TRIPLE ATRIA EXTRASTIMULI VS PULMONARY VEIN ISOLATION ALONE IN PERSISTENT ATRIAL FIBRILLATION (HSC-AF TRIAL)

TRIAL LOCAL IDENTIFIER: 3-Extra
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PROTOCOL VERSION: 7.3 (September 22nd 2022)

Protocol Version	Date of change	Description and comments	Control
V1	2019		
V2	11-12-2019		
V3	23-12-2019		
V4	08-01-2020		
V5	24-01-2020		
V6	31-Marzo-2020	Add Rocket Platform + Statistics	
V7	20-Mayo-2020	Add Wall Thickness	CEIC Presentation
V7.1	20-06-2020	Minor typo changes + Map definition	
V7.2	22-09-2020	Add- Time Schedule Add- Number patients per center Add- Rocket Platform	CEIC Reviewed
V7.3	21-09-2022	Add- New version catheters	New Catheters- SubStudy 2

ATRIAL HIDDEN SLOW CONDUCION IN ATRIAL FIBRILLATION

1. BACKGROUND:

Atrial fibrillation (AF) is a very common arrhythmia that increases the risk of stroke, impairs quality of life, and is associated with increased overall mortality. [1, 2]

Since Haissaguerre et al observed, that AF was often triggered by ectopic atrial activity emerging from the pulmonary veins and that after ablating these ectopic foci, AF initiation was prevented in some patients with paroxysmal AF, Pulmonary vein isolation (PVI) has become the cornerstone treatment for AF, irrespective of AF type.[3, 4]

However, the rates of success of PVI alone are unsatisfactory in patients with persistent AF (PsAF) and may be 15% to 40% lower than those quoted for paroxysmal AF (PxAF).[5] There has long been a hypothesis that additional ablation beyond pulmonary vein isolation is required to achieve better outcomes in the population with persistent AF. Creation of linear lesions across critical structures of the left atrium and ablation of complex fractionated Atrial electrograms (CFAEs) were commonly used, but after results of STAR AF II study that showed no advantage in freedom from AF or atrial arrhythmias compared with PVAI alone, these techniques have become less used.[6]

New potential targets for adjuvant ablation are being investigated, which currently include ablation of dynamic phenomena during AF such as rotational ("rotors") and focal activations, ablation of scar regions in the atria, isolation of the left atrial posterior or ablating regions of fibrosis identified by MRI.[1, 7-13] The results of these new techniques have been mixed, many of which require complex technologies or extensive ablations that are not exempt from possible complications.

Atrial fibrosis leads to a vulnerable substrate created by conduction slowing and blocks, which promote re-entry.[14] Fibroblast-myocyte interaction further alters conduction velocity and action potential duration, further promoting functional re-entry.[15] Identification of atrial scar (low voltage areas or late enhancement on MRI) predict AF recurrence after PV isolation and could be helpful to guide substrate ablation.[10, 16] The end stage of atrial remodeling is fibrosis. Electrical remodeling can precede fibrosis appearing reduction in conexin expression that results in reduced intercellular coupling with electrical impulse conduction impairment.

Jadidi et al.[17] described the locations of areas of continuously fractionated atrial electrograms during atrial fibrillation in patients with paroxysmal AF and with PsAF. Then correlated these areas with the locations of fractionated atrial potentials during sinus rhythm and coronary sinus (CS) pacing in the same patients. Their premise was that fractionation resulted from conduction abnormalities secondary to atrial remodeling (conduction slowing/block, pivot points, asynchronous activation, and wave collision). They postulated that areas exhibiting fractionation during all 3 rhythms may differentiate fixed atrial/anatomic substrate (structural remodeling) from wave collision or functional slow conduction. However, there was little or no correlation between the locations of continuously fractionated electrograms during AF, during sinus rhythm and/or during CS pacing.

Yang et al.[13] proposed the elimination of complex electrograms suggestive of slow conduction in transitional voltages zones during sinus rhythm in patients with PsAF but to this, they extended the ablation to the whole area of low voltage to homogenize the scar and they did not compare it to PVI alone but to PVI and an stepwise strategy that included LA roof, the mitral isthmus, and the CTI followed by ablation of the CFAEs. In their results they did not find a significant impact on late recurrence of AF.

Short-coupled stimulation is used for slow conduction identification during VT substrate mapping.[18] Abnormal ventricular areas related to VT display decremental conduction. Double ventricular extrastimuli technique permits identification of hidden slow conduction (HSC) improving arrhythmia substrate identification.[19] Unlike what happens during atrial fibrillation, in which the fractionation sites can be pivot points of wavelets or sites of wave collision, the appearance of fractionation when stressing intra-atrial conduction with short coupling mainly expresses areas of slow or poor conduction cell coupling. Analysis of the response to closely coupled atrial extrastimuli could identify areas of slow conduction that can promote reentry and AF maintenance. HSC identification could improve AF substrate mapping and guide ablation.

2. STUDY PURPOSE

The aims of the current study are

- To investigate the presence, characteristics and location of complex electrograms suggestive of slow conduction zones elucidated by triple atria extrastimuli during sinus rhythm in paroxysmal and persistent AF
- Correlate atrial HSC- electrograms during sinus with continuously fractionated electrograms during AF in patients with persistent AF
- Test the hypothesis that elimination of atrial HSC-EGM in addition to PVI would improve ablation outcomes in PsAF patients versus PVI alone in a randomized study.

3. STUDY INVESTIGATORS

3.1 STUDY INVESTIGATORS AND PARTICIPATING CENTERS

This clinical study will be conducted by qualified investigators who have proven experience with AF ablation procedures and clinical studies. The following investigators and centers will participate:

1. Etel Silva. Dr. Marcos Fernández. Hospital Universitario Puerta del Mar, Cádiz (Spain). EMail:esilgar@gmail.com, hattrieckmarcos@hotmail.com
2. Dr. Antonio Berruezo. Dr. Diego Penela. Dra Beatriz Jáuregui. Hospital Teknon, Barcelona (Spain). EMail: antonio.berruezo@quironsalud.es, dpenela30@gmail.com, beatrizjg86@gmail.com
3. Dr. Alonso Pedrote. Dr. Juan Acosta. Hospital Universitario Virgen del Rocío, Sevilla (Spain). EMail: pedroteal@hotmail.com, juan.acostamartinez@gmail.com
4. Dr. Felipe Bisbal. Hospital Universitari German Trias i Pujol, Badalona (Spain). EMail: f.bisbalvb@gmail.com
5. Oscar Cámara. Universitat Pompeu Fabra, Barcelona (Spain). Email: oscar.camara@upf.edu

Hospital Universitario Puerta del Mar, Hospital Teknon, Hospital Universitario Virgen del Rocío and Hospital Universitari German Trias i Pujol will be involved in the Sub-study 2, with patient recruitment not inferior of 15 patients per centre.

3.2 COORDINATING CLINICAL INVESTIGATOR

The following investigators will be the study Coordinating Clinical Investigators:

Drs. Lucas Cano Calabria y Juan Fdez-Armenta Pastor

Hospital Universitario Puerta del Mar. Sº Cardiología. Sección de Arritmias

Av. Ana de Viya, 21, 3ª planta. 11009 Cádiz.

