Fundació
La Marató de TV3
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Heart diseases

NON INVASIVE CHARACTERISATION OF LEFT ATRIAL REMODELLING AS A PREDICTOR OF PATIENT OUTCOMES AND PROGRESSION OF ATRIAL FIBRILLATION AND TO GUIDE ABLATION PROCEDURES

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1. Project summary

Justification

Atrial fibrillation is the most prevalent arrhythmia in clinical practice, and it is associated with an elevated morbidity and mortality.

This disease involves structural and functional alterations in the left atrium (atrial remodelling) which favour the progression and persistence of arrhythmia.

Pulmonary vein isolation is the established treatment in cases resistant to medical therapy. However, the long-term results of this procedure continue to be limited.

Advances in imaging and post-processed techniques (late gadolinium enhancement in cardiac magnetic resonance [LGE-CMR], high resolution computerized tomography (CT), advanced echocardiography) can aid in identifying atrial remodelling and help to better select candidates as well as individualize the management of patients with this disease who will undergo an ablation procedure.

Objectives

1) Identify the parameters of atrial remodelling in imaging technique in patients with atrial fibrillation which, together with other clinical parameters, can help to better select patients who are candidates for ablation and establish successful procedure outcomes.

- In LGE-CMR: Determine the optimal values of normalised signal intensity corresponding to healthy and pathological tissue.
- In LGE-CMR and CT: Evaluate the role that atrial sphericity, among other indices, has on the capacity to predict success following ablation of atrial fibrillation.
- In LGE-CMR, CT and echocardiogram: Evaluate the clinical parameters and structural remodelling (atrial volumes, fibrosis, atrial sphericity, atrial strain) as independent predictors of recurrence following an atrial fibrillation ablation procedure and attempt to generate a new prognostic score.

2) Determine the clinical benefits in terms of recurrence of atrial fibrillation of an ablation technique guided by the fibrosis substrate in LGE-CMR compared to a conventional approach based on individualised identification of left atrial fibrosis.

Methodology

This research project includes 4 interrelated sub-studies.

Sub-study 1: *Determination of a normalised and reproducible threshold of atrial fibrosis identified in LGE-CMR.*

Single centre study with 40 participants: 10 healthy young volunteers and 30 patients referred for an ablation procedure.
Acquisition of LGE-CMR images of volunteers and patients. Post-processing of the images with a software developed in our centre for the identification of fibrosis (atrial segmentation and analysis of fibrosis). The signal intensity values are normalised to facilitate comparability and standardisation among patients.
The threshold values of signal intensity corresponding to healthy and pathological tissue have been established (native fibrosis and fibrotic scar). These values were used in sub-studies 3 and 4.

Sub-study 2: *Multicentre validation of left atrial sphericity as a predictor of recurrence following AF ablation procedures.*

Retrospective, multicentre study in patients recruited from 9 Spanish hospitals.
CT or LGE-CMR was performed prior to a first AF ablation procedure, and the images were processed and analysed to determine the parameter of atrial sphericity.
Recurrence following the ablation procedure was analysed with a 12-month follow-up.
The objective of this sub-study is to validate sphericity as an independent predictor of recurrence following AF ablation.

Sub-study 3: *Randomised study of atrial fibrillation ablation guided by LGE-CMR comparer with a conventional approach.*

A prospective randomised study of magnetic resonance-guided ablation compared with a conventional approach. Two-centre study including 154 patients who will undergo an

ablation procedure (first-ablation or repeat ablation) with 1:1 randomisation to each ablation approach: magnetic resonance-guided ablation vs. conventional ablation.
Prior to the procedure all the patients underwent LGE-CMR and a clinical interview to collect all the demographic and clinical information.
The 3-dimensional (3D) enhancement sequences of LGE-CMR are processed and analysed prior to the procedure. A clinical follow-up of 12 months will be carried out.
The study endpoint will be recurrence reported during the 12 months following ablation in each of the study arms.

Sub-study 4: *Analysis of imaging predictors of the recurrence of atrial fibrillation following an ablation procedure.*

Prospective two-centre study including 200 consecutive patients referred for a first atrial fibrillation ablation procedure.
Prior to the ablation all the patients will undergo LGE-CMR and an echocardiogram as well as a clinical interview to obtain demographic and clinical data.
The 3D enhancement sequences of the LGE-CMR will be processed and analysed.
Clinical follow-up will be of 12 months. The primary objective of this study is to evaluate the predictive parameters of recurrence following an atrial fibrillation ablation procedure.

2. Results obtained

Sub-study 1: *Determination of a normalised, reproducible threshold of atrial fibrosis identified in LGE-CMR.*

This study included 10 healthy volunteers and 30 patients with atrial fibrillation (10 paroxysmal, 10 persistent and 10 repeat ablations).

