STUDY PROTOCOL

Title: Endocardial ablation of ganglionic plexuses versus pacemaker implantation in patients with symptomatic sinus node dysfunction (DIS NERVA-PACE study).

Protocol code: 2021/307

Sponsor: Hospital Universitario Clínico Universitario de Santiago

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Project background and rationale

Symptomatic sinus node dysfunction (SND) comprises a series of symptoms attributable to incapacity of the sinus node (SN) to conduct or generate stimuli, and therefore to generate a heart rate adapted to the needs of the individual[1]. According to the latest report of the Spanish Pacemaker Registry, sinus node dysfunction (SND), or sick sinus syndrome, was the second most common cause of pacemaker implantation, after atrioventricular block (AVB), representing 28.4% of all implantations—with bradycardia-tachycardia syndrome being the most common disorder in this subgroup (5.9%), followed by sinus bradycardia (5.1%)[2]. Although the main cause of SND is considered to be intrinsic due to idiopathic progressive fibrosis of the conduction system related to patient age, SND can also be of extrinsic origin due to dysfunction of the autonomic nervous system secondary to an excessive increase in vagal tone[3]. In some cases, however, it may be attributable to the coexistence of both conditions, i.e., SND overlying an accentuated parasympathetic tone (particularly in younger patients with paroxysmal episodes).

For over 20 years, the autonomic nervous system (ANS) has been known to influence the development of both ventricular and supraventricular arrhythmias, and the appearance of disorders in conduction of the cardiac rhythm[4]. The ANS is composed of both the parasympathetic nervous system and the sympathetic nervous system, organized into a complex structure of three interconnected levels: a first cerebral level, a second spinal cord level, and a third cardiac level. The latter level in turn is composed of the ganglionic plexuses located at epicardial level. From the anatomical perspective, these plexuses comprise the right anterior ganglionic plexus, the left upper ganglionic plexus, and the left and right lower ganglionic plexus. One way of assessing the contribution of the anatomical component in cardiac impulse conduction is the atropine test: a positive or normal response (defined as an increase in frequency > 25% or > 90 bpm after atropine infusion according to some studies) could be associated to a greater autonomic dysfunction component in these patients and to a lesser intrinsic component[5]. According to the latest European clinical guides, patients presenting SSS with clinical and electrocardiographic correlation are candidates for cardiac pacing (level of recommendation IB), which has been shown to improve the symptoms without modifying survival[6]. However, despite pacemaker implantation, the recurrence of syncope has been reported in up to 17.5% of all cases at 5 years in this patient population, in some series[7]. This may be due to the frequent association between SSS and a neurally mediated or reflex mechanism.

For over a decade and after the confirmation of effective denervation in experimental models in dogs, there have been reports of endocardial radiofrequency ablation of the ganglionic plexus (GP) in the treatment of patients with neurally mediated syncope, SND or functional AVB - even as an alternative to permanent pacemaker implantation. This percutaneous technique, also known as cardiac neuromodulation, involves the location and subsequent radiofrequency ablation of the atrial epicardial parasympathetic ganglia through high-frequency stimulation in search of vagal responses, the presence of fractionated electrograms, or an empirical anatomical approach[8]. The final objective of parasympathetic denervation is to induce vagal reflex attenuation, thereby preventing cardioinhibition in these patients. The evidence on this technique is mainly focused on the treatment of neurally mediated syncope. In patients (n = 43) with neurally mediated recurrent syncope and a normal atropine test result, Pachon et al. found that after left and right endocardial denervation, only 6.9% of the patients showed recurrence of syncope (in two-thirds with a vasodepressor profile) over a mean follow-up of 45 months[9]. On the other hand, Debruyne et al., in a series of 20 patients with syncope and a positive tilt test or SSS and sinus pause > 3 sec, recorded a 95% decrease in the frequency of syncopal episodes at 6 months of follow-up, performing single denervation of the right anterior ganglionic plexus (RAGP) through a strictly right-side approach with ablation on the posteroseptal side of the junction between the superior vena cava and the right atrium[10]. In the group with SSS (n = 8), only one patient presented recurrence of syncope with a pause > 3 sec, and required pacemaker implantation. These results coincide with those obtained in a series of 115 patients with neurally mediated