Mail: canocalabria@gmail.com, juanfdezarmenta@gmail.com

4. LEGAL AND ETHICAL ISSUES

Every patient will be informed and a procedural consent will be given to be signed agreeing with the protocol.

All procedures performed in this study will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study is framed in Real Decreto 1090/2015 and Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products.

4.1 Confidenciality.

All data will be confidential and treated according to the Data Protection Law (Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales y Reglamento General de Protección de datos). All images will be anonymized for the post processing analysis.

All data regarding patient information and images from every centre will be accurately pseudo anonymized in each centre before uploading them to a secure database integration platform located at Universitat Pompeu Fabra (Rocket platform).

The transfer process will be performed throughout a virtual network with allowed access just for the partners belonging to the project.

Sub-study 1 (ANALYSIS OF HIDDEN SLOW CONDUCTION ELECTROGRAMS IN PAROXISMAL AND PERSISTENT ATRIAL FIBRILLATION. HSC-AF STUDY):

1.1. OBJETIVES

HYPOTHESIS Left atrial EGM showing HSC elucidated by atria extrastimuli should be more manifest in persistent versus paroxysmal AF and should de more spatially and temporarily reproducible compared to fractionated EGM during AF

STUDY OBJETIVES

1.1 Describe the method to elucidate HSC using a triple atrial extrastimuli
1.2 Analyze the characteristics and location of HSC-EGMs
1.3 Compare the presence, burden, characteristics and location of HSC-EGMs in paroxysmal versus persistent AF
1.4 Compare the presence and location of HSC-ECGs with fractionated EGM during AF

1.2. METHODS

Summary of methods: 10 patients with paroxysmal AF and 10 patients with PsAF who undergoing a first-time ablation procedure for AF will be consecutively included to describe the complex electrograms (presence, distribution, number of deflections, amplitude, duration, delta of EGM width) elucidated by triple atria extrastimuli during sinus rhythm.

1.2.1 INCLUSION CRITERIA

Patients meeting all the inclusion criteria and none of the exclusion criteria could be considered for inclusion in the study. Patients can only be asked to participate if all of the following criteria apply:

- Age > 18 years.
- Patients undergoing a first-time ablation procedure for AF.
- Patients with persistent or long-lasting AF; persistent AF will be defined as a sustained episode lasting >7 days and <1 year; long-lasting persistent AF will be >1 year and <3 years
- Patients with PxAF; PxAF will be defined as a sustained episode lasting <7 days;
- Patients who must be willing and able to comply with all periablation and follow-up requirements
- Patients with AF who will accept the procedure of ablation
- Patients who signed the written informed consent for the study
- Patients who can endure the required follow-up.

1.2.2 EXCLUSION CRITERIA

Patients will be excluded from the study if they meet any of the following criteria:

- Age < 18 years.
- Pregnancy.
- Patients with PsAF with a sustained episode lasting >3 years
- Patients with previous radiofrequency (RF) ablation
- Patients with contraindications to systemic anticoagulation with heparin or Coumadin or a direct thrombin inhibitor
- Patients with thromboemboli in left atrial appendage
- Patients with left atrial size ≥55 mm (2-dimensional echocardiography, parasternal long-axis view)
- Patients with severe structural cardiac disease (severe mitral regurgitation, dilated cardiomyopathy, hypertrophy cardiomyopathy, other severe valvular heart diseases)

- Patients with the serum creatinine >3.5 mg/dL or creatinine clearance rate <30 mL/min;
- Patients with life expectancy <12 months;
- Medical, geographical and social factors that make study participation impractical, and inability to give written informed consent. Patient's refusal to participate in the study.

1.2.3 PREPROCEDURAL INTERVENTIONS

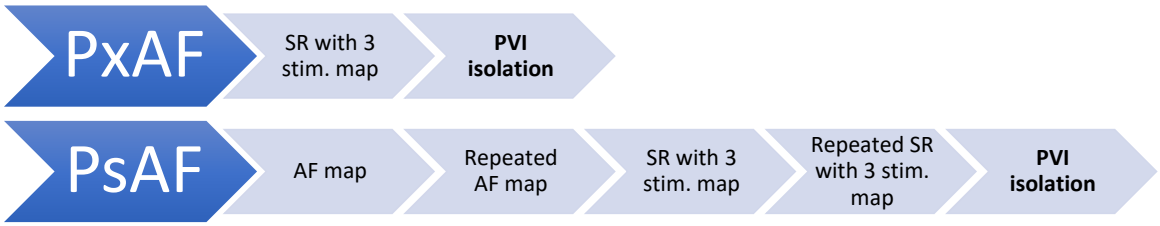
The usual clinical protocol for preparation for AF ablation will be followed. This includes as complementary tests: blood tests, echocardiography and cardiac CT. CT images will be analyzed with ADAS-3^{TM} (Galgo Medical, Barcelona, Spain) to obtain 3D wall thickness maps.

1.2.4 ELECTROPHYSIOLOGIC STUDY

High-density voltage mapping using a multipolar catheter (PentaRay, Biosense Webster, Diamond Bar, CA, USA) will be performed during sinus rhythm in PxAF patients. During mapping, manual points after a triple extrastimulus from LA appendage will be acquired to fill all color gaps on the LA map using Carto3 with an interpolation of 6 mm for the color threshold. Triple extrastimulus will be delivered at atrial effective refractory period (AERP)+60ms plus AERP + 60 ms plus AERP +40–20ms. Adequate endocardial contact will be confirmed by stable electrograms, the distance to the geometry surface. The bandpass filter will be set at 30–500 Hz. HSC-EGM are represented with green dots. Highly fragmented EGM in SR with pink dots. Double potentials (with isoelectric line) in blue.

In PsAF patients starting the procedure in AF, a high-density map will be acquired during AF. Visually detected CFAE will be annotated with pink dots. In this subgroup of patients (10 PsAF cases) a second map will be acquired to confirm the reproducibility of this methodology and compare the location and morphology of the complex electrograms between the two acquisitions. After this second map electrical cardioversion (≤3 external biphasic shock 200-360J) will be performed to restore sinus rhythm. During sinus rhythm two consecutive high-density maps with triple extrastimuli will be constructed as previously described.

Figure. Substrate maps acquisition workflow



1.2.5 RADIOFREQUENCY ABLATION

Procedures will be performed under conscious sedation or general anesthesia. Hemodynamic monitoring was done with a radial arterial catheter. Peri-procedural anticoagulation with a first 0,5 mg/kg IV dose of unfractionated heparin (UFH) immediately after transeptal puncture and periodic activated clotting time (ACT) sampling was obtained every 30 minutes to guide further bolus dosing with a target ACT between 300 and 350 seconds. Transeptal puncture was either guided by peri-procedural transesophageal echocardiography (TEE), intracardiac ultrasound or by a pressure and die method using a non-steerable sheath (Mullins, Cook Inc., Bloomington, IN, USA). If TEE was not performed during the procedure to guide transeptal access, it was performed previously to exclude intracavitary thrombus. The CARTO3® system (Biosense Webster, Diamond Bar, CA, USA) was used for ablation. An open irrigated, 3.5-mm tip, ablation

catheter (ThermoCool® SmartTouchTM, Biosense Webster, Diamond Bar, CA, USA) was used for mapping and ablation. First of all, a fast-anatomical map (FAM) of the PVs and the left atrium was acquired. PVI is performed by point-by-point RF applications guided with ablation index (350-450 *f)* to create a RF circle around the PV ostia (nephroid shape). In case of a common ipsilateral vein ostium, the line was drawn around the trunk. Acute PVI was confirmed after first pass with the usual local method by demonstrating entry and exit block with the ablation catheter placed sequentially in each of the PVs. A 10-minute waiting period after isolation of each ipsilateral PV pair was applied to assess for acute reconnections. Additional RF applications were performed if needed at reconnection sites until PVI was achieved.

