UNIVERSITAT DE BARCELONA

Final Degree Project

Biomedical Engineering Degree

“Non-invasive characterization of pro-arrhythmic areas in atrial fibrillation. Usefulness of ECGi and MRI for patient stratification “

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Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia in humans. It consists of an irregular and chaotic beating of the atria that is estimated to affect 1% of the total population. The annual healthcare costs associated to this pathology account for the 2.6% of the total healthcare spending. Catheter ablation procedures are one of the current treatment options for this pathology, however, recurrence appears in 50% of patients after the procedure.

As an effort to obtain better outcomes, non-invasive techniques are studied to characterize the atrial substrate to provide further information for catheter ablation procedures. Moreover, the information obtained from these techniques could be used for patient stratification to provide the best treatment possible for each patient.

In this final degree project, the capability of two non-invasive techniques, late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) and electrocardiographic imaging (ECGI), to characterize the atrial substrate is evaluated by looking whether there exists an association between their data.

Data from 38 patients is gathered and analyzed. The results obtained from the analysis show that there exists an association between low conduction velocities in the ECGI and fibrosis in the LGE-CMR, both indicators of unhealthy atrial tissue. This proving the capability of both non-invasive techniques to properly characterize the atrial substrate, in the case of ECGI, functionally, and in the one of LGE-CMR, structurally. Furthermore, their combined usage arises as an interesting opportunity for patient stratification.

Keywords

Atrial fibrillation · Non-invasive · Atrial regionalization · LGE-CMR · ECGI · Atrial substrate

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1. Introduction

1.1. Motivation

The sinus rhythm is the name given to the normal rhythm of the heart. [1] The normal sinus rhythm (NSR) is originated in a specialized region of the heart, the sinoatrial (SA) node, which is considered the natural pacemaker of the heart. [2] In this region cells present the automaticity, which means that these cells depolarize spontaneously generating action potentials. This electrical impulse generated in the SA node is conducted through the atria walls stimulating both atria. Then, it reaches the atrioventricular node (AV), which is the structure that electrically connects the atria and the ventricles. [3] When passing through the AV the signal slows down and it is then conducted through the His bundle, which its divided between the left and the right branches. [4] Both branches further branch out and the impulse eventually reaches the Purkinje fibers, which are the ones that distribute the impulse to the ventricle muscles. [5]

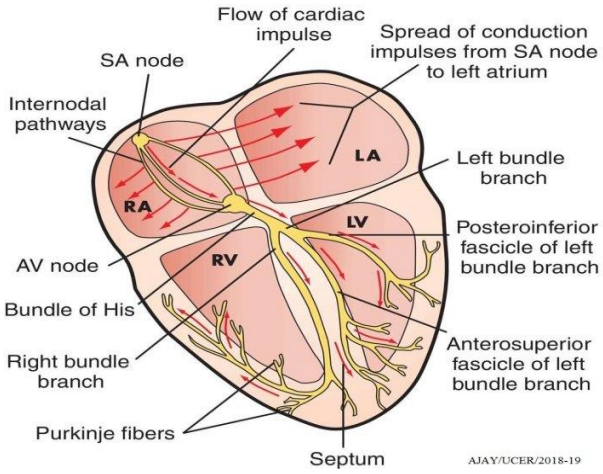


Figure 1. Flow of the electrical conduction of the heart

An arrhythmia is an abnormal change in the regular beat of the heart due to a disorder of the heart's electrical system. It may include irregular heartbeats, skipped beats, rapid heartbeats (tachycardia) which is considered for a heart rate higher than 100 bpm, or slow heartbeats (bradycardia) for heart rates lower than 60 bpm. [6] For the general population, arrythmias have an expected prevalence of 1.5-5%. [4] They can occur in the lower chambers of the heart, the ventricles, therefore being ventricular arrythmias, or in the area above the ventricles, supraventricular arrythmias, these usually occur in the upper chambers of the heart, the atria. [7]

The mechanisms which generally produce arrythmias can be divided into two major categories: enhanced or abnormal impulse formation and reentry. [8] Reentry circuits are the mechanism responsible for the majority of clinically important arrythmias. [9] They are produced when a group of isolated fibers are not activated during the initial cardiac cycle, these fibers recover excitability to be depolarized before the impulse dies out, which leads them to act as a link to reexcite areas which had already been depolarized and had recovered from the initial depolarization. In other words, the action potential in this case propagates in a similar way to a closed-loop circuit. [10] Atrial flutters and ventricular tachycardias are two examples of arrythmias produce by the reentry mechanism. However, not all arrythmias have a known causing mechanism, which is for instance, the case of the atrial fibrillation (AF).

Atrial fibrillation (AF) is the most common sustained arrythmia in humans. Electrocardiogram-based surveys suggest that it affects 1% of the total population. The prevalence of AF is age dependent,

and the growing prevalence of AF can be explained, in part, by the increasing average age in the population. [11] AF represents an important financial, economic, and human burden; in 2003 the mean cost of an AF patient inpatient admission of was 2315 €. [12] This type of arrythmia consists of the appearance of disorganized stimuli at atria which rate from 350 to 600 bpm. The AV node does not transmit as many impulses to the ventricles, producing a completely irregular ventricular stimulation with a ventricular heart rate lower than the atrial one. [13] It is one of the main causes of morbidity and mortality, and it increases the risk of heart failure, stroke, and death. [14] Due to the rapid atria beating, blood is not capable of flowing correctly, which increases the likeliness for the blood to clot. This clot can travel through the different body parts causing damage. Moreover, AF can decrease the pumping ability of the heart, and the irregularity of beating can cause a less efficient heart work. If AF occurs during a long period of time, both heart and lungs can be significantly weakened, which can lead to heart failure. [15]

At present, AF is mainly treated using antiarrhythmic drugs (AAD) and catheter ablation. However, both treatment options present some limitations. There are some patients that do not respond to the AAD therapy, also, when it comes to the catheter ablation, almost half of the patients undergoing this procedure present recurrence after a certain time. [16] Thus, an effective treatment for AF is yet to be found.

In order to increase the overall performance of catheter ablation procedures, several non-invasive characterization techniques are starting to be used to provide further information on which zones of the atria should be ablated to avoid recurrencies. Some examples are late gadolinium enhancement cardiac magnetic resonance (LGE-CMR), computer tomography (CT) scan and electrocardiographic imaging (ECGI). [17][18]

1.2. Objectives

The main objective of this final degree project is to characterize non-invasively the atrial substrate, both structurally, with LGE-CMR, and functionally, with ECGI.

In order to achieve this main objective, we will try to accomplish two more specific objects, the being:

- Provide support and some guidance in the catheter ablation procedure by describing which could be the more pathological regions
- Description of the areas where fibrotic tissue appearance is more probable in AF patients, which could potentially indicate that by isolating them better outcomes could be obtained.

In order to do so, the atria will be regionalized into nineteen regions and an analysis of the correlation between the conduction velocity and the fibrosis percentage for within each region will be performed.

1.3. Scope and limitations

During the development of this project, several limitations had to be considered. Starting with one of the main limitations which is time. Currently, the only success marker for an ablation procedure is the absence of recurrence after one year. Since this projects duration is less than one year and most of the data used is from patients who underwent ablation also less than one year ago, this success marker cannot be obtained. To resolve this problem, instead of addressing whether the ablation procedure was successful or not, the project focuses on the characterization of unhealthy

tissue. To ensure that the definition of the unhealthy tissue is done properly, it is done following two different procedures, one using LGE-CMR and the other ECGI.

Another limitation is the difference in spatial resolution of the different tools used. ECGi has low spatial resolution, and CMR has not the highest spatial resolution when it comes to describing the anatomy, however it is the most used one to characterize atrial tissue. This limitation is intended to be overcome by doing the analysis in a regionalized manner.

When it comes to the data, patients must give consent for their data to be treated, also, this data must be protected and must not go outside the hospital. Moreover, the number of patients used is small due to the limited number of procedures done in the hospital department and the limited duration of the project itself.

The scope of this study includes the following steps:

- Bibliographic research and literature review of the AF mechanism, non-invasive techniques to characterize the atria substrate and the related studies that have taken place
- Analysis of the software used to acquire data (Corify Care, ADAS 3D)
- Data acquisition in ECGI
- Data acquisition in LGE-CMR using ADAS 3D
- Statistical analysis of the acquired data
- Discussion of the obtained results

2. Background

2.1. Atrial fibrillation

As beforementioned, atrial fibrillation (AF) consists of an irregular and chaotic beating of the atria. This irregular beating of the upper heart chambers impedes them to sync with the lower ones (the two ventricles). Impeding therefore an effective blood flow to the ventricles. [19] [20]

AF molecular, cellular, neurohumoral and hemodynamic pathological mechanisms are complex and not clearly understood. The mechanisms underlaying appearance and maintenance of AF are still an open debate matter. Some investigators consider as the main sustaining AF mechanism the presence of multiple wavelets with a random propagation. Others, advocate that the maintenance of the AF is due to the existence of spatially localized drivers in the form of rotors.

