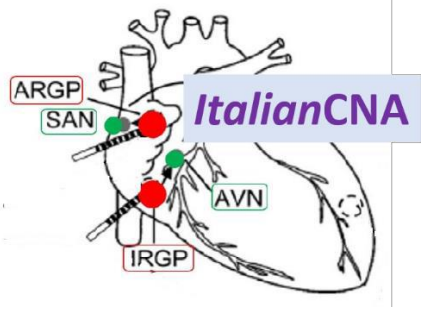


Efficacy of transcatheter ablation of ganglionic plexuses (Cardioneuroablation) in right atrium in patients with asystolic neuromediated syncope

Italian multicenter study sponsored by GIMSI

Acronym: *ItalianCNA*

Promoter	**GIMSI ASSOCIATION** "Multidisciplinary Group for the Study of Syncope" VIA SASSONIA N. 30 47924 RIMINI _ ITALY
Principal Investigator	Prof Leonardo Calò, Policlinico Casilino, Rome
Study phase	*Phase 2 Interventional Study*
Version and date	Version V1 _ March 30, 2021

Author

Name: Prof Leonardo Caló	Role: Coordinator Scientific and Principal Investigator
Signature:	Date:

Steering Committee

Prof Leonardo Caló	Coordinator
Dr Alessio Borrelli	Member
Prof Michele Brignole	Member
Dr Ermenegildo de Ruvo	Member
Dr Marco Rebecchi	Member
Prof Stefano Strano	Member

Summary

Introduction and purpose of the study

Neuro-mediated cardioinhibitory syncope (SCNM) represents the most frequent form of syncope in the young population without apparent cardiac or neurological pathology (1,2). Although affected young patients have an excellent prognosis, their quality of life can be seriously deteriorated by the frequency of episodes (2,3,4). Definitive cardiac pacing is an effective therapy and is recommended in patients >40 years old (1,2,5,6); there are no trials in patients <40 years old. The general scientific consensus is that in younger patients the role of the pacemaker raises some concerns arising from the need for numerous replacements and possible ventricular remodeling induced by right ventricular pacing over time.

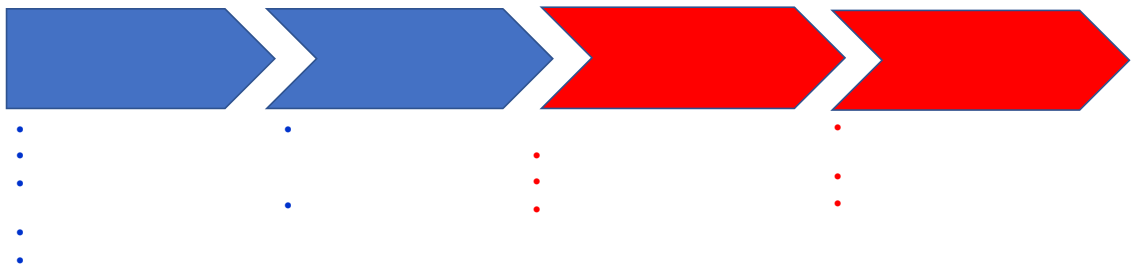
In patients <40 years old with severe recurrent syncope, current practice is to implant loop recorders in order to document the dominant mechanism of syncope, cardioinhibitory or vasodepressor. In cases of asystolic syncope, in the absence of proven effective therapies, recently, transcatheter radiofrequency ablation of the anatomical site areas of the ganglionic plexuses in the right and left atrium has shown promising results, both in the short and long term regarding the treatment of cardioinhibitory reflex syncope (7,8,9,10,11,12,13,14). In Italy, ganglion plexus ablation, so-called cardioneuroablation (CNA) has been current practice in selected cases since 2012 at Policlinico Casilino (15) and the results have been published recently (13). The technique proposed by Caló et al (13), consists of ablation of the ganglionic plexuses of the right atrium. No center currently has sufficient case series to establish long-term efficacy and safety results, for which a multicenter interventional study is therefore needed.

In view of these premises, the aim of the study will be to evaluate the efficacy and safety of NAC in patients with SCNM with ECG documentation of spontaneous asystolic episodes of reflex nature.

Study design

ItalianCNA is a multicenter Italian interventional "proof of efficacy" clinical trial that aims to evaluate the incidence of asystolic pauses and heart rate in patients with SCNM who performed CNA after documentation of asystolic pauses on ECG monitoring by implantable loop recorder.

The study is independent, "investigator-initiated," sponsored by a nonprofit scientific association called the Italian Multidisciplinary Group for the Study of Syncope (GIMSI).