1.2.6 SUBSTRATE MAPS AND ATRIAL ELECTROGRAM ANALYSIS

Low-voltage areas will be defined as sites of 3 adjacent low voltage (<0.5 mV) points, which were <5 mm apart from each other.[20]

Scar tissue < 0.05mV
Healthy tissue > 0.5mV
0.05mV < Border Zone < 0.5mV

EGMs with high electrical noise, or poor signal quality reducing accurate assessment of abnormal EGMs were discarded

The signals during sinus rhythm will be divided into 3 types according to their electrogram waveforms:

- *Normal* (sharp electrograms with <=3 positive or negative distinct peaks or electrogram duration <40 ms).[21, 22]
- *Complex EGM during SR*:
  - Fractionated (with >4 positive or negative distinct peaks and electrogram duration >=40 ms). Highly fragmented with ≥5 peaks ±63 ms.
  - Double potential: 2 or more separate deflections separate by an isoelectric interval.[21, 22]
- *HSC-EGM*: sites that show highly fragmented or double electrograms in response to triple extrastimuli, presenting normal or fractionated electrogram in sinus rhythm (see figure). Sites will be determined by visual analysis during EAM acquisition and will be analyzed offline after the procedure. Delta of duration of the bipolar EGM (third stimulated atrial EGM duration – atrial EGM duration of the sinus beat prior to triple extrastimuli) in milliseconds will be recorded.

Electroanatomical maps acquired during AF will be used to draw automatic CFAE maps using the CFAE-CARTO® module with the nominal setting of SCI CFAE maps.

CARTO-Finder module will be used to identify areas of potential driver activity. During AF mapping PentaRay catheter will be sequentially positioned at various LA sites. A potential driver is defined as repetitive patterns of activation that was either *focal* with radial activation over ≥2 consecutive wavefronts or *rotational* activity with ≥1.5 rotations of 360º.[23]

1.2.7 HOW TO NAME THE MAPS AND TAGS

How to label the Maps:

The different maps will be named according to the branch of the study:
Two branches, 10 PxAF Patients and 10 PsAF patients.

a) 10 PxAF Patients: 10 maps in Sinus Rhythm with 3 extra protocol

Name of the map to analyze: **RS_PxAF_SubStudy1**

b) 10 PsAF Patients (Protocol): Maps in AF Rhythm → ECV →Maps in RS With 3 extra protocol

1st Map in AF: to check CFAES: **AF_PsAF_ Std1**

2nd Map in AF: Re-Check CFAES: **AF_PsAF_ Std1_Rep**

1st Map in SR: apply 3 extra: RS_PsAF: **RS_PsAF_3Extra_ Std1**

2nd Map in SR: apply 3 extra: RS_PsAF: **RS_PsAF_3Extra_ Std1_Rep**

How to label the tags:

1.- AF Rhythm Maps:

CFAE (Pink): CFAE_AF

2.- SR Maps:

Highly Fragmented (Pink) : Highly_Fragmented

Double Potential Blue): Double_Potential

Positive for 3 extra (Green): Positive_3Extra

Negative for 3 extra (Orange): Negative_3Extra

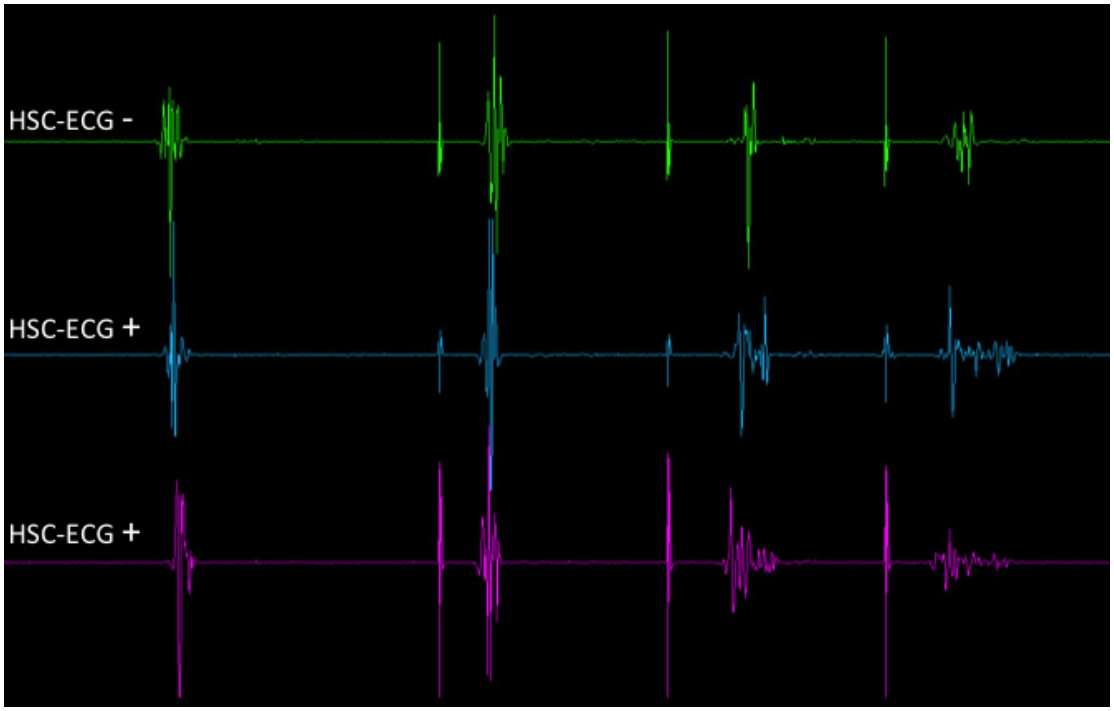


Figure: Examples of HSC-EGM

The left atrium will be divided into six regions according to Nuñez-Garcia et al.[24], as follows (Figure) : inter-atrial septal wall (R1), posterior wall and LA floor (R2), left lateral Wall (R3), anterior Wall (R4), roof and posterior Wall(R5).

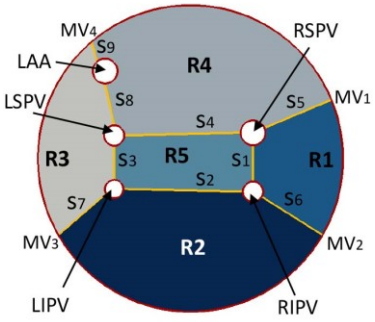


Figure: LA segmentation[20]

After the first descriptive part of the study, all patients who fulfill the inclusion criteria will be consecutively enrolled and randomized on a 1:1 basis to PVI alone vs PVI plus slow conduction ablation.

