

STUDY PROTOCOL

**Prospective Randomized Comparison of Efficacy and Safety in Pacemaker and Defibrillator Implantation
Via Cephalic Versus Axillary Vein Access.
The CEPHAX Study.**

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1) Overview.

Cardiac implantable electronic devices (CIED), a term that includes pacemakers and cardiac defibrillators, are essential therapeutic tools for the management of arrhythmias in different clinical contexts. A fundamental step in the procedure of implant of a CIED is to establish a central venous access to be able to insert one or more catheters electrodes and to place them in the cardiac chambers. The most widespread venous access technique in our midst is the subclavian pathway. However, published studies confirm the superiority of axillary and cephalic venous access in terms of efficacy and safety in the short and long term. In spite of this, there are no recommendations on the part of the scientific societies, so the choice of the access route is totally dependent on the experience and preferences of the implant physician. To date, there are no studies in our midst comparing axillary and cephalic venous accesses performed with the technique optimized by trained electrophysiologist cardiologists.

A clinical trial is designed to compare the efficacy and safety of fluoroscopy-guided axillary venous access versus improved cephalic venous access in the CIED implant. The scope of the study will be constituted by the patients who are first implanted with a CIED and the study population will be the patients who are first implanted with a CIED in the Hospital General Universitario of Ciudad Real, Spain.

2) Introduction.

Cardiac implantable electronic devices (CIED) are essential therapeutic tools for the management of arrhythmias in different clinical contexts (1, 2). Under the name of CIED are grouped pacemakers and cardiac defibrillators. Worldwide, more than 1 million implants of these devices are carried out annually (3). In Spain CIED implants are made in 230 centers, 4 most CIED are implanted in electrophysiology laboratories by electrophysiologist and the number of implants follows an increasing trend, being in the year 2015 the incidence of pacemaker first implantations/million inhabitants of 611 and that of defibrillators of 118 (5, 6).

A fundamental step in the implant procedure of a CIED is to establish a central venous access in order to insert the electrode catheters and place them in the cardiac chambers. In most procedures ($> 80\%$) it is accessed by the left axilo-subclavian axis, reserving the right side for left-handed patients or with vascular problems on the lefthand side. According to data from the European Heart Rhytm Association (7), 60% of implanters use as a preferential access vein cephalic, 20% axillary vein and 20% subclavian. In our midst, however, this proportion is quite different, with subclavian access being much more widespread.

The access route for the implant of a CIED has prognostic implications. Cephalic access has shown, in the short term, a null incidence of pneumothorax compared with the axillary or subclavian pathway, (8-10) because it does not require puncturing the subclavian region. On the other hand, in the medium and long term, when the access roads are compared, the subclavian approach has been related to a higher incidence of electrode problems as insulation defects and conductor fractures (11-13) which seems due to anatomical factors that condition the electrode's crush (14).

The technique of access through the cephalic vein for the implant of CIED has been carried out for more than five decades (15). Since it requires greater surgical dexterity, it was initially performed preferably by thoracic or cardiac surgeons. With the time, thanks to the technical improvements that have increased their percentage of effectiveness (16-22). However, the main problem for its universalization remains the

lack of knowledge of the technique on the part of many operators and an effectiveness of less than 85%.

The subclavian vein technique of access for the implant of CIED has been carried out for more than four decades without variations in it (23). It has the advantage of specifying a lower learning curve and being a fast and reliable way of access. The risk of pneumothorax, and the damage problems of the electrodes in the medium and long term, make this technique the least desirable as a way of first choice.

The technique of access through the axillary vein has been the subject of multiple improvements to become a technique that brings together advantages of the previous two (24-28). On the one hand, its speed and low incidence of complications and, on the other, its high effectiveness and capacity to accommodate a greater number of electrodes than the cephalic pathway. However, in our midst it is a technique of scant diffusion among the implanters.

There are some studies that compared the safety and efficacy of venous access techniques in the CIED implant.

Three studies have compared the axillary vein against the subclavian. The retrospective study of Sharma G et al (29), which included 478 patients undergoing a fluoroscopy-guided subclavian or axillary pacemaker implant, showed a similar efficacy of both techniques and a greater incidence of pneumothorax with the subclavian pathway. The retrospective study of Kim KH et al (30), which included 1161 patients with an average follow-up of 8 years, was able to objectively lower long-term incidence of electrode-related complications by the axillary pathway. Finally, the prospective and randomized study of Liu P et al (31) that compared the axillary pathway "optimized" against the subclavian pathway, found a 5 times greater incidence of peri-procedural complications with the second.

Two studies have compared the axillary vein against cephalic. The prospective and randomized study of Calkins H et al (32) compared the safety and efficacy of CIED implant by cephalic access to axillary access guided by venography. It found a higher percentage of success and shorter duration of the procedure by the axillary pathway and there were no differences in the rate of peri-procedural complications. The limitation of this study is that the use of an axillary venous access technique guided by venography limits its applicability and increases the possible complications of the technique. The prospective and randomized study of Squara F et al (33) compared the safety and efficacy of CIED implant by Cephalic access to axillary access guided by fluoroscopy and performed by physicians without any training in the technique. This particular study found no difference in success or complications with both techniques, although it was objective a shorter time to get venous access by axillary. Finally, the prospective observational study of Chan NY et A (113) analyzed the success rate and long-term electrode problems of the techniques of cephalic, subclavian and axillary access guided by venography. The success of cephalic access was significantly lower than the other two. After an average follow-up of 73.6 months, the problem-free survival of the electrode was significantly higher with axillary and cephalic access.

3) Justification.

The studies published so far demonstrate the superiority of the axillary and cephalic venous accesses against subclavian venous access in the CIED implant in terms of efficacy and safety. However, the most widespread venous access technique in our midst remains the subclavian pathway.

