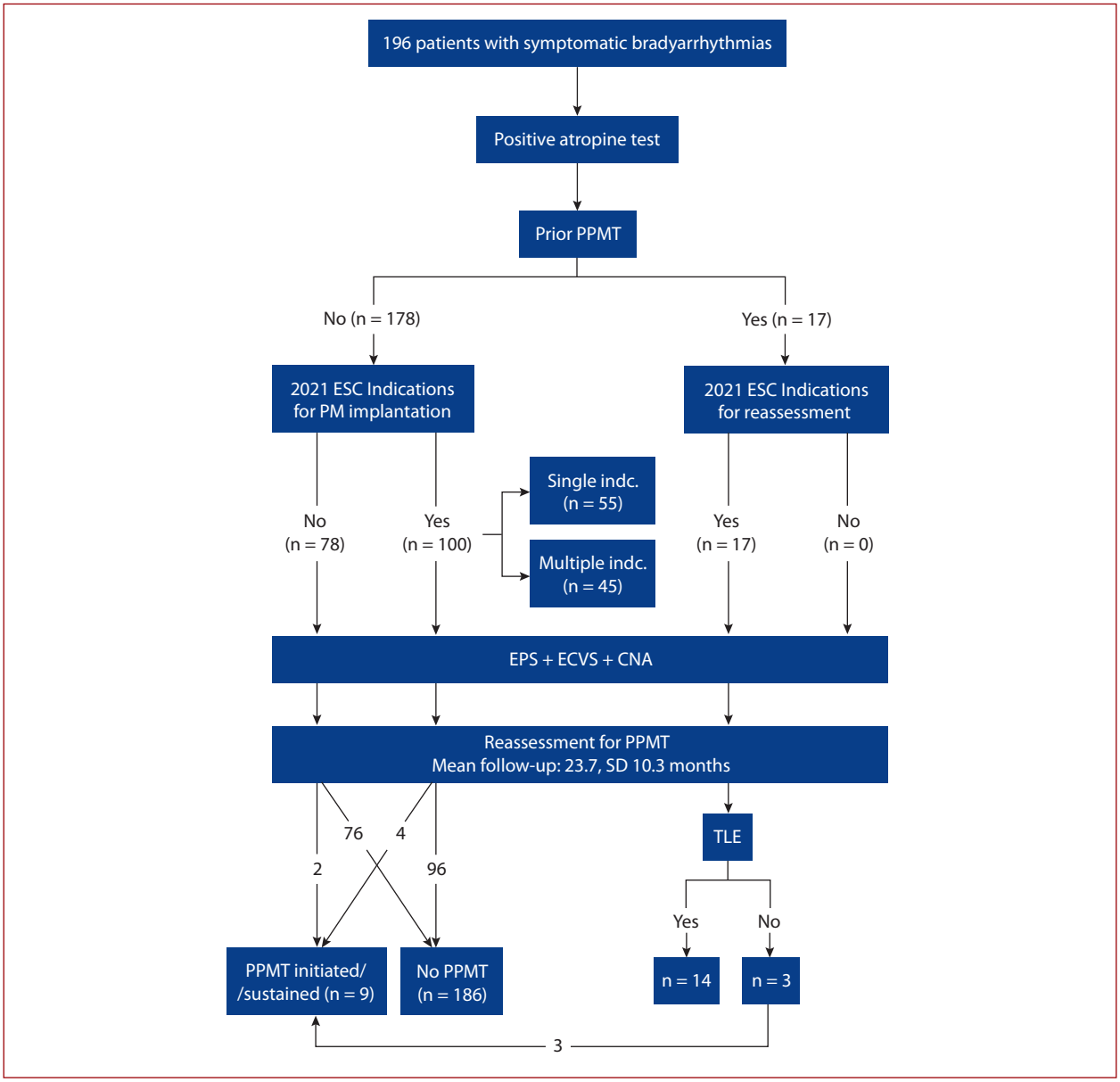

Figure 1. Flowchart of the study

Abbreviations: CNA, cardioneuroablation; ECVS, extracardiac vagal nerve stimulation; EPS, electrophysiological study; ESC, European Society of Cardiology; PM, pacemaker; PPMT, permanent pacemaker therapy; SD, standard deviation; TLE, transvenous lead extraction

although without a direct comparison with permanent pacing in patients older than 40 years [3].