Those supporting the multiple wavelet hypothesis accentuate the disorganized electrical activity during AF and the observance of multiple simultaneous propagation wavelets. Nevertheless, animal, and human models have proven the presence of hierarchical spatiotemporal organization in AF, which is inconsistent with the previously mentioned hypothesis, and suggests that localized sources are responsible for AF maintenance. [21] Hypotheses have been formed regarding this discrete atrial fibrillatory sources, considering them either ectopic foci or rotors. In a rotor, the wavefront has a curved or spiral form, and they are considered, by some investigators, as a special form of functional re-entry. [22] The main hypotheses for AF maintenance are illustrated in Figure 2A.

Furthermore, the hypotheses of focal and rotor as AF drivers are not mutually excluded since rotors can be initiated by a focal discharge due to a waveform break. Besides, the presence of drifting and fast rotors everywhere can explain the presence of multiple wavelets in their periphery. Therefore, the rotor hypothesis is compatible with both focal discharges and multiple wavelets presence. This compatibility of rotor maintenance with other mechanisms is illustrated in Figure 2B.

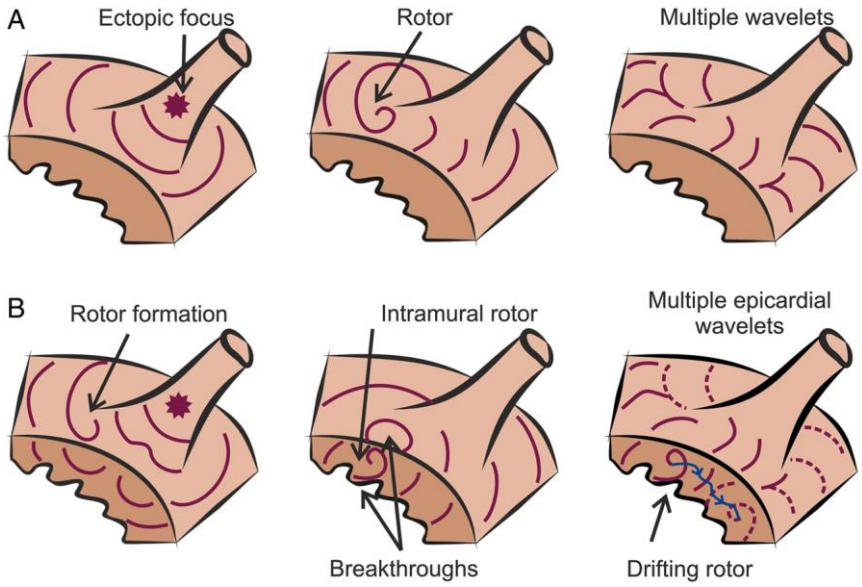


Figure 2. (A) Current hypothesis for AF maintenance. (B) Compatibility of rotor maintenance with other mechanisms

AF is defined by the presence of chaotic atrial electrical activity, however, the proarrhythmic mechanisms are recognized to be extremely heterogeneous. Wide variations can be found between different individuals, regarding the relative contributions of potential AF mechanisms.

These contributions might even change within the same individual over time. Figure 3 shows the progression of AF mechanisms over time. [23][24]

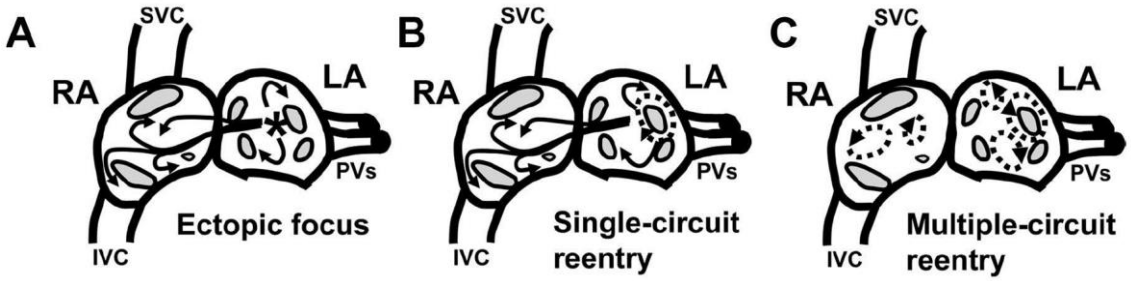


Figure 3. Progression in atrial fibrillation (AF) mechanisms over time. (A) Local ectopic firing. (B) Single-circuit re-entry. (C) Multiple-circuit re-entry

Moreover, electrical, contractile, and structural remodeling are important contributors to the AF substrate. Atrial fibrosis is the most prominent feature of atrial structural remodeling, which is characterized by the aberrant activation, proliferation, and differentiation of fibroblasts. Thus, leading to an excessive synthesis and irregular deposition of extracellular matrix (ECM) proteins, which are the substrate of AF and are involved in its initiation and perpetuation. [25] Therefore, there is an association between atrial fibrosis and AF, even though the causal importance of tissue fibrosis in AF occurrence and persistence is yet to be determined. In animal models, atrial fibrosis has been proven to cause localized regions of slow conduction, increasing conduction heterogeneity and providing an AF substrate. [26]

AF can be paroxysmal, persistent, or permanent according to a consensus regarding temporality. Paroxysmal AF describes sporadic episodes that terminate spontaneously within a week. If it lasts longer than a week or requires cardioversion (electrical or pharmacological) to restore sinus rhythm, then, AF is persistent. When cardioversion attempts have failed or have not been attempted, AF is considered permanent. These temporal descriptive terms must be considered since the treatment outcome can be different. [27] Yet, this classification is limited and does not approximate treatment personalization according to patient characteristics. It only considers AF episode duration and not whether there exists atrial substrate remodeling or how this remodeling takes place. [28]

2.2. Current AF treatment

The current AF treatment options basically consist of antiarrhythmic drugs and AF ablation. However, these strategies show complications and low long-term success rates.

Catheter ablation arises from discovering that ectopic atrial activation emerging from pulmonary veins (PV) could trigger AF. PV are the predominant source of triggers; thus, catheter ablation procedures involve isolating all of them from the rest of the atria. [27] When it comes to antiarrhythmic drug (AAD) therapy, it is still a cornerstone of rhythm-control therapy, despite the increasing usage of catheter ablation. Often AAD therapy is used as hybrid therapy in combination with ablation. [29]

AF ablation is mainly indicated for those patients experiencing symptomatic AF who have failed conventional treatment (antiarrhythmic drugs and/or cardioversion) and those with AF undergoing cardiothoracic surgery for another reason. Until recently, it could not be proven whether catheter ablation provided any advantage over AAD, since no clinical trials were performed to demonstrate it. [27]

The efficacy and safety of catheter ablation as a treatment for AF have been demonstrated in numerous trials and while examining catheter ablation, high enough success rates were proven, suggesting that this technique may be related with a lasting cure. On the contrary, AAD therapy examining trials have been disappointing. From here arises the need for randomized trials directly comparing catheter ablation and AAD therapy for maintenance of normal sinus rhythm (NSR).

Noheria et al. [30] published a review combining all the available trials comparing both treatments at that moment and they found that 75% of patients that underwent ablation remained free of recurrence, compared with only a 19% in the case of those following AAD therapy. [31] However, this review presents some limitations that need to be considered, mainly regarding the limited number of patients enrolled and the fact that they were conducted at leading centers regarding these procedures. Therefore, large, multicenter, randomized trials are required to support the idea of placing catheter ablation as the first-line treatment for AF.

RAAFT-2 is a randomized multicentric trial aiming to compare radiofrequency (RF) ablation and AAD as first-line treatments of paroxysmal AF. It consisted of 61 patients in the AAD group and 61 in the RF ablation group, which were followed up for two years. Results showed that among patients with paroxysmal AF without previous AAD treatment, there were lower recurrence rates in those who underwent RF ablation. Nevertheless, recurrence was frequently found in both groups, in approximately 50% of patients.