Inclusion criteria

- Age between 18 and 60 years
- Patients with a clinical diagnosis of neuromediated syncope according to class I criteria of the ESC guidelines, Table 1
- Clinical history of recurrent syncope (≥2 in the last year or ≥3 in the last 2 years), severe, not tolerated by the patient
- Documentation of ≥2 asystolic pauses >3 sec daytime on ECG monitoring by implantable loop recorder (ILR), with or without syncope
- Refusal by patient to perform pacemaker implantation

Table 1. Diagnostic criteria of reflex syncope according to ESC guidelines (1,2)

Recommendations	**Class**	**Level**
Reflex syncope		
1. VVS is highly probable if syncope is precipitated by pain or fear or standing, *and* is associated with Typical progressive prodrome (pallor, sweating, nausea).	**I**	**C**
2. Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers.	**I**	**C**

Tilt test is recommended but not mandatory. Patients with negative tilt test are also enrollable. It can be either positive or negative.

Exclusion criteria

- Absence of sinus dysfunction and atrioventricular node disease.
- Absence of structural heart disease
- Possible alternative diagnoses of syncope

Ablative procedure

The ablative procedure involves applying radiofrequency deliveries in the two Right atrium anatomical sites close to the two main ganglionic plexuses of the right atrium:

- **Inferior-posterior area (site of first ablation)** corresponding to the right inferior atrial ganglion located between the inferior vena cava, coronary sinus ostium and near the atrioventricular node
- **Upper-posterior area (site of second ablation)** corresponding to the right superior atrial ganglion located between the superior vena cava and the posterior surface of the right atrium

The method of the ablative procedure is described in detail in the Appendix (see)

Acute success is defined as:

- Shortening of AH interval >20 ms, relative to baseline, persisting for 30 min, and/or Wenckebach point <500 ms at end of procedure
  plus
- P-P interval <70% of basal P-P interval, or P-P interval <600 ms (calculated as the average of 10 consecutive cycles), after 10 min since the last delivery

The procedure will be continued until the acute efficacy criteria are met. In case the procedure is terminated without having reached the target, this will be noted as "acute failure"

Follow up (study phase)

It consists of remote monitoring and quarterly questionnaire completed by the patient himself (see appendix).

- *Remote monitoring*. Central, by an ad hoc established Single Laboratory. All episodes of asystole >3 sec and average monthly heart rate will be recorded

- *Patient's self-administered questionnaire*. The syncope follow-up questionnaire validated in the BioSync study (6) will be used. Every 3 months the patient will send the questionnaire to the Single Laboratory.

An "Adjudication Committee " consisting of 3 physicians not involved in the study will validate ECG events and questionnaire responses

Endpoint

Main analysis according to intention-to-treat principle. Exploratory subgroup analysis with acute success.

Primary endpoint: Intrapatient comparison of monthly incidence of episodes. asystolic >3 sec before and after CNA
Secondary endpoints:

- Intrapatient comparison of mean heart rate, before and after CNA
- Intrapatient comparison of monthly incidence of (pre)syncopal episodes before and after CNA
- Intrapatient comparison of beat-to-beat variability of heart rate in the short term (spectral analysis) before and after CNA (limited to auxiliary HRV study)

Ancillary substudy (ancillary study): spectral analysis

It consists of acquiring digitized ECG monotrace for 5 minutes the day before and the day after the procedure using surface ECG recording equipment provided free of charge by the promoter. Spectral analysis of the oscillatory components of R-R interval variability will be performed on the ECG trace. This study is optional

Sample calculation

Considering clinically effective a 50% reduction in the monthly incidence of asystole episodes of >3 sec, which before the ablative procedure is assumed to be 0.82±0.67 (16), with 24 patients undergoing ablation, the null hypothesis (Ho: null difference in asystole incidence pre/post-ablation) can be rejected with 80% statistical power at a two-sided t-test with alpha error 0.05.

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Appendix

Mapping and Ablation procedure

The day before ablation procedure, an ECG is performed in resting conditions and after intravenous administration of atropine. Atropine test is carried out in fasting state with up to 2 mg intravenous atropine sulfate, under continuous ECG recording for 30 minutes (two injections of 1 mg atropine with an interval of 5 minutes). A decrease more than 25% in PP interval is accepted as a positive response.

Mapping and ablation are performed under mild sedation and local anesthesia. Three right femoral vein punctures are performed: a) a decapolar catheter is inserted into the coronary sinus; b) a quadripolar catheter is positioned in the hisian region; c) and a quadripolar deflectable irrigated tip ablation catheter (Navistar SmartTouch, Biosense Webster, Inc or Tacticath, Abbott Inc) is used for mapping and ablation. Electroanatomical mapping of the right atrium (RA) is performed by means of CARTO 3™ (Biosense Webster, Inc) or by EnSite Precision (Abbott Inc). A three-dimensional anatomical mapping of the RA is performed, during which volume data are recorded continuously during manipulation of the catheter inside the RA. From the outer surface of the volume data acquired, the system generates a surface reconstruction. Tagging the phrenic nerve capture points on the lateral RA allowed us to map the phrenic nerve course. The parameters considered during basal electrophysiological study are: basal cycle length, AH interval and Wenckebach cycle length.