The image intensity ratio (IIR) of the LA *(left atrium)* was calculated by dividing the absolute intensity signal by the mean intensity signal of the blood pool. The value of healthy atrial tissue was established in the healthy volunteers (IIR+2SD). The value of dense fibrotic scarring was obtained from the resonance images made in patients who had undergone previous ablation.

The normalised values of the fibrosis threshold were obtained in the 3 Tesla LGE-CMR. An IIR value of 1.20 was calculated to be the limit of normality of atrial intensity in healthy tissue. Values above an IIR of 1.32 identified dense scarring. *(Ref. 2)*

Sub-study 2: *Multicentre validation of left atrial sphericity as a predictor of recurrence following atrial fibrillation ablation procedures.*

The 9 participating centres included 243 patients. All the patients were followed for 12 months.

The factors independently associated with recurrence following the ablation procedure were the presence of paroxysmal atrial fibrillation (Protector factor: hazard ratio [HR] 0.54, P = 0.032) and atrial sphericity (HR 1.87, P = 0.035). A 5-point risk score was created (type of atrial fibrillation, structural heart disease, CHAD-VASC ≤ 1, LA diameter and sphericity) classifying the patients according to the risk of recurrence: low (≤2 points) and high (≥3 points) (35% vs. 82% recurrence at 3 years of follow-up, respectively; HR 3.10, P < 0.001). *(Ref. 10)*

Sub-study 3: *Randomised study of LGE-CMR-guided atrial fibrillation ablation.*

A total of 155 patients were included and randomised: 76 were randomised to undergo conventional ablation and 79 to LGE-CMR-guided ablation. All the patients were included in the analysis independently of whether they presented atrial fibrosis or not or whether they had undergone their first or a repeat ablation procedure. The mean atrial fibrosis found was low, affecting only 12% of the atrial surface. Approximately 50% of the patients presented some fibrosis outside the veins. The objective of this study was to compare LGE-CMR-guided ablation with the conventional approach in the general group of patients. No significant differences were obtained in the principal endpoint of recurrence at one year of follow-up between the groups (27.6% vs. 27.8%), and compared with the conventional approach, the fibrosis-guided approach showed no clinical benefit in this non selected population. This study is pending publication.

Sub-study 4: *Analysis of imaging predictors in the recurrence of atrial fibrillation following an ablation procedure.*

Two hundred patients were included and the LGE-CMR images of 100% of the patients were processed.
The echo-strain of quality was analysed in 45% of the patients. The follow-up has finished and a preliminary analysis of the result is underway. *Definitive results of this study are not yet available.*

Other results obtained thanks to the La Marató de TV3 project during this period, which were not included in the project:

- A retrospective analysis of the location of atrial fibrosis measured from these threshold values was performed in the patients who had undergone an ablation procedure and in whom magnetic resonance had been performed prior to the procedure. The results of this analysis showed that the zone most frequently presenting fibrosis and of the greatest quantity was that located around the atrium of the inferior left pulmonary vein (Ref. 4). The predictive value of recurrence of fibrosis and sphericity was retrospectively analysed in this population. *(Ref. 3)*

- A comparative case-control study was performed using the dense scar threshold among the lesions produced by radiofrequency and those produced by ablation laser in the magnetic resonance studies undertaken 3 months after the procedure. *(Ref. 9)*

- A comparative case-control study was performed in a sub-population of patients who underwent ablation with radiofrequency and cryoablation, analysing the lesions caused by both methods visualised in the magnetic resonance studies performed 3 months after the procedure. No significant differences were found between the two groups. *(Ref. 11)*

- A retrospective analysis of the role of the scar visualised in the magnetic resonance study performed 3 months after the radiofrequency ablation procedure was performed. The recurrence of atrial fibrillation during follow-up was used, finding the relative size of the anatomical gaps in the lines of ablation to be a predictor of recurrence. *(Ref. 12)*

3. Relevance and possible implications generated

The present project has established standardised thresholds for the determination of atrial fibrosis which can be compared among patients with atrial fibrosis in LGE-CMR and can be used in our centre and other research centres and may even be included as a tool in routine clinical practice. The determination of fibrosis in our centre is already part of the healthcare protocols carried out in this type of patients.

CT and LGE-CMR can be used as a tool to analyse atrial remodelling and help to optimise the selection of patients who are candidates for an ablation procedure. Better patient selection helps avoid the performance of unnecessary procedures and risk to the patients. The determination of atrial remodelling also allows individualised management of patients undergoing atrial fibrillation ablation.

It is possible to analyse the lesions produced by ablation procedures in the magnetic resonance study performed after the procedure. The size of these lesions is correlated with posterior patient evolution which can guide the treatment and follow-up, providing greater attention to patients with low possibilities of success. Likewise, in patients undergoing repeat ablation procedures, these studies can help guide the procedure, reducing intervention times and the application of radiofrequency, thereby reducing the overall risk to the patient.

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