Another interesting multicentered randomized clinical trial is CABANA. This clinical trial purpose is to determine whether catheter ablation is more effective than conventional medical therapy for improving AF outcomes. The results obtained proved that catheter ablation is associated with a lower AF recurrence rate than drug therapy, 50% vs 69% respectively in 3 years. It also showed that ablation is not curative for many patients and 17% of them required repeat ablation during the follow-up period. Even with an initially successful ablation, patients are propense to recurrence due to the underlying pathophysiology that leaded to the initial onset of AF. Thus, further understanding on the AF initiation mechanism is needed to reduce recurrence rates. [16]

2.3. Non-invasive techniques providing atria substrate information

Non-invasive techniques aiming to provide a better understanding of the atrial substrate are currently under research. The idea is to provide useful information for the catheter ablation procedure, aiming to obtain better outcomes, lower recurrence post-ablation rates. Moreover, this information can be used for patient stratification, so that patients can further benefit from their treatment.

2.3.1. Late Gadolinium Enhanced Cardiac magnetic Resonance (LGE-CMR)

Starting with Late Gadolinium Enhancement Cardiac Magnetic Resonance (LGE-CMR), it has proven to be capable of identifying structural changes of cardiac tissue. Its usage in studies has contributed significantly to have a better understanding of the pathophysiology and progression of arrhythmias.

This technique consists of using gadolinium as a contrast agent. Gadolinium is a paramagnetic metal that accumulates in the extracellular space of the myocardium and modifies water's magnetic properties. [32] By exploiting the slow washout kinetics of gadolinium in extracellular space, this technique is capable of determining preexisting fibrotic tissue. [17] In fibrotic areas there is an accumulation of contrast [33] due to the increased extracellular space and, as a result, fibrotic tissue has higher signal intensity in comparison with healthy myocardium in T1-weighted MRI scans. [34] T1 (the longitudinal recovery time) is shortened in fibrosis and scar areas due to this

accumulation of contrast, whereas in normal myocardium T1 is longer due to a faster wash out of the contrast agent. [35] Thus, LGE-CMR allows the detection and quantification of fibrotic tissue.

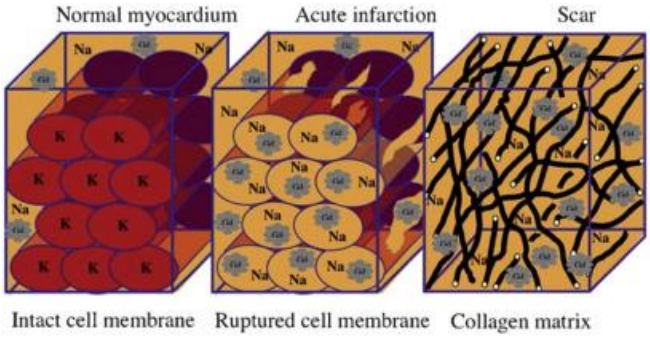


Figure 4. Extracellular space of the myocardium variation

Obtaining atrial wall images is a challenge, since atria walls are much thinner than the left ventricular myocardium, which means that better spatial resolution is needed. For this, an intravenous bolus of gadolinium contrast is injected to the patient and, after a delay of 15-30 min the image is acquired. This delay allows the obtention of T1 differences between blood and scar to improve image contrast. [36]

There exist several methods to discriminate atrial fibrosis, including visual assessment, thresholding techniques or image intensity ratio (blood-pool mean normalization). Starting with visual assessment, this method consists of a visual inspection of images and a manual contour drawing around non-viable myocardium. Currently it is used as the reference method to test semi-automatic and automatic algorithms. However, this technique is associated with subjectivity and non-repeatability of the results.

Thresholding techniques include different methods, the most widespread one to detect atrial scar being standard deviations above reference. It requires a reference value, and a number of standard deviations are added. The reference value is generally obtained from a region of interest (ROI), for instance the blood pool (a ventricle cavity filled with blood, so it does not include the myocardium) or the myocardium, or from the pixel intensity histogram of the atrial wall. The resulting threshold separates healthy from diseased tissue.

The image intensity ratio (IIR) normalizes myocardial image intensities by the mean blood-pool intensity, thus giving normalized results intended to mitigate the differences in the measurements due to patient-level variables, such as contrast dose or delay time of image acquisition after the injection of contrast. IIR has proven to be a good normalization strategy to detect fibrosis, however, the correct IIR threshold to separate fibrotic from healthy tissue is still to be determined. Also, it is not clear yet whether there could exist a universal IIR threshold or if each center should find its optimal one. [36]

New methods are studied to standardize the thresholds and thus overcome the lack of reproducibility. In Benito E.M. et al [32], the upper limit of normal local IIR was assessed to be 1.20. It was calculated as the ratio of the absolute pixel intensity to mean blood pool intensity ratio. IIR values above 1.32 were considered dense scar. Therefore, IIR values above 1.20 identify fibrosis. Despite this, further research is needed to clinically confirm the validity of these results. [32]

It is important to keep in mind that LGE-CMR is contraindicated in some cases. The contraindications of this technique are mainly the same as for conventional MRI scans, thus, cardiac rhythm devices, severe claustrophobia, and patients with an estimated glomerular filtration rate lower than 30 ml/min, amongst others at the discretion of the physician. [34]

2.3.2. Electrocardiographic imaging (ECGI)

Another interesting non-invasive technique to diagnose fibrotic atrial cardiopathy is Electrocardiographic Imaging (ECGI). Whereas LGE-CMR characterizes the substrate structurally, ECGI does so functionally.

The 12-lead electrocardiogram (ECG) is currently the standard non-invasive assessment of most heart diseases. However, it has some limitations when it is used as a support tool in cardiological procedures. This method is limited when it comes to detecting the arrythmias precise location or providing detailed information of the electrical activation pattern. Moreover, it has poor spatial resolution. ECG arises as a novel method intending to address these limitations. It is a non-invasive imaging tool that allows visualizing in 3D the cardiac geometry with activation maps.

The electrocardiographic imaging procedure consists of placing multiple electrodes, from 50 to 300 depending on the manufacturer, on the patient's torso. The electrodes can be contained in a vest or strips, and they record the body surface potentials created by the heart. Then, a computer tomography (CT) scan or magnetic resonance imaging (MRI) is used to display a 3D image of the heart, thus, obtaining the patient-specific heat-torso geometry. [37]

ECGI has two input data, the electrical, coming from the electrodes, and the geometrical, from the CT scans. The combination of this data in a mathematical algorithm allows computing epicardial potentials, electrograms, isochrones and repolarization patterns. [38] Therefore, with the geometry of the heart and the torso, as well as the body surface potentials, ECGI systems provide a functional representation of the cardiac activity.