The ablation procedure consists of RF delivering (RF energy at 43°, 30-35 W for 30-60 s) at right atrial anatomic sites where the underlying presence of GP clusters is regarded as highly probable: 1**) *the inferior-posterior area*** (**first ablation site)**: inferior right GP placed between inferior vena cava, coronary sinus ostium and near the atrio-ventricular groove, **2) *the superior-posterior area*** (**second ablation site)**: superior right atrial GP, adjacent to the junction of the superior vena cava and the posterior surface of RA. The identification of the anatomical target is improved by the
presence of high amplitude fractionated electrograms (HAFE, number of deflections☐ 4, amplitude ☐ 0.7 mV and duration ☐ 40ms) by using of a single beat analysis in order toquantify number of signal deflections and total activation time and differentiating them by normal electrograms (number of deflections < 4 or duration < 40 ms).

Care is taken to avoid ablations in the proximity of the mapped course of the phrenic nerve. To avoid phrenic nerve injury, high amplitude stimulation is performed just before radiofrequency delivery to the superior right atrial GP.

Considering that the exact anatomic borders of GP clusters are unknown, an expanded number of RF applications are delivered in order to form a cloud-like shape ablation surrounding the HAFE tags. An irrigated tip catheter using a contact force >5 g is recommended. P-P interval is carefully monitored. The duration of each single ablation is generally prolonged for at least 30 seconds after stabilization of P-P intervals but does not exceed 60 seconds at the same location. RF applications are interrupted if no significant shortening of the P-P interval is observed within 30 seconds or an ablation index target value of >350-500 or lesion stability index target

value of 4-5.5 is achieved. Points acquired during ablation are annotated by 2 mm tags.

It is recommended that ablation is continued until atrial electrical activity (HAFE) is significantly reduced (peak to peak bipolar electrogram < 0.05 mV) and vagal reflex disappears if present.

It is also recommended, at the end of ablation procedure, to confirm the significant reduction of atrial electrical activity by using of a final voltage map and by showing inability to capture at high output. In addition, a backup stimulation in the right ventricle is performed through a quadripolar catheter in case of prolonged asystolic response evoked during RF.

Basal cycle length, AH and Wenckebach cycle length are reassessed after RF ablation.

After catheter removal, atropine 2 mg (1m + 1m 5 min later) is administrated intravenously > 30 minutes after the last ablation.

Acute procedural **success** is defined as:

- Persistent AH shortening > 20 msec and/or persistent reduction in Wenckebach point cycle length < 500 msec

and

- Post RF P-P interval <70% of the baseline procedural P-P interval or P- P interval >600 msec after 10 minutes of waiting time (as mean value of 10 consecutive cycles)

Post RF inappropriate sinus tachycardia is temporarily treated with beta-blockers or ivabradine.

Patient questionnaire

PATIENT QUESTIONNAIRE

Patient ID:	CNA----------

Date of completion (dd-mm-yyyyy): _____- _____- _____

QUESTIONNAIRE	
(a) Did you completely lose consciousness for a moment? (syncope, fainting)	☐ Yes ☐ No
If yes, do you remember the date it happened? Go to question (c)	dd-mm-yyyyy: _____- _____- _____
(b) Or, alternatively, did you recognize any premonitory symptoms of impending loss of consciousness, without being followed by complete loss of consciousness? (presyncope)	☐ Yes ☐ No *(Note. Answers to (a) and (b) should not both be "Yes.")*
If yes, do you remember the date when it happened?	dd-mm-yyyyy: _____- _____- _____
(c) Was the episode characterized by rapid initiation, short duration, and complete spontaneous recovery?	☐ Yes ☐ No
(d) Is the episode similar to those you have had before?	☐ Yes ☐ No
(e) Did you have time to stop and lie down/sit down?	☐ Yes ☐ No
(f) Did other people witness the episode?	☐ Yes ☐ No

(g) Where did the episode happen?	☐ At home ☐ At work ☐ On public transportation ☐ On a private transportation vehicle, while driving. ☐ On a private transport, but I was not driving ☐ As I walked down the street Other, ☐ please specify: _____ _____
(h) What were you doing immediately before the event?	☐ I was lying ☐ I was ☐ sitting I ☐ was ☐ standing I was sitting down from a lying position ☐ I was standing up from a lying position ☐ I was eating ☐ I was under emotional stress Other, please specify: _____
(i) Did you experience any trauma as a result of the event?	☐ Yes ☐ No
(j) Did you go to the emergency room because of the trauma?	☐ Yes ☐ No
(k) Were you hospitalized because of the trauma?	☐ Yes ☐ No