***Sub-study 2* PULMONARY VEIN ISOLATION PLUS SLOW CONDUCTION ABLATION ELUCIDATED BY TRIPLE ATRIA EXTRASTIMULI VS PULMONARY VEIN ISOLATION ALONE IN PERSISTENT ATRIAL FIBRILLATION (HSC-AF TRIAL)**

2.1 OBJETIVES

HYPOTHESIS Elimination of atrial HSC-EGM in addition to PVI would improve ablation outcomes in PsAF patients versus PVI alone

STUDY OBJETIVES

1. Analyze the characteristics and location of HSC-EGMs in PsAF
2. To evaluate feasibility, safety and efficacy of HSC ablation plus PVI
3. To assess other procedural outcomes obtained from both ablation procedures: Procedure time, mapping time, RF time, number of RF applications.
4. To compare the clinical outcomes (freedom from AF after procedure) between both ablation procedures (PVI plus HSC ablation vs. PVI alone).

2.2 METHODS

Summary of methods: 105 patients with PsAF who undergoing a first-time ablation procedure for AF and fulfill inclusion criteria will be consecutively enrolled and randomized on a 1:1 basis to PVI alone vs PVI plus HSC ablation.

2.2.1 ENDPOINTS

PRIMARY ENDPOINT

The primary end point of the study (efficacy) will be freedom from any atrial arrhythmia (other than isthmus dependent atrial flutter) without the use of antiarrhythmic drugs at 12 months after a single ablation procedure. Patients with AF that occur in the first 3 months after the ablation (blanking period) will be censored. Each episode that lasted >30s is regarded as a recurrence.

SECONDARY ENDPOINTS

The following secondary endpoints will be considered: time to first persistent AF (more than 7 days) after blanking period (efficacy), any atrial arrhythmia (other than isthmus dependent atrial flutter) on antiarrhythmic drugs at 12 months after a single ablation procedure after blanking period (efficacy), AF burden (% time AF in 24h Holter) (efficacy), incidence of periprocedural complications (safety), procedure time (feasibility), fluoroscopy time (feasibility), number of RF applications (efficiency), RF delivery time (efficiency).

2.2.2 INCLUSION CRITERIA

Patients meeting all the inclusion criteria and none of the exclusion criteria could be considered for inclusion in the study. Patients can only be asked to participate if all of the following criteria apply:

- Age > 18 years.
- Patients undergoing a first-time ablation procedure for AF.
- Patients with persistent or long-lasting AF; persistent AF will be defined as a sustained episode lasting >7 days and <1 year; long-lasting persistent AF will be >1 year and <3 years
- Patients who must be willing and able to comply with all periablation and follow-up requirements
- Patients with AF who will accept the procedure of ablation
- Patients who signed the written informed consent for the study

- Patients who can endure the required follow-up.

2.2.3 EXCLUSION CRITERIA

Patients will be excluded from the study if they meet any of the following criteria:

- Age < 18 years.
- Pregnancy.
- Patients with PxAF; PxAF will be defined as a sustained episode lasting <7 days;
- Patients with PsAF with a sustained episode lasting >3 years
- Patients with previous radiofrequency (RF) ablation
- Patients with contraindications to systemic anticoagulation with heparin or Coumadin or a direct thrombin inhibitor
- Patients with thromboemboli in left atrial appendage
- Patients with left atrial size ≥55 mm (2-dimensional echocardiography, parasternal long-axis view)
- Patients with severe structural cardiac disease (severe mitral regurgitation, dilated cardiomyopathy, hypertrophy cardiomyopathy, other severe valvular heart diseases)
- Patients with the serum creatinine >3.5 mg/dL or creatinine clearance rate <30 mL/min;
- Patients with life expectancy <12 months;
- Medical, geographical and social factors that make study participation impractical, and inability to give written informed consent. Patient's refusal to participate in the study.

2.2.4 STUDY SIZE AND DURATION

105 patients undergoing a first-time ablation procedure for AF will be consecutively enrolled and randomized on a 1:1 basis to PVI alone vs PVI plus slow conduction ablation.

An enrollment log with all the patients included in the study, even drops out, will be collected.

Data will be collected at enrollment, baseline and at three, six and 12-month follow-up visit.

2.3 PROTOCOL DESCRIPTION

VISIT / **PROCEDURES**	Enrollment	Baseline	Randomization 1:1	Ablation	Pre-discharge	3 M	6 M	12 M
Informed Consent	X							
Inclusion/Exclusion criteria	X							
Re-evaluation Inclusion/exclusion criteria		X						
Demographic Data		X						
Medical History		X						
Cardiovascular medication		X			X	X	X	X
Transesophageal echocard. (TEE)				X(*)				
Transthoracic Echocard. (TTE)	X				X(*)			
Randomization			X					
Ablation Data (RF, time, etc.)				X				
12 lead ECG		X				X	X	X
24-hour Holter						X	X	X
Protocol Deviation	X(*)	X(*)	X(*)	X(*)	X(*)	X(*)	X(*)	X(*)
Adverse Event	X(*)	X(*)	X(*)	X(*)	X(*)	X(*)	X(*)	X(*)
Termination	X(*)	X(*)	X(*)	X(*)	X(*)	X(*)	X(*)	X(*)

(*) If applicable

2.3.1 ENROLLMENT VISIT

During the Enrollment visit the following tasks will be completed:

- Patient eligibility check (inclusion/exclusion criteria). Only patients that meet all of the inclusion criteria and none of the exclusion criteria can be approached to participate.
- Patient agrees in participate and signs and dates the patient informed consent.
- Prior reports of cardiac imaging studies (transthoracic echocardiography) will be collected

2.3.2 BASELINE VISIT

The baseline visit must be performed after the patient has signed the informed consent form and prior to the AF ablation procedure. The patients will be evaluated clinically and the following data will be collected and procedures performed:

- Patient demographic data
- Clinical evaluation with a physical examination
- Medical and cardiovascular history
- Pre-procedure TTE/TEE
- Current cardiac medication
- 12-lead ECG
- Adverse Events Notification (if applicable)
- Protocol Deviation (if applicable)
- Termination (if applicable)

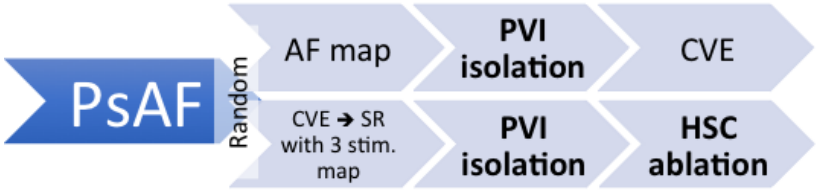
2.3.3 PREPROCEDURAL INTERVENTIONS

The standard clinical protocol for preparation for AF ablation will be followed. This includes as complementary tests: blood tests, echocardiography and cardiac CT. CT images will be analyzed with ADAS-3TM (Galgo Medical, Barcelona, Spain) to obtain 3D wall thickness maps.