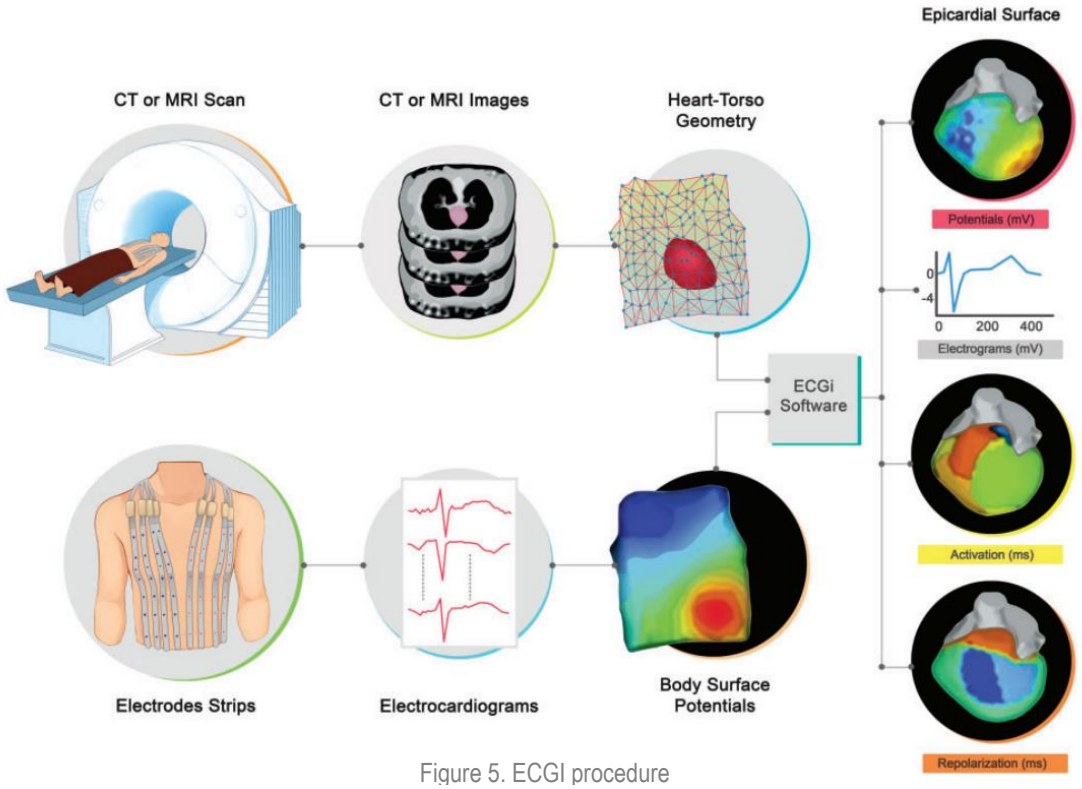


Figure 5. ECGI procedure

The physics of ECGI is based on the Maxwell electromagnetic wave equations, where the electric field generated by the hearth's excitation is propagated to the body surface through a volume with passive electrical conduction. [39] Computing the body surface potentials from the potentials of the epicardial surface of the heart can be done by solving the Laplace's equation in the volume between the torso and the epicardial surfaces. However, ECGI intends to do exactly the opposite, meaning that it aims to compute the epicardial surface potentials from the measured body surface potentials. This "inverse problem" is very sensitive to noise, thus, small errors or noise recorded in the ECGs can cause large errors in the computed epicardial potentials. The Tikhonov regularization method, which imposes constrains on the epicardial potentials, is used to overcome the previously mentioned limitation. [18] These algorithms allow the obtention of 3D reconstructed images of the heart along with beat-by-beat activation maps that illustrate accurately the electrical activation. [37]

ECGI has proven to be a tool capable to provide essential information in various heart rhythm disorders non-invasively. There exist several studies related to the ECGI effective in atrial arrythmias (atrial tachycardia (AT) and atrial fibrillation (AF)), ventricular arrhythmias (ventricular tachycardia (VT), Wolf-Parkinson-White syndrome (WPW), and premature ventricular complexes (PVC)) along with other arrhythmogenic syndromes such as Brugada syndrome (BrS) or long QT syndrome (LQTS). Moreover, ECGI has also been studied as a tool for cardiac resynchronization therapy (CRT). [37]

Here are some examples of the current usefulness of ECGI. For AT, two studies reported an almost complete agreement in arrhythmia site detection between ECGI and invasive procedures. [40][41] Furthermore, several studies have investigated ECGI's capability to provide accurate mapping sequences of ventricular activation sites and the localization of the VT and PVC pacing sites by ECGI mapping proved to be correlated with the invasive mapping system. [42] [43] It is thought that ECGI might also be useful to help differentiating BrS form right bundle branch clock (RBBB), and for WPW patients, it has been reported to provide an accurate detection of accessory pathway insertion sites. [44]

Even though there already exist various studies demonstrating that ECGI is useful technology for the localization of arrhythmia, most of the existing studies were performed in a reduce number of patients. Thus, multicenter large-scale randomized studies are still required to confirm the results. [37]

3. Current situation

3.1. State of the art

Nowadays there exist different non-invasive techniques, including LGE-CMR and ECGI, that are being used to try to make the arrythmia catheter ablation procedure more efficient. However, there is no evidence yet proving that their usage improves patient outcomes.
In this section, the state of the art of LGE-CMR and ECGI is reviewed for a specific type of arrythmia, atrial fibrillation, which is the one concerning this project.

3.1.1. LGE-CMR applied to AF

At the moment, LGE-CMR can be used for different purposes related to AF. Starting with its usage for imaging atrial fibrosis, a multicenter study conducted in 15 clinical centers, the DECAAF (Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial fibrillation), came up with a protocol that describes how to obtain a 3D fibrosis model from LGE-CMR acquisition.
However, there are several challenges in imaging atrial fibrosis. The spatial resolution of the technique goes from 1.2 to 1.5mm, and the atrial walls have a thickness of 2-4 mm, being 2 or 3 times thinner than ventricular walls. Thus, there exists an important risk of wrongly characterizing the adjacent tissue as the atria wall. A possible solution to improve spatial resolution could be increasing the acquisition time. Nonetheless, image artifacts and blurring caused by patient's motion appear. Also, the prolonged acquisition time could cause a reduction in contrast between normal and fibrotic tissue. Another solution is using higher field strength scanners (from 3-T to 9.4-T). Apart from spatial resolution, cardiac and respiratory motion are a main issue in atrial MRI scans. The data acquisition process has to be ECG-triggered, since the data for LGE-CMR for atrial walls cannot be acquired within a single heart cycle.
Despite these limitations, the DECAAF data showed that the primary source of poor-quality scans were errors from the attending technologists, the second one was patient-related issues and only 7% of these scans were due to hardware issues. The patient-related issues were mainly due to arrythmias and irregular respiratory patterns, thus, it is recommended to have an accurate rate control or cardiovert the patient before the acquisition. [34]

LGE-CMR is also being studied as a tool for upstream approaches for AF treatment. It is thought that the atrial substrate visualization using this technique can determine the effect of upstream interventions, since it could document the atrial remodeling process. [34]
Moreover, in those cases of recurrence after catheter ablation, the assessment of changes of fibrotic alterations could provide useful information for AF treatment strategies. LGE-CMR is being studied to be able to visualize the temporal behavior of atrial fibrosis after ablation. To do so, the post-ablation scar is subtracted from the total extent of initial fibrotic atrial tissue. The hypothesis for this is that in case of extensive fibrosis progression post-ablation, there would be no need for another invasive procedure, unless there were no other treatment options. [45] For those cases where a redo procedure is indicated, LGE-CMR could be useful to identify gaps in the PV isolation and guide the procedure, since even though it is still under discussion, it is believed that a complete PV isolation is a requirement for AF long-term freedom. [46]

Furthermore, it is thought that fibrosis could be an interesting ablation target to improve patient outcomes. The current gold standard to assess the extent of fibrosis is voltage mapping by sampling electrical signals form the atrial tissue. It assumes that fibrotic areas give low voltage

signals. [47] In order to clarify the role that atrial fibrosis could have as a target for catheter ablation of AF, the DECAAF II trial was carried out.

An unpublished trial, the DECAAF II trial, analyses the efficacy of LGE-MRI-guided fibrosis ablation versus conventional catheter ablation of atrial fibrillation. It is the first randomized multicenter trial that uses imaging defined atrial fibrosis as a treatment target in patients with persistent AF. It compared the outcome of patients that received conventional pulmonary vein isolation (PVI) ablation with those who received PVI plus fibrosis guided ablation. The flow chart of the study is the following:

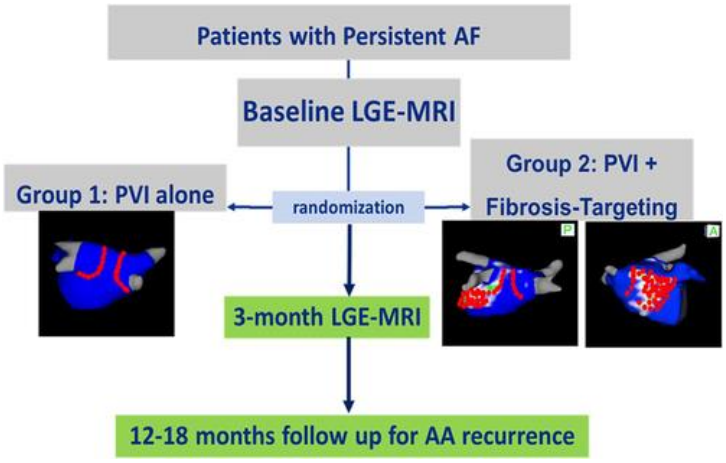


Figure 6. DECAAF II trial study flow chart

For Group 1 patients, the PV were electrically isolated by crating lesions around the PV antra, and the entrance blockage for all PV was confirmed. The abolishment of PV electrograms was the indicator used to determine the success of the ablation procedure.
Otherwise, for Group 2 patients, the LGE-CMR images were merged with the 3D mapping system, and all patients underwent the just described PVI procedure. In these cases, the ablation procedure continued by ablating the perimeter of the fibrosis and/or covering all the fibrotic area with ablation lesions, ensuring the loss of capture in the region when stimulated at 10mA. The ablation of the fibrotic area in this trial was limited to the LA. [48] Even though it has not been published yet, the results are known, and they show that PVI plus fibrosis-targeting does not provide better ablation success rates than PVI alone. [49]

A recently published study, ALICIA trial, also assessed the difference between PVI versus PVI plus CMR-guided fibrosis ablation. The results showed no difference in terms of AA recurrence after a follow-up period of one year. [50] However, the population used was relatively healthy and most participants ha paroxysmal AF, and thus, only 50% of participants had fibrotic patches beyond the PVs and most of them where small and reachable by PV lines. The DECAAF II study includes more patients with persistent AF, thus a wider distribution of LA fibrotic burdens is expected. Which will allow to obtain a better assessment of the efficacy of LGE-CMR guided ablation targeting fibrosis compared to PVI alone. [48]

3.1.2. ECGI applied to AF

ECGI is an interesting technology that can be useful for many types of arrhythmias. When it comes to the specific case of atrial fibrillation, several studies have been performed to determine its usefulness.