syncope, in which ablation of the RAGP was the procedure most associated to an increase in heart rate, and where after 18 months a total of 92.2% of the patients had not presented recurrence of syncope (11). Lastly, the largest series in patients with SSS was published by Qin et al.[12]. These authors performed endocardial ablation of the four main left GP and of the plexus located between the aorta and the superior vena cava in 62 patients with symptomatic sinus bradycardia, achieving an increase in mean heart rate that proved less manifest in the group of patients > 50 years of age (n = 22). Despite this, only 13.6% of the patients in this subgroup required pacemaker implantation after 12 months—with no pacemaker implantation being needed in those under 50 years of age. At present, our center performs this intervention in patients with such characteristics, with good outcomes, and having avoided pacemaker implantation in 7 patients.

Scientific and practical interest of the project

Although this is a promising technique, no randomized studies have warranted its use in functional SSS. Furthermore, no solid long-term data are available, and most of the studies carried out to date involve heterogeneous groups of patients. At present, there is a randomized trial in the recruitment phase (NCT04149886) that will randomize patients to cardiac neuroablation followed by pacemaker versus direct pacemaker implantation, in which the primary endpoint will be percentage atrial stimulation. However, this trial will not contribute data on the safety of the strategy or any conclusions from the clinical perspective. Consequently, at this time, its usefulness in the context of more elderly patients—which are traditionally the subjects excluded from studies of this kind—is not known.

On the other hand, although pacemaker implantation is firmly indicated in the context of SND, it only affords symptomatic benefits, with no impact upon survival, and moreover has a non-negligible incidence of complications—particularly problems related to infection associated with the device. The fact that a technique is available, described as safe according to the published series and able to reduce the recurrences of syncope in certain groups of patients with associated autonomic dysfunction could modify the therapeutic algorithm—avoiding permanent pacemaker implantation from the start and thus obviating unnecessary ventricular pacing.

References:

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Methods:

Hypothesis

Cardiac neuroablation in patients with symptomatic SND with an autonomic component affords improved quality of life and is not inferior to dual chamber pacemaker implantation in terms of the recurrence of syncope.

Primary objective:
To assess differences in the improvement of quality of life at 6 months in both groups and between the two groups. The SF-36 health questionnaire will be used to evaluate symptoms. This is a widely validated instrument comprising 36 items or questions that address aspects referred to perceived health: physical function, physical role, bodily pain, general health, vitality, social function, emotional role and mental health. In addition, the questionnaire includes an item that evaluated the change in health condition versus the previous year. The SF-36 offers the advantages of being easy and rapid to complete, and simple to evaluate. Each health dimension or scale is scored from 0 (most negative perception) to 100 (most positive perception).

Secondary objectives:
- Pacemaker-free survival in the cardiac neuroablation group at 6 months.
- Differences in the recurrence of syncope and syncope-free survival at 6 months between the two groups.
- Change in maximal heart rate and chronotropic incompetence in the exercise test
- Differences in safety (complications) between the two procedures.

Material and methods:

1) *Study design*

A randomized, open-label multi-center clinical trial is proposed, coordinated by the Electrophysiology Unit of Hospital Clínico Universitario de Santiago (HCUS)(Spain). The study will include patients with syncope symptomatic SND and atropine test positivity, contrasting direct permanent pacemaker implantation from the start versus a ganglionic plexus ablation strategy, in terms of the improvement of symptoms and the recurrence of syncope at one year. Prior to inclusion in the study, all patients will undergo an electrocardiographic study, echocardiography, an atropine test, and a 6-minute walking test.

Treatment groups:
- Intervention group: Endocardial ablation of the ganglionic plexus (cardiac neuroablation).
- Control group: Dual chamber pacemaker implantation without cardiac neuroablation. Pacing programmed in AAIR-DDDR mode.

2) *Study setting*

The study will be carried out as proprietary research of the Electrophysiology Unit of Hospital Clínico Universitario de Santiago (HCUS). This will be a single-center study, and will be carried out in patients pertaining to this basic healthcare zone.