CONCLUSIONS

More than 50% of patients referred for CNA had indications for permanent pacing (half of them had complex indications). While some patients may require permanent pacing due to failed can, coexisting, or *de novo* complex structural bradyarrhythmia, in pure functional bradycardia patients, CNA may be an alternative to permanent pacing as the first-line treatment option. This allows postponement or cancellation of permanent pacing in the majority of patients with suspected functional bradyarrhythmia. Based on these findings, ongoing comprehensive monitoring is required in patients with functional bradyarrhythmia to introduce patient-centered therapy and management strategies based on shared decision-making. Randomized controlled trials are warranted to validate indications for CNA and PPM therapy in this population.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: SS is the author of several patents in the field of cardiology and cardiac surgery and a shareholder in Medicine S.A. No specific product of any company was used or investigated in this trial. All other authors declare that they have no conflicts of interest.

Funding: None.

REFERENCES

1. Pachon JC, Pachon EI, Pachon JC, et al. „Cardioneuroablation" — new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. Europace. 2005; 7(1): 1–13, doi: 10.1016/j.eupc.2004.10.003, indexed in Pubmed: 15670960.
2. Pachon JC, Pachon EI, Cunha Pachon MZ, et al. Catheter ablation of severe neurally meditated reflex (neurocardiogenic or vasovagal) syncope: cardioneuroablation long-term results. Europace. 2011; 13(9): 1231–1242, doi: 10.1093/europace/eur163, indexed in Pubmed: 21712276.
3. Piotrowski R, Baran J, Sikorska A, et al. Cardioneuroablation for reflex syncope: efficacy and effects on autonomic cardiac regulation — a prospective randomized trial. JACC Clin Electrophysiol. 2023; 9(1): 85–95, doi: 10.1016/j.jacep.2022.08.011, indexed in Pubmed: 36114133.
4. Aksu T, Gopinathannair R, Bozyel S, et al. Catheter ablation of atrioventricular block: from diagnosis to selection of proper treatment. JACC Case Rep. 2020; 2(11): 1793–1801, doi: 10.1016/j.jaccas.2020.07.050, indexed in Pubmed: 34317058.
5. Brignole M, Moya A, de La, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018; 39(21): 1883–1948, doi: 10.1093/eurheartj/ehy037, indexed in Pubmed: 29562304.
6. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Europace. 2022; 24(1): 71–164, doi: 10.1093/europace/euab232, indexed in Pubmed: 34455427.
7. Chung MK, Fagerlin A, Wang PJ, et al. Shared decision making in cardiac electrophysiology procedures and arrhythmia management. Circ Arrhythm Electrophysiol. 2021; 14(12): e007958, doi: 10.1161/CIRCEP.121.007958, indexed in Pubmed: 34865518.
8. Wileczek A, Polewczyk A, Kluk M, et al. Ultrasound-guided imaging for vagus nerve stimulation to facilitate cardioneuroablation for the treatment of functional advanced atrioventricular block. Indian Pacing Electrophysiol J. 2021; 21(6): 403–406, doi: 10.1016/j.ipej.2021.06.008, indexed in Pubmed: 34186197.
9. Stec S, Jankowska-Polańska B, Jagielski D, et al. Rationale and design of SAN.OK randomized clinical trial and registry: Comparison of the effects of evidence-based pacemaker therapy and cardioneuroablation in sinus node dysfunction. Cardiol J. 2022; 29(6): 1031–1036, doi: 10.5603/CJ.a2022.0103, indexed in Pubmed: 36385604.
10. Reichert A, Wileczek A, Stec S. Cardioneuroablation for the effective treatment of recurrent vasovagal syncope to restore driving abilities. Kardiol Pol. 2022; 80(11): 1158–1160, doi: 10.33963/KP.a2022.0189, indexed in Pubmed: 35946179.
11. Brignole M, Aksu T, Calò L, et al. Clinical controversy: methodology and indications of cardioneuroablation for reflex syncope. Europace. 2023; 25(5), doi: 10.1093/europace/euad033, indexed in Pubmed: 37021351.