2.3.4 RANDOMIZATION

Patients will be randomly assigned to each of the ablation procedures (PVI plus HSC ablation vs. PVI alone) on a 1:1 basis before the procedure

2.3.5 ELECTROPHYSIOLOGIC STUDY



ABLATION PROTOCOL IN THE PVI PLUS HSC ABLATION GROUP:

Procedures will be performed under conscious sedation or general anesthesia. Hemodynamic monitoring was done with a radial arterial catheter. Peri-procedural anticoagulation with a first 0,5 mg/kg IV dose of unfractionated heparin (UFH) immediately after transeptal puncture and

periodic activated clotting time (ACT) sampling was obtained every 30 minutes to guide further bolus dosing with a target ACT between 300 and 350 seconds. Transeptal puncture was either guided by peri-procedural transesophageal echocardiography (TEE), intracardiac ultrasound or by a pressure and die method using a non-steerable sheath (Mullins, Cook Inc., Bloomington, IN, USA). If TEE was not performed during the procedure to guide transeptal access, it was performed previously to exclude intracavitary thrombus.
Cardioversion will be delivered to restore SR (≤3 synchronized, biphasic direct current shocks (150 J, 200 J, and 200 J). High-density voltage mapping using a multipolar catheter (PentaRay or Octaray, Biosense Webster, Diamond Bar, CA, USA) will be performed. During mapping, manual points after a triple extrastimulus from LA appendage will be acquired to fill all color gaps on the LA map using Carto3 with an interpolation of 6 mm for the color threshold. Triple extrastimulus will be delivered at atrial effective refractory period (AERP)+60ms plus AERP + 60 ms plus AERP +40–20ms. Adequate endocardial contact will be confirmed by stable electrograms, the distance to the geometry surface. The bandpass filter will be set at 30–500 Hz. HSC-EGM are represented with green dots and highly fragmented EGM with pink dots, double potentials in blue.

Then, PVI will be performed with the standard protocol, using entrance and exit block as the electrophysiological end point. An open irrigated, 3.5-mm tip, ablation catheter (ThermoCool® SmartTouchTM or QDot Micro™, Biosense Webster, Diamond Bar, CA, USA) was used for mapping and ablation. First of all, a fast-anatomical map (FAM) of the PVs and the left atrium was acquired. PVI is performed by point-by-point RF applications guided with ablation index (350-450 f) to create a RF circle around the PV ostia (nephroid shape). In case of a common ipsilateral vein ostium, the line was drawn around the trunk. Acute PVI was confirmed after first pass with the usual local method by demonstrating entry and exit block with the ablation catheter placed sequentially in each of the PVs. A 10-minute waiting period after isolation of each ipsilateral PV pair was applied to assess for acute reconnections. Additional RF applications were performed if needed at reconnection sites until PVI was achieved.
After PVI isolation point-by point ablation targeting HSC-EGMs will be performed. HSC-EGMs with a distance less than 5 mm between them will be addressed with a single application. The ablation index will be defined based on the LA wall thickness (LAWT) at the location of the HSC-EGM: LAWT < 1mm: 300 *f*, LAWT 1-2 mm: 350 *f*, LAWT 2-3 mm: 400 *f* and LAWT >3 mm: 450 *f*. This is the experimental intervention added to pulmonary veins isolation. This intervention, in terms of risks, is superimposable to the ablation of CFAEs or rotational activity, which are stablished techniques for PsAF catheter ablation.[24]

Substrate maps and atrial electrogram analysis will be performed as described in sub-study 1 (1.2.6)

ABLATION PROTOCOL IN THE PVI GROUP:

High-density voltage mapping using a multipolar catheter (PentaRay or Octaray, Biosense Webster, Diamond Bar, CA, USA) will be performed during AF. PVI will be performed with the standard protocol (previously described). If needed electrical cardioversion will be performed after PVI ablation. A 10-minute waiting period after isolation of each ipsilateral PV pair was applied to assess for acute reconnections. Additional RF applications were performed if needed at reconnection sites until PVI was achieved. (see 2.3.5).

2.3.6 HOW TO NAME THE MAPS

How to label the Maps:

The different maps will be named according to the branch of the study:

a) PVI alone : Ablation in AF Rhythm and ECV post: **AF_PsAF_ Std2**

b) PVI plus HSC ablation : ECV + 3Extras +PVI ablation + HSC Ablation: **RS_PsAF_3Extra_ Std2**

How to label the tags:

1.- AF Rhythm Maps:

CFAE (Pink) : CFAE_AF

2.- SR Maps:

Highly Fragmented (Pink) : Highly_Fragmented

Double Potential Blue): Double_Potential

Positive for 3 extra (Green): Positive_3Extra

Negative for 3 extra (Orange): Negative_3Extra

2.3.7 PRE-DISCHARGE

The pre-discharge visit must be performed within 3 days of the ablation procedure and before the patient is discharged from hospital. For all patients, the following procedures must be performed:

- Adverse Events Notification (if applicable)
- Protocol Deviation (if applicable)
- Termination (if applicable)

Regarding medications prior discharge, antiarrhythmic drugs will be reinitiated after the procedure. A control TTE will be done at 8 hours after the procedure and after reintroduction of oral anticoagulation and will be advisable in case any procedure-related complication is suspected.

2.3.8 FOLLOW-UP

THREE-MONTH FOLLOW-UP

Clinical follow-up will include an outpatient clinic visit three months after ablation procedure. 12-lead ECG and 24-hour ambulatory Holter monitoring will be performed.

Successful ablation will be defined as absence of episodes of any atrial arrhythmia (other than isthmus dependent atrial flutter) that last >30 seconds.

SIX-MONTH FOLLOW-UP

Clinical follow-up will include an outpatient clinic visit six months after ablation procedure. 12-lead ECG and 24-hour ambulatory Holter monitoring will be performed.

Successful ablation will be defined as absence of episodes of any atrial arrhythmia (other than isthmus dependent atrial flutter) that last >30 seconds.

TWELVE-MONTH FOLLOW-UP

Clinical follow-up will include an outpatient clinic visit twelve months after ablation procedure. 12-lead ECG and 24-hour ambulatory Holter monitoring will be performed.
Successful ablation will be defined as absence of episodes of any atrial arrhythmia (other than isthmus dependent atrial flutter) that last >30 seconds.

2.4. STATISTICAL METHODS

2.4.1 SAMPLE SIZE: The sample size calculation will be based on the hypothesis and study design. Previous studies shown 50% success rate based on PVI alone, we expect 70% of success rate based on PVI plus HSC ablation. To test whether on PVI plus HSC ablation strategy was superior PVI alone, we determined that 105 patients were needed, with a randomization ratio of 1:1 for the study to have a power of 85% at an alpha level of 0.05 and Assuming a dropout rate of 10%.

2.4.2 STATISTICAL ANALYSIS

Statistical analysis will be performed using SPSS (version 23, SPSS Inc., Chicago, IL).
The primary end point analysis will be based on an intention to-treat principle that compared treatments that were randomized. All protocol deviations will be included. In each group, the length of time before the recurrence of AF will be compared using Kaplan–Meier curves. All times to event end points will be analyzed using log-rank tests, and a P value of <0.05 was considered to indicate statistical significance. For the purposes of this study, a Cox regression model with treatment and center will be used. Subgroup analyses based on age, LA size, AF duration, and health of the LA will be performed with Cox proportional hazards regression, and the interaction of each subgroup factor and treatment will be tested. Continuous variables will be summarized using descriptive statistics (mean, SD, median, and range), comparisons between the randomization groups will be performed using t tests, and the equivalent nonparametric method and Wilcoxon rank tests will be used in cases in which the assumptions required for a t test were violated. The normality of the data will be checked using box plots, normal quartile plots, and normality tests. The results will be expressed in terms of P values. All categorical data will be presented as frequencies and percentages, and comparisons between the randomization groups will be performed using $\chi 2$ tests or Fisher exact test. The results will be expressed as P values.