In one of them, Cuculich et al., the ECGI accuracy was evaluated by comparing the ECGI results with co-registered images from the navigation system during atrial pacing, in six patients. Also, correlative observations from catheter mapping and ablation were compared with ECGI, in three patients. The results showed that the spatial accuracy of the technique for determining the initiation sites from pacing was 6 mm. What's more, it was capable of determining the critical locations for AF maintenance during the ablation procedure and ablations close to these sites restored the sinus rhythm. Therefore, ECGI proved to offer a non-invasive way to map AF epicardial activation patterns in a patient-specific manner.

During this study, AF maps were obtained from twenty-six patient. They were analyzed to determine the underlying mechanisms of the arrythmia and its complexity. The results showed that the most common patterns of AF were multiple wavelets with pulmonary vein and non-pulmonary vein focal sites. Moreover, they highlighted a coexistence of a variety of mechanisms and a variable complexity among patients, which increased, generally, with AF duration. [51]

Another study, Molero R. et al, showed that patients with positive outcomes after PVI presented more reproducible ECGI metrics over time than those with AF recurrence. Which suggests that ECGI's derived metrics may be capable to select the patients that could benefit from the ablation procedure. [52] Furthermore, it has been seen that the analysis of the total atrial conduction time (TACT) in ECGI contributed to accurately diagnosing patients with atrial cardiomyopathy (ACM). This pathology is directly associated with a significantly increased risk for recurrence after PVI. [53]

The TARGET-AF1 trial results have been recently published. This study aimed to use ECGI mapping to guide localized driver ablation in patients with persistent AF. From the forty patients enrolled in the trial, in eight AF terminated with PVI, the other thirty-two patients underwent ECGI-guided driver ablation. The results indicated that PVI plus ECGI-guided ablation result in high freedom from AF during the follow-up period along with an ablation response in a large proportion of patients. [54]

The steps required to estimate the electrical potentials on the atrial epicardial surface in ECGI for AF patients are shown in the figure below.

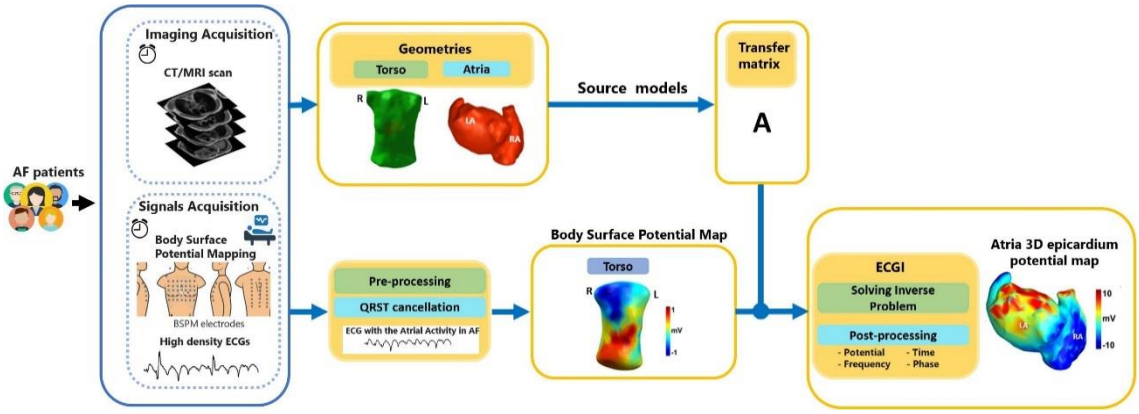


Figure 7. ECGI process for AF patients

When working with the AF patients, the maps that are aimed to obtain are those of the epicardium of the atria. For this, the signal must be processed. This processing involves the QRST cancellation to remove the ventricular activity and thus, enable focusing only on the atrial activity. [55] In addition, to obtain accurate maps other processing methods are used, for instance, involving phase transformations and spectral analysis. [56]

3.2. State of the situation

Even though the efficacy of the two previously discussed technologies for AF is still being studied, and at the moment there is not enough strong data supporting their usefulness in providing better patient outcome with fewer recurrence rates, they seem to be a good opportunity in patient discretization.

For instance, in the case of LGE-CMR, Linhart M. et al. study aimed to determine the impact of anatomic gaps on AF recurrence after the first PVI. These gaps were assessed using LGE-CMR, and the results showed that the total relative gap length in the PV ablation line was associated with AF recurrence a year after PVI, specifically, a 10% increase of the relative gap length increased a 16% the risk of AF recurrence. However, when considering the number of anatomic gaps, no association with AF recurrence was found. [57] Thus, this technique proved to be useful to differentiate those patients with less likelihood of obtaining a good PVI outcome.

On the other hand, ECGI has also proven to be an interesting tool to discretize patients, in this case by considering the reproducibility of its metrics over time. As mentioned in the previous section, reproducible ECGI metrics is associated with better PVI outcomes, whereas low reproducibility indicates more likelihood of AF recurrence. Moreover, the Molero R. et al study also showed that poor ECGI reproducibility predicts PVI outcome better than the type of AF. Thus, this reproducibility information could be used as an indicator to select those patients that could actually benefit from the ablation procedure. [58]

In order to prove the accuracy of LA fibrosis detection with LGE-CMR, the correlation between this technique results with the endocardial voltage and the conduction velocity were analyzed in the Caixal et al. study. The bipolar voltage and local conduction velocity were measured in LA with high intensity electroanatomic maps (EAM) in sinus rhythm. Then, these points were projected into the LGE-CMR, and a semiautomatic point-by-point correlation was performed between the electroanatomic mapping and the LGE-CMR. It was observed that in areas with higher LGE (indicator of the presence of fibrosis) presented lower voltage and slower conduction in sinus rhythm. Therefore, higher intensity proved to be correlated with low bipolar voltage and slow conduction velocity in the analysis. [59]

Also related with the capability of these techniques to discretize patients, Eichenlaub et al. performed a study to assess whether ECGI could be used as a tool to diagnose atrial cardiomyopathy (ACM). Currently this diagnosis is obtained from endocardial contact mapping of the LA low-voltage substrate (LVS) or LGE-CMR. Fibrotic remodeling in ACM causes alterations in the atrial myocardium electrical properties which causes slower conduction velocities within fibrotic areas, this resulting in a p-wave duration prolongation.
For this study, thirty-nine consecutive patients with persistent AF underwent ECGI in sinus rhythm. Later, high-density LA voltage and biatrial activation maps were acquired also in sinus rhythm prior to PVI. Recurrence freedom was assessed after a year of follow-up period. The results showed

that. An increased duration of the total atrial conduction time (TACT) in ECGI showed to be associated with both increased invasive atrial activation time (IAAT) and an extension of LA-LVS in EAM. Arrhythmia freedom was significantly higher in patients with a TACT lower than 148 ms compared with those with higher TACT values. Thus, the non-invasive analysis of the TACT showed up to be a good diagnosis tool for ACM, which is associated with a higher recurrence likelihood after PVI. [53] However, on limitation of this study is the fact thar the functional measures are obtained invasively. ECGI would allow obtaining conduction velocity measures in a non-invasive way, which makes it a valuable tool to characterize and stratify patients.

Having these two last studies in mind, this project aims to use LGE-CMR as the tool that determines the presence of fibrosis, which has already proven to correlate with EAM low conduction velocities and correlate these fibrotic areas with the conduction velocity information coming from the ECGI. Thus, it aims to prove whether the results coming from the two different non-invasive techniques correlate for AF patients. The key factor in this case is that all the data that is going to be used is obtained in a non-invasive way.

4. Market analysis

4.1. Market sector

The market sector contemplated in this project is related with electrophysiology, concretely with non-invasive techniques to assess arrhythmias, specifically AF. The electrophysiology market growth is related to the technological advancements and to the increased incidence of the target diseases and procedures. In the specific case of AF, this type of arrhythmia accounted for the largest share, 36%, of the global electrophysiology market in 2021. This can be explained by the increasing prevalence of atrial fibrillation, the augment of live expectancy and amount of aging population in the world, and the development of advanced cardiac mapping systems for its early diagnosis. [60]

In order to understand this market, the different major brands for the two non-invasive techniques used in this project, LGE-CMR and ECGI are described below.