3) *Patient selection and withdrawal*

*Inclusion criteria:
- Patients over 40 and under 80 years of age.
- Syncope symptomatic SSS (at least one syncopal episode in the last year) with electrocardiographic evidence (sinus pause > 3 sec, sinus bradycardia with heart rate < 40 bpm, sinoatrial block or chronotropic incompetence in the exercise test).

*Exclusion criteria:
- Relevant structural heart disease (left ventricular ejection fraction < 50%, severe valve disease, hypertrophic cardiomyopathy, previous ischemic heart disease).

- Advanced atrioventricular conduction disorders (second-degree AVB [Mobitz II], complete AVB, advanced AVB).
- QRS interval >130 ms
- A mean life expectancy of less than 12 months.

*Therapeutic failure: in the cardiac neuroablation group, this is defined as the recurrence of syncope at one year. Failure of the procedure is defined as the impossibility of achieving adequate denervation, with a persistently positive atropine test.

*Study withdrawal criteria:
- Syncope secondary to SND registered with electrocardiographic evidence. These patients will be offered pacemaker implantation.
- Impossibility of achieving adequate denervation in the cardiac neuroablation group. In these cases, dual chamber pacemaker implantation will be indicated.

4) *Patient recruitment*

Recruitment will be made of consecutive patients admitted due to syncope secondary to SND in the Department of Cardiology or referred for outpatient pacemaker implantation due to symptomatic SND. The patients who meet the baseline inclusion criteria will be invited to participate in the study, with the selection of those presenting a positive atropine test result.

5) *Sample size*

The estimate sample size is 20 patients in each treatment arm.

6) *Study period*

The study will comprise a follow-up period and will have a duration of one year from the time of the intervention (pacemaker or endocardial ablation). During this year all the complementary tests and necessary clinical follow-up will be carried out. In total, from the presentation of this project, the estimated duration is two years.

7) *Randomization procedure*

Randomization will be performed independently using the OxMar (Oxford Minimization and Randomization) application. This is an open-access minimization and randomization application for clinical studies that operates online in a web setting. After adapting it to our study and following the design of a form, on entering the patient code the program performs minimization or simple randomization correcting for different variables. In our study, we will use sample randomization without stratification for any variable.

8) *Measurements and interventions (primary and secondary endpoints)*

*Primary endpoint:
- Differences in the improvement of quality of life between the two groups at 6 months. As commented above, this will be based on the SF-36 questionnaire, involving a numerical score of 0–100 for each of its 8 scales. The score obtained before the intervention will be compared with that recorded in the last year in both groups for each scale and as regards the total sum. In addition, to evaluate the difference in the improvement of quality of life, comparison will be made of the difference in the score at baseline and after one year between the two groups for each scale and as regards the total sum.

*Secondary endpoints:
- Pacemaker-free survival in the cardiac neuroablation group at 6 months. This will be based on clinical follow-up of the recruited patients.
- Differences in the recurrence of syncope and syncope-free survival at 6 months between the two groups. Comparison will be made of the number of syncopal episodes between both groups per patient and at one year. On the other hand, syncope-free survival will be analyzed. All this will be based on the clinical follow-up.
- Differences in baseline and 6 months exercise test between the two groups.

- Serious complications due to the procedure: in the cardiac neuroablation group, complications will be defined as cardiac tamponade, stroke, the need for urgent surgery and major vascular problems (fistula, aneurysm, bleeding requiring blood product transfusion). In the pacemaker group, complications will be defined as device-related infection, pneumothorax and hemothorax.

9) *Description of the intervention, test to be performed and program of visits*

*Description of the cardiac neuroablation technique: After obtaining informed consent and explaining the risks of the procedure, the patients randomized to the cardiac neuroablation group will undergo the technique under mild sedation. We first will measure the baseline AH and HV intervals, as well as the corrected sinus node recovery time after atrial pacing. Electro-anatomical mapping will be performed (Biosense Webster, USA) using a multipolar catheter both in the right atrium (RA) and in the left atrium (LA) following trans-septal puncture. The ganglionic plexus will be located in a hybrid manner: anatomical (RAGP, left upper GP, right lower GP, left lower GP) and searching for vagal responses after high-frequency pacing (bursts of 10 s, 20 Hz at 25 mA/1 ms duration) in the previously described anatomical zones with an ablation catheter. A new atropine test will be performed after the procedure, with adequate denervation being confirmed if the test proves negative. The patients in this group will remain admitted under continuous monitoring for at least 48 hours.