ABBREVIATIONS

AF = Atrial Fibrillation

PxAF = Paroxysmal AF

PsAF = Persistent AF

PVI = Pulmonary Vein Isolation

CFAEs = Complex Fractionated Atrial Electrograms

HSC = Hidden Slow Conduction

EGM = ElectroGraMs

CS = Coronary Sinus

ACT = Activated Clotting Time

TEE = TransEsophageal Echocardiography

TTE = TransThoracic Echocardiography

FAM = Fast-Anatomical Map

RF = RadioFrequency

AERP = Atrial Effective Refractory Period

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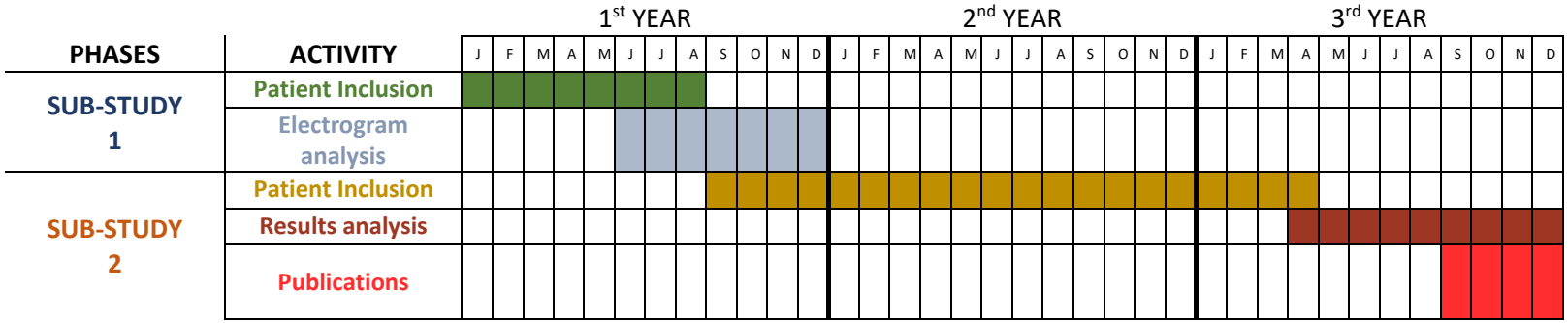
APPENDIX B: Time Schedule



APPENDIX C: Data collection sheet

PATIENT ID: ……

ABLATION DATE: ..... /..... /.....

CENTER: HUPM / Teknon /HUVR/HGTP

DEMOGRAPHICS:

- DOB: ..... /..... /..... - Age: …… - Sex: M / F
- Height: …… cm - Weight: …… Kg
- Hypertension: NO / YES - Diabetes: NO / YES
- Dyslipidemia: NO / YES - Smoker: NO / YES
- COPD: NO / YES - Sleep apnea: NO / YES
- CKD: NO / YES (CrCr:…… ml/min)

HEART DISEASE:

- Cardiomyopathy: Ischemic / Valvular / Idiopathic / Hypertensive / Other:
- NYHA Functional Class: I / II / III / IV
- Atrial fibrillation: Persistent / Long-lasting
- Conduction disease: NO / YES: ……

MEDICATIONS:

- Betablockers: (……) Dose (……) - Digoxin: NO / YES: Dose (……..)
- ACEI: (……) Dose (……) - ARA-II: (……) Dose (……)
- Sacubitrilo/Valsartán: NO / YES: Dose (……..)
- Spironolactone: NO / YES: Dose (……..) - Furosemide: NO / YES: Dose (……)
- Anticoagulant: Rivaroxaban/Apixaban/Edoxaban/Dabigatran Dose (……)/Sintrom
- Others:

IMAGING:

ECHOCARDIOGRAPHY:

- Date: ..... /..... /.....
- LVEF (Simpson 4C): …… %
- LVEDD: …… mm - LVESD: …… mm
- LVEDV: …… mL - LVESV: …… mL
- AI: …….. mm (PEL) ……. ml
- Segmental wall motion abnormalities: NO / YES: Segments: ……
- Significant valvular disease: NO / YES: Specify: ……

CARDIAC CT: NO / YES

HOLTER ECG 24 HORAS (FOLLOW UP 3,6,12 MONTHS):

- Nº AF that last >30 seconds: ……../……./…….
- % of time in atrial fibrillation: ……../……./…….
- % ESV: ……../……./…….

ABLATION PROCEDURE:

- Basal rhythm: AF,SR
- Ablation catheter:
- Fusion with TAC: YES/NO
- MAPPING DATA:
- HSC-EGM recorded? Yes / No (reason: absence of HCS-EGM / recurrent AF / other …)
- Number of HSC-EGM:……..
- Number of RF applications: ……
- Total RF time: …… sec
- Total number of points: ……

- Total fluoroscopy time: …….. min
- Total mapping time: Start: …… Finish: …… Total: …… min
- Total procedure time: Start: …… Finish: …… Total: …… min
- Complications: ……

PAROX AF (SR)	Septal	Anterior	Roof & posterior	Floor & Posterior	Lateral	Total
Surface area mm^2						
N Fractionated EGM (PINK)						
N HSC-EGM (After 3ST GREEN)						
Correlation fEGM (SR &3ST) (%)						
Low voltage zones Area (%)						
PERSIST AF (FA)						
N Fractionated EGM (CFAE) (PINK)						
Low voltage zones (%)						
PERSIST AF (SR)						
N Fractionated EGM (PINK)						
N HSC-EGM (After 3ST GREEN)						
Correlation fEGM (SR &3ST) (%)						
Correlation between CFAE & HSC-EGM (%)						
Low voltage zones (%)						

APPENDIX D: Informed consent material

PATIENT INFORMATION SHEET AND INFORMED CONSENT FOR A RESEARCH STUDY.

Study Name: *Sub-study 1* *(ANALYSIS OF HIDDEN SLOW CONDUCTION ELECTROGRAMS IN PAROXISMAL AND PERSISTENT ATRIAL FIBRILLATION. HSC-AF STUDY):*

Principal Investigators:

Drs. Lucas Cano Calabria & Juan Fdez-Armenta Pastor
Hospital Universitario Puerta del Mar. Sº Cardiología. Sección de Arritmias
Av. Ana de Viya, 21, 3ª planta. 11009 Cádiz.

We invite you to participate in a research study. First and foremost, we want you to know that your participation is completely voluntary. This informed consent document contains important information about the research study. We kindly ask you to read it carefully before deciding to participate. No one can force you to participate, and you may withdraw from the study at any time. If you agree to participate, you will be asked to sign this informed consent document. You will receive a signed copy for your records. This study has been reviewed and approved by the Clinical Research Ethics Committee of the Hospital.