On the one hand, for CMR the main market are hospitals, followed by diagnostic laboratories and research institutions. Its market is expected to grow due to the increasing number of cardiology diseases and growing preferences towards non-invasive procedures. [61] The main players in the Cardiovascular Magnetic Resonance Imaging market are [62]:

- General Electric Company
- Koninklijke Philips N.V.
- Siemens Healthcare
- Canon Medical Systems Corporation
- Bruker
- Hitachi Medical Systems
- Mindray
- Neusoft Medical Systems
- Ningbo Jansen NMR Technology

On the other hand, for ECGI, the market is still very limited, since it is a new technology that is mainly used for research purposes at the moment. The companies currently under research on the market are:

- CardioInsight™ from Medtronic
- EP solutions
- Acorys from Corify Care (it is not on the market yet)

4.2. Future market perspective

The electrophysiology market is expected to register a compound annual growth rate (CAGR) of 8.5% from 2022 to 2027. By 2060 it is expected that 17.9 million people in Europe suffer from AF. Thus, it is expected to become one of the largest public heath challenges and the AF burden worldwide may increase in more than 60% in 2050. [63]

AF annual healthcare costs account for approximately the 2.6% of the total healthcare spending. [64]. Considering that the current budget of Departament de Salut de la Generalitat are 11.244 M €, approximately 330 M € are dedicated towards AF, which is a huge amount of money for a single pathology.

The ablation procedure in AF patients has evolved during the past two decades leading to a global consensus that PVI is the most efficient treatment approach. However, this approach does not provide satisfactory enough results yet, since its efficacy is estimated to be less than 50%. [65] In an effort to improve these outcomes, researchers are currently studying non-invasive techniques to assess the atrial substrate and use them as tools to guide ablation procedures with the final goal of making procedures faster, more personalized, and thus, obtaining better outcomes. However, further research is still needed in both LG-CMR and ECGI cases before their implementation into the clinical practice in patients referred for AF ablation.

5. Concept Engineering

In this section the different solutions studied to develop the project will be exposed to be able to properly select the options that are going to work better in this case. They can be observed in the Table 1. Starting by reviewing the different options available in the market for the two non-invasive techniques, LGE-CMR and ECGI. Since a part of the project consists of working with CMR, a proper segmentation program has to be selected, and for the part that uses ECGI, a programming environment that enables the data extraction is needed. Finally, all the recollected data has to be placed into a database, and a proper statistical environment to be able to work with this database is needed.

	Solutions studied
LGE-CMR	• Siemens • Philips • General Electric
Segmentation program	• ADAS 3D • CARTOSEG CT Module • Segment CMR
ECGI	• Acorys • CardioInsight • EP solutions
Programming Environment	• Matlab • Python
Statistics software	• SPSS Statistics • Microsoft Excel

Table 1. Solution studied for the project development

5.1. Solutions studied

5.1.1. LGE-CMR

In the case of LGE-CMR, two aspects have to be considered. One being the gadolinium bolus that is going to be injected to the patient, and the other being the resonance machine that is going to be used. The acquisition of these type of images is performed following a predefined protocol. This is the reason why the bolus of gadolinium, it is going to be the one defined by the protocol. [36]

Regarding the resonance machine itself, there exist several options on the market. Most of the studies that evaluate AF use 1.5 or 3 T scans. The three most used manufacturers are:

- Siemens
- Philips
- General Electric

However, the important selection to take into account when considering LGE-CMR is whether the scan is 1.5T or 3T. 3T systems allow higher signal-to-noise ratio, which is a key factor to generate high quality images, providing increased image resolution capabilities.

5.1.2. Segmentation program

When it comes to choosing the segmentation program to obtain the 3D reconstruction of the atria, two options were considered, them being ADAS 3D form Adas3D Medical S.L. and Segment CMR from MEDVISO.

- **ADAS 3D**

It is a medical software that allows the extraction of key information from cardiac MRI and CT images. Its main features involve obtaining anatomical information, since it allows the 3D visualization of the atria and their surrounding anatomical structures, such as the esophagus, moreover it provides information on tissue characterization, a 3D cardiac model segmentation with an automatic classification of tissue based on IIR using selectable imaging thresholds can be obtained. Moreover, the structures, including anatomy and fibrosis information) are exportable to the EP navigation system that is going to be used to perform the ablation procedure, thus it can be used as a support during the intervention. Also, it is capable of quantifying the amount of enhanced fibrosis to differentiate the fibrotic substrate from healthy tissue. [66]

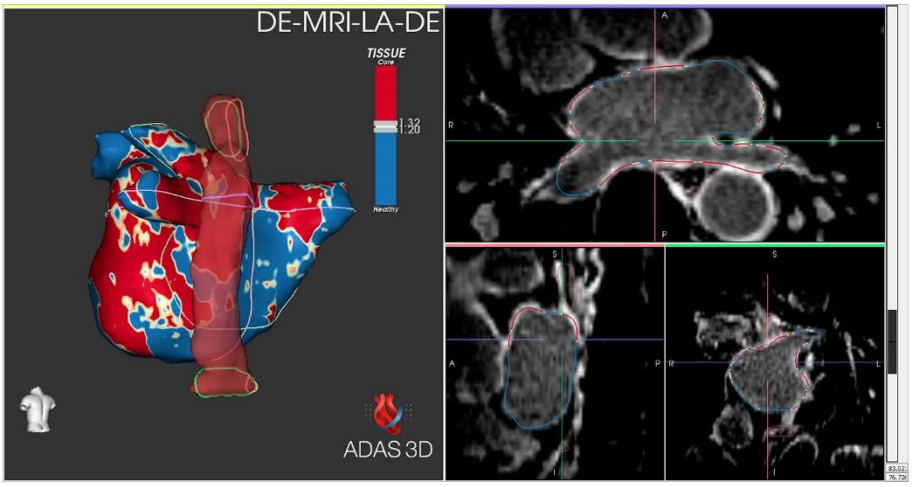


Figure 8. Screenshot of an ADAS3D LA segmentation and the esophagus

- **CARTOSEG CT Module**

It automates the CT segmentation process, providing detailed anatomic 3D image integration in the specific navigation system, CARTO 3 System. This module semi-automatically segments the four heath chambers, the aorta, the coronary sinus, the coronary arteries and the esophagus. The anatomical detail obtained enables planning the ablation strategy more efficiently when complex arrhythmias have to be treated. [67]

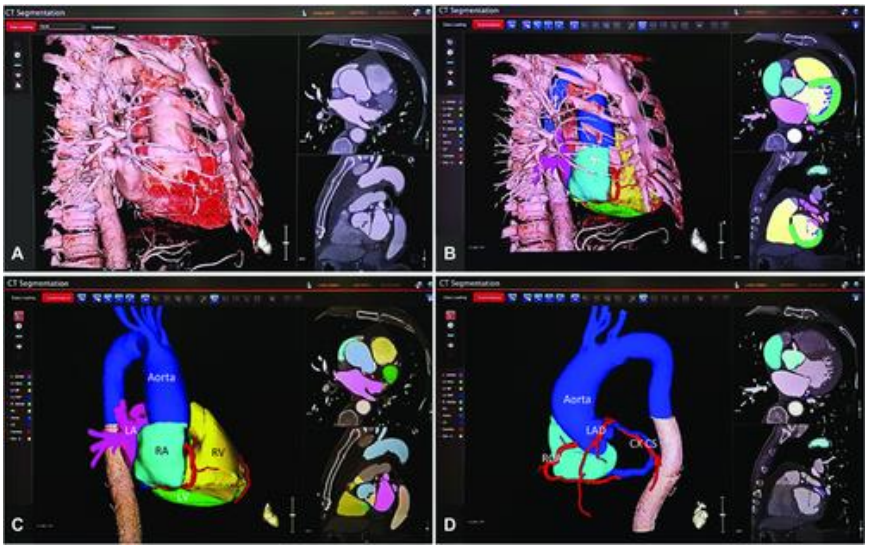


Figure 9. Screenshot of a CARTOSEG CT module segmentation

- **Segment CMR**

It is a high-quality and complex software for CMR analysis. It uses deep learning algorithms to obtain the contours in a quick and exact way. It covers the whole range of cardiac MR analysis, and it bears the CE-mark of conformity. Its main features include fully automatic analysis of both ventricles, flow analysis with automatic vessel tracking, measurements and annotation points in 2D and 3D, signal intensity analysis for unlimited number of regions of interest (ROIs) and viability analysis by fully automated segmentation of scar tissue. [68]