There are no recommendations from scientific societies on which access road should be the first choice, so the technique used is totally dependent on the experience and preferences of the implant physician.

To date, there are no studies comparing axillary and cephalic venous accesses performed with the most optimized technique by trained personnel.

4) Hypothesis.

- The axillary venous access pathway is superior in terms of efficacy to the cephalic access.
- The axillary venous access pathway is equal in terms of safety to the cephalic access.

5) Main objective.

To compare the efficacy and safety of fluoroscopy-guided axillary venous access to improved cephalic venous access in the cardiac stimulation device implant.

6) Secondary Objectives:

- To compare the success rate of the accesses.
- To compare the duration of access procedures.
- To compare the duration of the implant according to the access.
- To compare the proportion of peri-procedural complications of the accesses.
- To compare the proportion of electrode problems at follow-up.

7) Methodology.

Design: randomized and open clinical trial in parallel groups.

Study population: The reference population is the patients who are implanted for the first time a CIED. The target population of the study will consist of patients who were first implanted with a CIED at the General University Hospital of Ciudad Real.

Selection criteria.

-Inclusion criteria: adults patients (>18 years old) with CIED implant indication at the General University Hospital of Ciudad Real who agree to participate in the study.

-Exclusion criteria: patients with one or more of the following characteristics:

- * pre-existing ipsilateral electrode,
- * ipsilateral lymphadenectomy,
- * cardiac resynchronization therapy indication.

Sample size and sampling procedure.

It is estimated that a sample size of 240 patients is needed for the study to have a 80% statistical power, an alpha value of 0.05 and taking into account the estimated losses due to lack of monitoring and/or data.

The selection of cases that will form the sample shall be conducted by consecutive sampling of all patients who are going to implant a CIED, meet the inclusion and

exclusion criteria, and give their consent to participate in the study. The cases will be allocated to each group (axillary venous access or cephalic venous access) by a procedure of 1:1 randomization by balanced blocks. Sealed envelopes with the number assigned to each of the subjects to be included will contain a card in which the type of venous access assigned will be required.

Period and scope of recruitment.

Patient recruitment will begin in september 2017 and continue until the required sample size is reached with an estimated time limit in december 2019.

Every patient, once recruited and performed the implant of the CIED, will be followed in the same way: before the discharge hospital with review of the device, the surgical wound and the chest X-ray and, later, ambulatory controls at 3, 6, 12 and 24 months of the Device and the generator bag.

The follow-up time will end with the completion of the study, but it may be sooner if the patient dies or moves from the hospital.

Variables:

1. Independent:

Age, sex, hypertension, diabetes, dyslipidemia, obesity, type of heart disease, renal failure, COPD, CIED indication, type of implanted CIED, assigned access route, number of implanted electrodes, type of electrode implanted.

2. Dependents:

- Efficacy: success of assigned access, duration of the access technique, duration of the procedure, time of copying, cephalic canalization, axillary canalization, finally canalized route, main cause in case of failure.
- Safety: Complications of the procedure, Pneumothorax, hematoma, dislocation electrode, venous thrombosis, long-term electrode problems, insulation defect, driver's fracture, need for new electrode implant.

8) Phases of the project and Plan of work.

The research project will be carried out in the arrhythmia unit of the General University Hospital of Ciudad Real. The two investigators will be in charge of the recruitment of the patients, the implant of the CIED and the data collection. The principal investigator will be in charge of the analysis of the data. Advice and collaboration for analysis will be requested from the HGUCR Research support unit. The commencement of recruitment will be in the fourth quarter of 2017 and completion in the fourth quarter of 2019. No funding is necessary for the realization of the project.

9) Sources of information and data analysis.

The data for the study will be obtained from the patient himself (data of filiation and personal history), of the data collection sheet that will be filled during the implant and in the postoperative and the ambulatory monitoring of the device. All data will be entered in a database with SPSS software for further analysis.

The quantitative variables will be represented by means of the mean +/-standard deviation and the qualitative variables as percentages.

To evaluate the degree of adjustment to the normality of the quantitative variables will be used the test Kolmogorov-Smirnov.

The comparison between the two study groups will be done through an intention-to-treat analysis. The comparison of quantitative and qualitative variables will be carried out with the Student's t test. The comparison of quantitative and qualitative variables with the test of the U of Mann-Withney and the comparison of two Qualitative variables with the χ^2 test. A logistics linear regression analysis will be used for multivariate analysis.

A level of statistical significance shall be considered a value of $p < 0.05$.

10) Ethical aspects.

- General ethical considerations:

The study compares two techniques of venous access for the implant of CIED that are perfectly described in the literature. Given the lack of rigorously compared to each other, there are currently no recommendations from scientific societies about which should be the first choice. Therefore, the decision to make one or the other depends fundamentally on the operator's preference and experience. Therefore, the impact on this patient population and the potential benefits derived from the results of an efficacy and safety study are important.

The prospective and randomized design of the study is justified by the greater scientific and methodological rigour that it involves.

The operators that will perform the study are perfectly trained in the realization of both techniques so that randomization will not cause any harm to the patient.

The investigators undertake to follow the procedures established by the Protocol and to inform and request the consent of all the participants. The institution is committed to ensuring the maintenance of assistance to the participants. Each of the Parties mentioned shall ensure the security and confidentiality of the identity of the subjects of the investigation.

The study will be conducted in accordance with the provisions of the Helsinki declaration (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

- Information to participants:

The patients will be informed by the Investigator of the characteristics of the study and the possibility of inclusion in it. The acceptance of the patient to participate will be recorded in writing in the informed consent.

The subjects will be informed about the confidentiality of their identity and the registered clinical information that can only be reviewed by the authorized personnel.

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