1. WHAT IS THE PURPOSE OF THE STUDY?

You are being asked to participate in this study because you have a heart rhythm disorder called atrial fibrillation (AF). Your medical team, in agreement with the Arrhythmia Unit, believes that the best treatment for your condition is to undergo an electrophysiological study to ablate (eliminate) the arrhythmia using radiofrequency energy. Radiofrequency ablation of AF is a procedure that involves the use of a thin, long catheter to deliver radiofrequency energy to the opening of the pulmonary veins with the left atrium to electrically isolate these veins from the left atrium. This has been done in this way for more than 20 years, since the origin of this arrhythmia was described in the pulmonary vein openings in the left atrium. The efficacy of an ablation procedure after one year is approximately 75-80%, requiring a second ablation procedure in some cases to isolate any point that may have reconnected any of the pulmonary veins with the atrium.

However, the success of ablating only the pulmonary veins is lower once the arrhythmia becomes persistent due in large part to degeneration of the cardiac muscle of the atria that allows the arrhythmia to originate and persist anywhere in the atria.

The objective of this study is to investigate the presence, characteristics, and location of sites in the atria that may facilitate the maintenance of the arrhythmia by analyzing abnormal electrical signals (fractionated electrograms) by stimulating the heart with brief stimuli, similar to a pacemaker.

2. HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

If you decide to participate in the study, we will perform a medical evaluation before the ablation. After the procedure, the usual follow-up visits will be conducted at 3, 6, and 12 months.

3. WHAT ARE THE RISKS AND POSSIBLE DISCOMFORTS THAT MAY ARISE FROM PARTICIPATING IN THIS RESEARCH STUDY?

If you decide to participate in the study, an ablation of the pulmonary vein ostium will be performed. The procedure may involve risks, although the percentage of risk is low. A navigation system and catheters approved for use in atrial fibrillation will be used during the procedure. Participation in this study will involve an extension of the duration of the procedure, specifically the time dedicated to the reconstruction and mapping of the cardiac chambers.

Among the risks of complications that are described for this type of procedure are: mild discomfort in the puncture site or the appearance of a hematoma that will almost always spontaneously absorb; less frequent are other complications (phlebitis, venous or arterial thrombosis, bleeding that requires transfusion, cardiac perforation with tamponade, pulmonary or systemic embolism, narrowing of the opening of one of the pulmonary veins, diaphragmatic paralysis due to injury to the phrenic nerve, or formation of a communication -fistula- between the left atrium and the esophagus), although some of them are serious and require urgent action (<1 in 100); the risk of death is exceptional (<1 in 1,000).

4. WHAT ALTERNATIVES ARE THERE TO PARTICIPATING IN THIS STUDY?

If you decide not to participate in this research study, you will undergo the same tests and ablation procedure as has been performed so far in the hospital.

5. WHAT ARE THE POSSIBLE BENEFITS OF PARTICIPATING IN THIS STUDY?

The research team believes that participating in the study, in addition to not involving any additional risk by not interfering with the usual protocol of the procedure except for slightly prolonging its duration, may provide very useful information that could eventually be used as a standard for the treatment of persistent atrial fibrillation. If you are pregnant or think you may be, please notify your doctor as you cannot participate in this study.

6. IS PARTICIPATION IN THIS STUDY VOLUNTARY?

Yes. Participation in this research study is voluntary. You can decide not to participate and can also change your mind later and withdraw from the study at any time, without affecting your care.

7. IF I PARTICIPATE IN THIS RESEARCH STUDY, HOW WILL MY PRIVACY BE PROTECTED?

Access to your medical history:

The members of the research team for this study will need access to your medical history, including medical records or previous test results, for the purposes of this study. By signing this consent form, you authorize them to access this information and to contact your primary care physician or other health professionals to access your medical history during the study. In

accordance with current data protection regulations, you expressly consent to the inclusion of your clinical history data, as well as the results of your participation in the study, in a personal data file under the responsibility of the Center. Access to your personal information will be restricted to the study physician and his/her collaborators, health authorities, and the Research Ethics Committee.

Confidentiality of information about your health:

Information about your health related to the trial will be included in a database, but you will not be referred to by name or identified in any report or publication.

Withdrawal from the study:

You can withdraw your consent at any time without giving explanations. If you no longer wish to participate in the study and request it, all your identifiable samples will be destroyed to prevent further analysis. You should also be aware that you may be excluded from the study if the study investigators deem it appropriate. You have the right to be informed of any proposed new analyses of the identifiable material retained not foreseen in this study. In that case, the researcher will have to request a new consent from you, which you could refuse.

Compliance with current legislation on confidentiality of health information:

Your data will be treated with the utmost confidentiality in accordance with the provisions of Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights and the General Data Protection Regulation. In accordance with these regulations, you can exercise your rights of access, rectification, opposition, erasure, restriction of processing, right to be forgotten, and portability, for which you should contact the responsible researcher of the study, Drs Cano Calabria/Fdez-Armenta Pastor (Hosp. U. Puerta del Mar 956266028).

The data and images for the study analysis will be pseudonymized by the research team of each center, assigning an identifying code and storing them on a secure digital platform located at Pompeu Fabra University.

Access to your personally identifiable information will be restricted to the research team, health authorities (Spanish Agency of Medicines and Medical Devices, foreign health authorities), the Research Ethics Committee, and authorized personnel by the sponsor (study monitors, auditors), when necessary to verify the data and procedures of the study, but always maintaining confidentiality according to current legislation.

If the study results are published, your personal data will not be published and your identity will remain anonymous.

8. WHO SHOULD I TALK TO TO KNOW MY RIGHTS OR TO ASK QUESTIONS?

Before signing this document, you should ask about anything you do not understand. The study team will answer your questions before, during, and after the study. If you feel that your question has not been fully answered or if you do not understand the response, keep asking until you are satisfied.

If you have any concerns or complaints about this study or how it is being conducted, please do not hesitate to discuss it with the study team. Dr. _____, Cardiology Department. Phone: _____

I, _____

(Name and Surname)

- I have spoken with: _____
- I have received sufficient information about the reason why I am being asked to participate in the study.
- I have been able to ask questions about the study.
- I understand that my participation is voluntary.
- I understand that I can withdraw from the study at any time, without having to give any explanations, and without it affecting my medical care.
- I consent to the collection and processing of my personal and medical data according to the specified conditions.
- And I have expressed my agreement to participate.

SUBJECT PARTICIPANT

_____ _____ _____

Participant's signature Date Time

RESEARCHER

_____ _____ _____

Researcher's signature Date Time

APPENDIX E: Informed consent material

PATIENT INFORMATION SHEET AND INFORMED CONSENT FOR A RESEARCH STUDY.

Study Name: ***Sub-study 2*** *PULMONARY VEIN ISOLATION PLUS SLOW CONDUCTION ABLATION ELUCIDATED BY TRIPLE ATRIA EXTRASTIMULI VS PULMONARY VEIN ISOLATION ALONE IN PERSISTENT ATRIAL FIBRILLATION (HSC-AF TRIAL)*

Principal Investigators:

Drs. Lucas Cano Calabria & Juan Fdez-Armenta Pastor
Hospital Universitario Puerta del Mar. Sº Cardiología. Sección de Arritmias
Av. Ana de Viya, 21, 3ª planta. 11009 Cádiz.