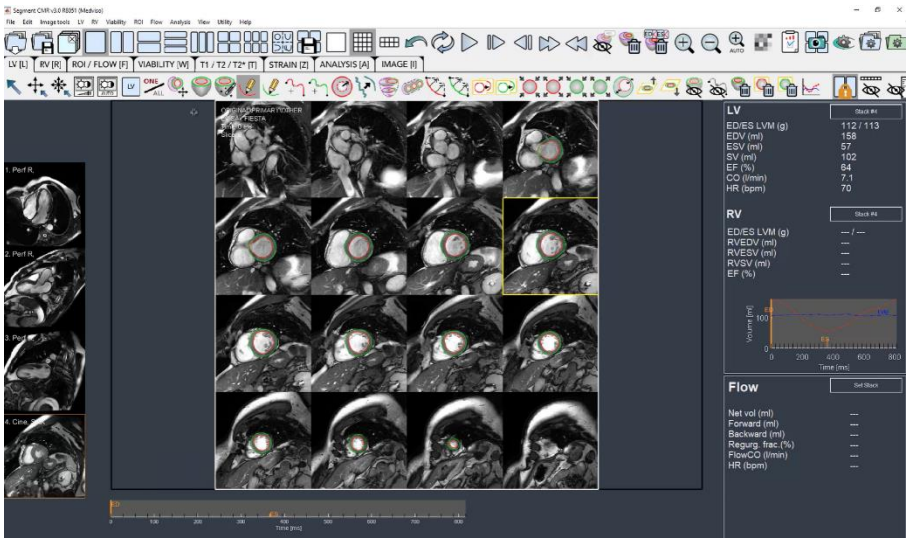


Figure 10. Screenshot of a Segment CMR left ventricle segmentation

5.1.3. ECGI

Regarding EGCI, three options were considered: Acorys by CorifyCare S.L., CardioInsights by Medtronic and EP solutions by EP Solutions SA.

- **Acorys**

It is a cardiac mapping system that allows clinicians to see the electrical activity of the heart's surface non-invasively. It is a novel ECGI system for beat-to-beat, multi-chamber, and 3-D mapping of the cardiac activity. It uses a biopotential amplifier and high-density sensor vest along with innovative image and signal processing technologies to obtain cardiac electroanatomic maps. [69]

- **CardioInsight**

It is a non-invasive system that allows obtaining maps outside the EP lab anytime throughout the patient care pathway. It captures and panoramically displays rhythms that span multiple chambers or vary in cycle length. Furthermore, single beat maps can be obtained for those cases of infrequent, unstable rhythms. A single-use, disposable multi-electrode vest is used to capture the electrical signals from the body surface, then the software provides various cardiac signal analyses and displays interactive 3D color maps. [70]

Figure 11. CardioInsight multi-electrode vest

- **EP solutions**

This system merges electrophysiological and anatomical information to improve outcomes for cardiac resynchronization therapy (CRT). The anatomical information comes from a CT or MR and the electrophysiological information is based on non-invasive measurements using electrodes attaches to the patient's torso. [71]

5.1.4. Programming environment

After the maps from the ECGI are obtained, its information is exported as an episode. A programming environment is needed to extract the data that is going to be analyzed in this project from the episode obtained. Two programming environments were constructed: MATLAB and Python.

- **MATLAB**

It is a computing platform useful for data analysis and signal and image processing among others. A license is required to use it, however, in this case the university provides it. Its standard library includes integrated toolkits that are developed by exerts, rigorously tested and well-documented. [72]

- **Python**

It is a general-purpose programming language. Its main advantage is that Python and most of its libraries are free. When it comes to image processing, many external packages are available, however, for this cases MATLAB is faster because it has native toolboxes designed for this purpose. [72]

5.1.5. Statistics software

The data obtained from both MATLAB and ADAS 3D platforms needs to be placed in a software capable of performing statistical analysis in order to obtain the results if the project. The options considered in this case were SPSS Statistics and Microsoft Excel.

- **SPSS Statistics**

It is a powerful statistical software platform that offers a user-friendly interface. It includes data preparation and management, data analysis and reporting. [73] It is mainly used to perform statistical calculations and data manipulation.

- **Microsoft Excel**

It is a spreadsheet software where some statistical analysis can be performed. Used to manage and store data with formulas and functions. [74]

5.2. Proposed solutions

Once the reviewed all the different solutions, the election of the ones that best and allow the accomplishment of this project are selected. In this section the selected options are exposed.

The LGE-CMR images were acquired using a 3 T General Electric's scan. This selection can be explained by the scans available of the Hospital Clinic de Barcelona. However, it is important to consider that the results would not have varied much if one of the other options was selected, since the acquisition protocol would be the same in any case.

Regarding the segmentation platform, ADAS 3D was the one used. The CARTOSEG CT Module works with CT images, thus it is not useful for LGE-CMR images, and Segment CMR is a platform mainly oriented to ventricle segmentation. Therefore, ADAS 3D is a better suitor for the project than the other options. Moreover, this platform allows the quantification of the amount of enhanced fibrosis, which is a key aspect of the project.

For ECGI, the choice was Acorys. EP solutions was discarded because it's oriented to CRT and not for atrial mapping. Between the other two options Acorys was selected because it is the one disponible in the Arrhythmia's Unit and it has already been used in the unit for many patients and other research projects. Furthermore, Acorys is a cheaper option than CardioInsight, which vests

cost 3000€ each. Moreover, Acorys does not always require the usage of imaging tools to obtain the geometries, which is another advantage to consider.

The programming environment selection was mainly due to the fact that this project is a part of a bigger one and MATLAB was the preferred choice for this bigger project and for the collaborations with other research groups. Moreover, the back end of Acorys runs with MATLAB, thus giving another reason to choose it as programming environment. Despite of this, MATLAB is faster in cases of image processing because it already has toolkits designed specifically for this matter.

Lastly, as statistics software, SPSS Statistics was the chosen one. SPSS is specifically designed to develop statistical analysis; thus, it is more powerful and can offer more accurate analysis and results than Excel.

6. Detailed Engineering

As it has been previously mentioned, the aim of this project is to characterize non-invasively the atrial substrate, both structurally, with LGE-MRI, and functionally, with ECGi. In this section, the details of the project implementation are provided in order to understand how it was carried out. This information is divided into the data used, the methodology followed, the results obtained and a final discussion.

6.1. Data

For this project, the data used comes from 38 patients that underwent an ablation procedure due to their AF condition at the Arrythmia's Unit of Hospital Clinic de Barcelona, which were enrolled on a clinical trial. The data that was extracted from each patient came from both ECGI mapping and LGE-CMR.

6.2. Methodology

The methodology followed to obtain the data needed to do the analysis can be divided in two main groups, which correspond to the two non-invasive techniques used.

6.2.1. ECGI

Before the ablation procedure, 64 electrodes are placed in the patient's torso. The location at which each electrode should be placed is illustrated by the ECGI program, in this case, Acorys. Once the electrodes are placed, a 360º video of the whole torso is recorded along with some photos. Form the video, a 3D object of the torso is obtained, where all the electrodes can be clearly seen.

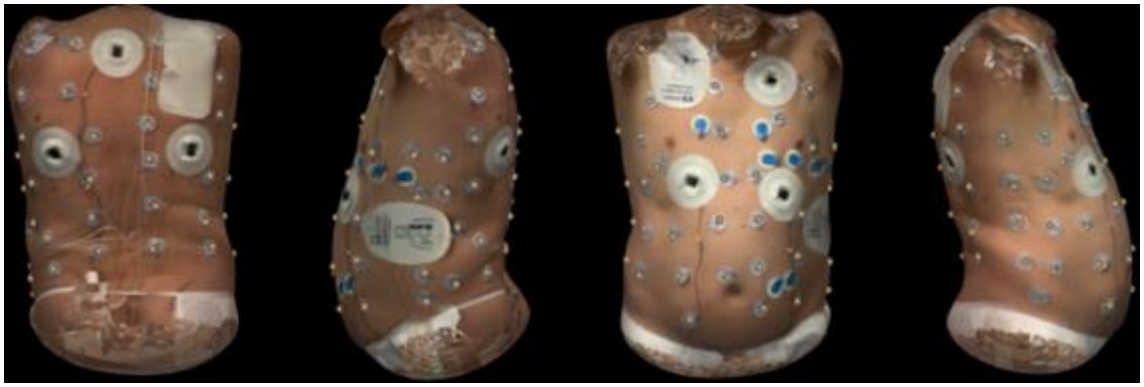


Figure 12. 3D torso reconstruction with all 64 electrodes placed

In order to make the ECGI results more personalized, in some cases, an MRI image of the torso is previously obtained, and both the torso and the heart are segmented, thus obtaining a 3D geometric representation of them. For those cases where no MRI image has been obtained, standard artificial intelligence generated geometries are used for both heart and torso.