*Description of the pacemaker implantation technique: After obtaining informed consent and under local anesthesia in the left infraclavicular zone, the subclavian vein will be cannulated, with the insertion of two electrodes: one in the right atrium and the other in the right ventricle. They will be connected to the pacemaker generator, and the surgical wound will be closed. Programming will be made in AAI-DDDR mode. These patients can be discharged after 24 hours with no need for monitoring.

*Clinical follow-up: Clinical follow-up will be carried out at one, three, 6 and 12 months. Follow-up may be performed by telephone. The presence of symptoms and recurrence of syncope will be assessed over follow-up. The SF-36 quality of life questionnaire will be administered at 6 and 12 months.

*Confirmation of adequate denervation: The atropine test will be repeated after 6 months in the cardiac neuroablation group.

*Functional class assessment: The exercise test will be performed in both groups at 6 months.

*Electrocardiographic monitoring and follow-up of conduction disorders: Twenty-four hour Holter monitoring will be made at 2, 6 and 12 months in the cardiac neuroablation group. The patients with implantation of a dual chamber pacemaker will undergo interrogation of the device after 6 months and one year, with special attention to the evaluation of percentage atrial and ventricular pacing.

*Program of visits:

A) Cardiac neuroablation group:

- Month 1: Face-to-face visit for the atropine test, followed by 24-hour Holter monitoring.
- Month 3: Clinical follow-up via telephone.
- Month 6: Face-to-face visit for 24-hour Holter monitoring, exercise test, SF-36 questionnaire and clinical follow-up.
- Month 12: Face-to-face visit for 24-hour Holter monitoring, SF-36 questionnaire and clinical follow-up.

B) Pacemaker group:

- Month 1: Clinical follow-up via telephone.
- Month 3: Clinical follow-up via telephone.
- Month 6: Face-to-face visit for 6-minute walking test, SF-36 questionnaire, clinical follow-up, and interrogation of the device.
- Month 12: Face-to-face visit for 6-minute walking test, SF-36 questionnaire, clinical follow-up, and interrogation of the device.

10) *Timetable and planned study ending date. Distribution of tasks.*

*Timetable and phases of the project:

- Phase 1 (months 1 and 2): Development of the protocol and approval of the study by the local Ethics Committee. Preparation of all the documentation required for registry of the study with the

Spanish Agency for Medicinal Products and Medical Devices (AEMPS). Contact with the SCREN platform for trial monitoring and counseling. Following validation by the AEMPS, registry of the study with the Spanish Clinical Trials Network (REEC) and clinicaltrials.gov.
- Phase 2 (8–10 months): Recruitment and randomization of consecutive patients at Hospital Clínico Universitario de Santiago.
- Phase 3 (12 months): Clinical follow-up of the included patients.
- Phase 4 (1 month): Analysis of results.
- Phase 5 (2 month): Diffusion and publication of results.

Estimated study ending date: from the start of recruitment, the estimated duration of the study is two years.

*Distribution of tasks:
- Protocol design and preparation of the required documentation : Moisés Rodríguez/Carlos Minguito
- Patient recruitment: Department of Cardiology, HCUS.
- Pacemaker implantation: Electrophysiology Unit, HCUS.
- Endocardial ablation of ganglionic plexus: Moisés Rodríguez-Mañero
- Patient follow-up: Electrophysiology Unit, HCUS.
- Analysis and publication of results: Electrophysiology Unit, HCUS.

11) *Response assessment:*
Six months after the start of the study, monitoring will be made of the results obtained up to that time, and a report will be presented if required. This same evaluation will be repeated at one year and after 24 months.