We invite you to participate in a research study. First and foremost, we want you to know that your participation is completely voluntary. This informed consent document contains important information about the research study. We kindly ask you to read it carefully before deciding to participate. No one can force you to participate, and you may withdraw from the study at any time. If you agree to participate, you will be asked to sign this informed consent document. You will receive a signed copy for your records. This study has been reviewed and approved by the Clinical Research Ethics Committee of the Hospital.

1. WHAT IS THE OBJECTIVE OF THE STUDY?

You are being asked to participate in this study because you have a heart rhythm disorder called atrial fibrillation (AF). Your medical team, in agreement with the Arrhythmia Unit, believes that the best treatment for your condition is to undergo an electrophysiological study to ablate (eliminate) the arrhythmia using radiofrequency energy. Radiofrequency ablation of AF is a procedure that uses a catheter (thin, long wire) to apply radiofrequency energy at the entrance of the pulmonary veins with the left atrium, in order to electrically isolate these veins from the left atrium. This has been done this way for over 20 years, since the origin of this arrhythmia was described in the pulmonary vein entrance in the left atrium. The success rate of an ablation procedure at one year is around 75-80%, sometimes requiring a second ablation procedure to isolate any point that may have reconnected a pulmonary vein with the atrium.

However, the success with exclusive pulmonary vein ablation is lower once the arrhythmia becomes persistent, largely due to degeneration of the atrial heart muscle that allows the arrhythmia to originate and persist anywhere in the atria.

The study aims to demonstrate that it is possible to improve the results of ablation by identifying and eliminating sites outside the pulmonary veins that may be responsible for maintaining the arrhythmia. These sites will be searched for by stimulating the heart (like a pacemaker) and analyzing the characteristics of the electrical signal recorded with the catheter.

2. HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

If you decide to participate in the study, we will perform a medical evaluation before the ablation. After the ablation, we will have follow-up visits at 3, 6, and 12 months to study your clinical evolution, and after that, you will have routine follow-up visits.

3. WHAT ARE THE RISKS AND POSSIBLE DISCOMFORTS THAT MAY ARISE FROM PARTICIPATION IN THIS RESEARCH STUDY?

If you decide to participate in the study, we will perform a standard ablation of the pulmonary veins, which is the usual catheter treatment for atrial fibrillation. Half of the study participants will be randomly assigned to also receive ablation of sites with abnormal electrical activity in the left atrium, which involves some focal ablations in locations other than the pulmonary veins. The procedure may carry risks, although the percentage of complications is low. We will use a navigation system and catheters that are approved for use in atrial fibrillation.

The risks of complications that have been described for this type of procedure include: mild discomfort in the puncture site or the appearance of a hematoma that will almost always spontaneously resolve; less frequent are other complications (phlebitis, venous or arterial thrombosis, bleeding requiring transfusion, cardiac perforation with tamponade, pulmonary or systemic embolism, narrowing of the orifice of one of the pulmonary veins, diaphragmatic paralysis due to phrenic nerve injury or formation of a communication -fistula- between the left atrium and the esophagus), although some of them are serious and require urgent action (<1 per 100); the risk of death is exceptional (<1 per 1,000).

4. WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?

If you decide not to participate in this research study, you will undergo the same tests and ablation procedure as has been performed in the hospital until now.

5. WHAT ARE THE POSSIBLE BENEFITS OF PARTICIPATING IN THIS STUDY?

The research team believes that participating in the study will allow for the reporting of very useful information on the proposed protocol, allowing for the evaluation of the long-term effectiveness of ablation and, eventually, facilitating its use in the future by other arrhythmia teams as a standard to benefit other patients like you. If you are pregnant or think you may be pregnant, please inform your doctor, as you will not be able to participate in this study.

6. IS PARTICIPATION IN THIS STUDY VOLUNTARY?

Yes. Participation in this research study is voluntary. You may decide not to participate, and you may also change your mind later and withdraw from the study at any time without it affecting your care.

7. IF I PARTICIPATE IN THIS RESEARCH STUDY, HOW WILL MY PRIVACY BE PROTECTED?

Access to your medical history:

The members of the research team for this study will need to access your medical history, including medical records or previous test results for the purposes of this study. By signing this consent form, you authorize them to have this access and to contact your primary care doctor or other healthcare professionals to access your medical history during the study if necessary. In accordance with current data protection regulations, you expressly consent to the inclusion of your medical history data, as well as the results of your participation in the study, in a

personal data file under the responsibility of the Center. Access to your personal information will be restricted to the study doctor and their collaborators, health authorities, and the Research Ethics Committee.

Confidentiality of health information:

Information about your health related to the trial will be included in a database, but you will not be referred to by name nor identified in any report or publication.

Withdrawal from the study:

You may withdraw your consent at any time without having to provide any explanations. If you no longer wish to participate in the study and so desire, all your identifiable samples will be destroyed to prevent further analysis. You should also know that you may be excluded from the study if the study investigators deem it appropriate. You have the right to be informed of any plans for new analysis of identifiable material retained beyond this study. In that case, the investigator will need to seek your new consent, which you may refuse.

Compliance with current legislation on the confidentiality of health information:

Your data will be treated with the utmost confidentiality in accordance with Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights, and the General Data Protection Regulation. In accordance with these regulations, you may exercise your rights of access, rectification, opposition, deletion, limitation of treatment, right to be forgotten, and portability, for which you should contact the responsible investigator of the study, Drs Cano Calabria / Fdez-Armenta Pastor (Hosp. U. Puerta del Mar 956266028).

The data and images for the study analysis will be pseudonymized by the research team of each center, assigning an identifying code and storing them in a secure digital platform located at the Pompeu Fabra University. Access to your identified personal information will be restricted to the research team, health authorities (Spanish Agency for Medicines and Health Products, foreign health authorities), the Research Ethics Committee, and authorized personnel from the sponsor (study monitors, auditors), when necessary to verify the data and procedures of the study, but always maintaining their confidentiality in accordance with current legislation.

If the study results are published, your personal data will not be published, and your identity will remain anonymous.

9. WHO SHOULD I TALK TO TO KNOW MY RIGHTS OR TO ASK QUESTIONS?

Before signing this document, you should ask about anything you do not understand. The study team will answer your questions before, during, and after the study. If you feel that your question has not been fully answered or if you do not understand the response, keep asking until you are satisfied.

If you have any concerns or complaints about this study or how it is being conducted, please do not hesitate to discuss it with the study team. Dr. _____, Cardiology Department. Phone: _____

I, _____

(Name and Surname)

- I have spoken with: _____
- I have received sufficient information about the reason why I am being asked to participate in the study.
- I have been able to ask questions about the study.
- I understand that my participation is voluntary.
- I understand that I can withdraw from the study at any time, without having to give any explanations, and without it affecting my medical care.
- I consent to the collection and processing of my personal and medical data according to the specified conditions.
- And I have expressed my agreement to participate.

SUBJECT PARTICIPANT

_____ _____ _____

Participant's signature Date Time

RESEARCHER

_____ _____ _____

Researcher's signature Date Time