Calculation of sample size and statistical analysis

*Calculation of sample size: Comparisons of two means will be made for the primary endpoint. On one hand, comparison will be made of the mean baseline SF-36 score and the mean score of the same questionnaire at 12 months in each group. Assuming a standard deviation of 20 points and an increase of 20 points in the SF-36 score at one year versus baseline, with a statistical power of 20% and an alpha risk of 5%, the estimated sample size is 20 patients in each treatment arm, assuming no losses over the period of follow-up.

*Statistical analysis of the variables: The normal distribution of the variables will be assessed using the Shapiro-Wilk test. Continuous variables will be reported as the mean and standard deviation, or as the median and interquartile range (IQR) in the absence of a normal data distribution. Comparisons will be made using the Student t-test or Wilcoxon test, as applicable. Categorical variables will be reported as percentages, and comparisons will be made using the Fisher exact test or the chi-squared test. Comparisons between the SF-36 score at baseline and after 12 months will be made using the Student t-test for paired samples. Likewise, the Student t-test for independent samples will be used to evaluate differences in the improvement of quality of life between the two groups. Survival analysis will be made based on the Kaplan-Meier method to assess pacemaker-free survival in the treatment group. This study will be repeated to evaluate syncope-free survival, and the log-rank test will be used to compare the two survival curves. The Student t-test will be used to evaluate differences in the 6-minute walking test between the two groups. The Fisher exact test will be used to evaluate differences in the proportion of patients with serious complications between the two groups. Statistical significance will be considered for $p < 0.05$. The STATA version 15.1 statistical package will be used throughout.

Safety and adverse effects
Safety of the cardiac neuroablation technique:
Despite its promising future in the treatment of SND with an associated autonomic component, this technique has been known for over 15 years. In the studies published to date in which ganglionic plexi ablation has been used concomitant to pulmonary vein ablation in the treatment of atrial fibrillation, the incidence of serious complications such as cardiac tamponade, death or stroke has been less than 1%. In fact, in the largest series published to date in the context of SND

(n = 62), no adverse events related to the procedure were reported. The greatest risk of serious complications is usually associated to trans-septal puncture. However, in our center, with over 150 trans-septal punctures a year, and with extensive experience in the ablation of atrial fibrillation, the complications rate is similar to that reported in other registries. On the other hand, the most frequent complications in ablation procedures are usually of a vascular nature, though these problems are mostly mild.

Safety of dual chamber pacemaker implantation:
Dual chamber pacemaker implantation is a safe and well-known procedure with a complications rate of 1–6%. The most relevant complications are pneumothorax secondary to access to the subclavian vein (0.9–1.2%) and electrode displacement (1.8–5.7%), with device-related infection being the most feared problem (1–1.3%), requiring removal of the system. However, in our center, with over 600 devices implanted yearly, the complications rate likewise coincides with the data found in other contemporary registries.

Ethical and legal aspects
1) Statement on compliance with the applicable regulations:

The investigators of this study agree to:
- Abide with the current regulations and to follow the guidelines of the Declaration of Helsinki and the Convention of Oviedo (Act 14/2007).
- Guarantee confidentiality of the information of the patients participating in the study, in accordance with current legislation on data protection (Organic Law 3/2018 (LOPD and GDD), RD 1720/2007 and Regulation (UE) 2016/679).
- Regulate access to the clinical histories of the patients and deliver informed consent (Act 3/2001, Act 3/2005, Act 41/2020, Decree 29/2009 (Galicia), Decree 164/2013 (Galicia) and instruction 6/2007 (Galicia)).

2) Documentation attached to the form (see in annexes): The following is submitted, attached to this form:
- Request for informed consent (in Spanish and Galician).
- Case report form (CRF) with the variables to be evaluated.
- Insurance policy.

Publications policy
The investigators of this project agree to complete the study and disclose and publish the results obtained.

Financial memorandum
The study is a proprietary initiative of the Electrophysiology Unit of Hospital Clínico Universitario de Santiago (HCUS), and has no benefit or commercial interests of any kind. Neither the investigators nor the Research Unit will receive any economic benefits derived from conduction of the present study.

This project will be financed by a research support grant of the cardiac rhythm section of the Spanish Society of Cardiology, following a public tender. The amount assigned by this grant for carrying out the study is 25,000 euros.