At this point, both 3D representations, the one coming from the video taken and the one coming from the MRI are aligned using CloudCompare. Thus, we are capable of knowing the heart's position with respect to the electrodes.

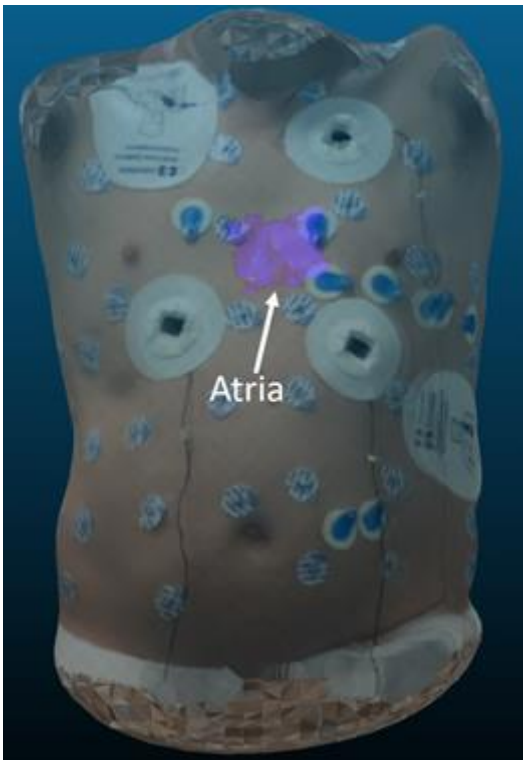


Figure 13. Alignment of heart and torso geometries. The figure shows the atria location within the patient's torso.

Now, within the Acorys program, the geometry of the patient is imported, and each electrode is selected from the 3D image of the torso, so that the program knows which electrode is which and where is it placed exactly. By knowing the coordinates of the body surface potentials, ECGI software can solve the inverse problem previously mentioned and obtain the ECGI electrograms, from which activation maps can be obtained.

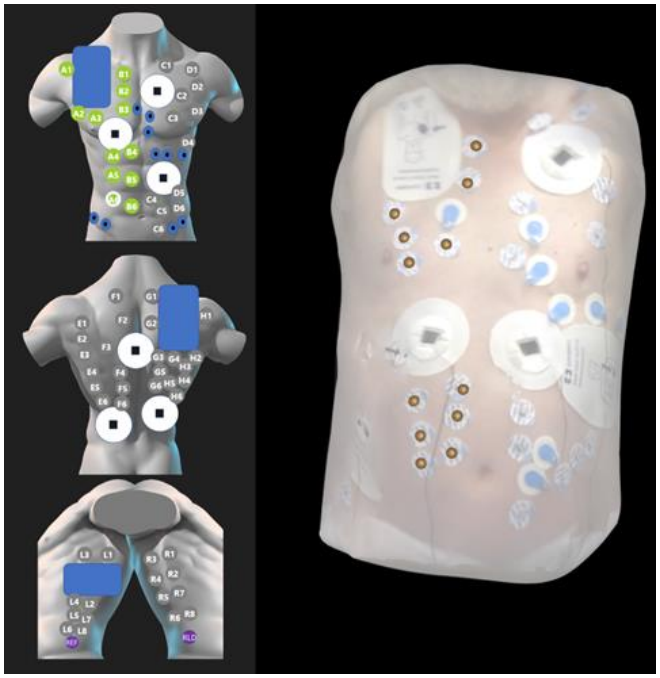


Figure 14. Selection of the electrodes. Each electrode within the torso geometry is paired up with its corresponding electrode represented in the Acorys platform.

With all the electrodes correctly selected, the ECG signals coming from each electrode are obtained. During the procedure, one-minute recordings take place at the different stages. First, a recording of the sinus rhythm before the procedure, then usually the heart is stimulated from the coronary sinus, and a recording of this paced rhythm is also done. Then, the ablation takes placed and another paced and sinus rhythm recording are taken.

From these recordings, ten second segments are used to create the maps, selecting the p-waves of the signals.

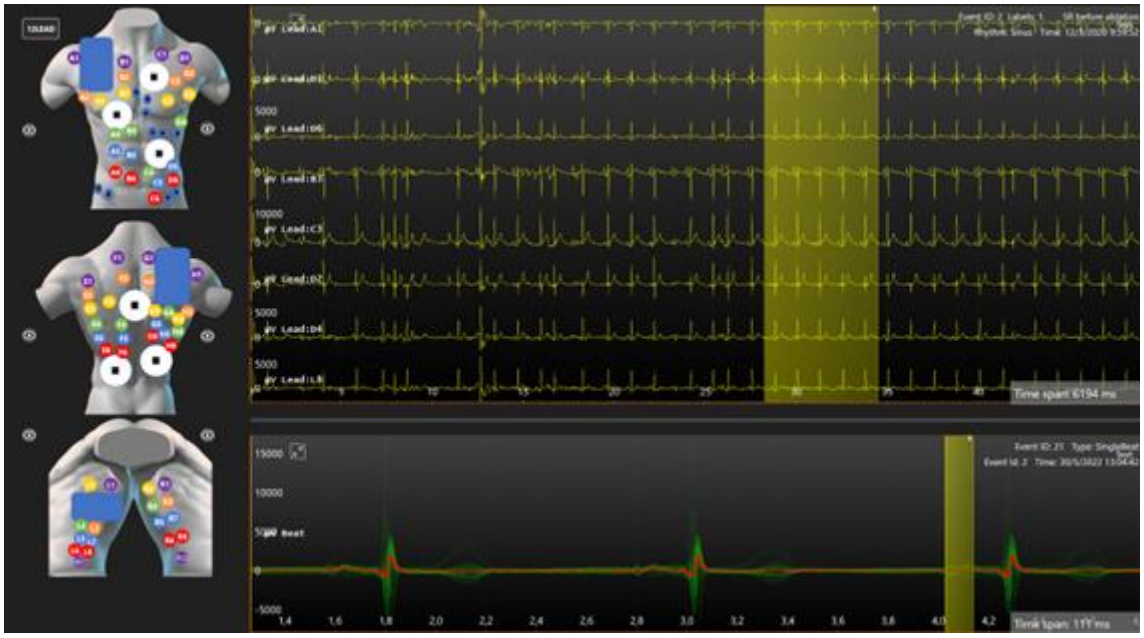


Figure 15. Selection of the p-wave in a ten second segment obtained from a recording taken during an ablation procedure

Once an accurate map is obtained, the data is saved in episode format.

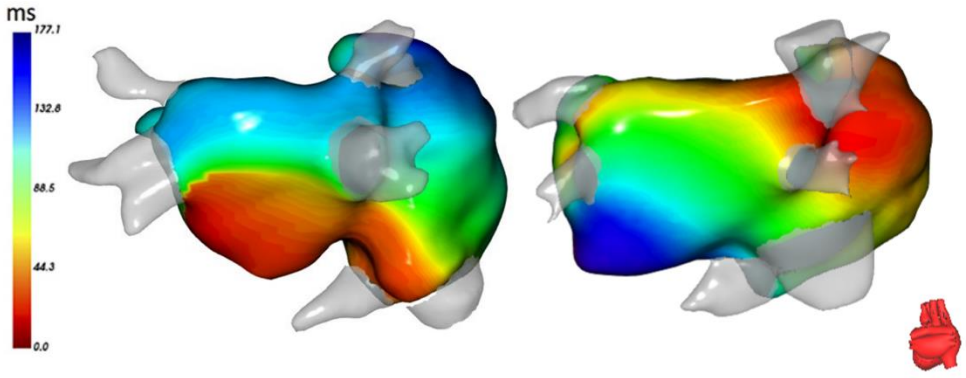


Figure 16. Activation maps obtained in sinus rhythm (right) and in coronary sinus stimulation rhythm (left)

Now, from each patient we have four episodes, the sinus rhythm pre-ablation, the sinus rhythm post- ablation, the coronary sinus stimulated rhythm pre-ablation and the coronary sinus stimulated

rhythm post-ablation. Using a Matlab program, the geometries of these maps are converted to objects (.obj files) to allow the geometry characterization.

From this point forward the project focuses only on the maps obtained in sinus rhythm, since it is the least invasive approach possible. To obtain the stimulated maps a catheter is placed into the coronary sinus, therefore, it is a more invasive approach.

In order to be able to characterize the atrial substrate, the atria are regionalized into nineteen areas. The left atrium is divided in twelve regions, following the proposed twelve segments of the Benito E.M. et al article [], them being:

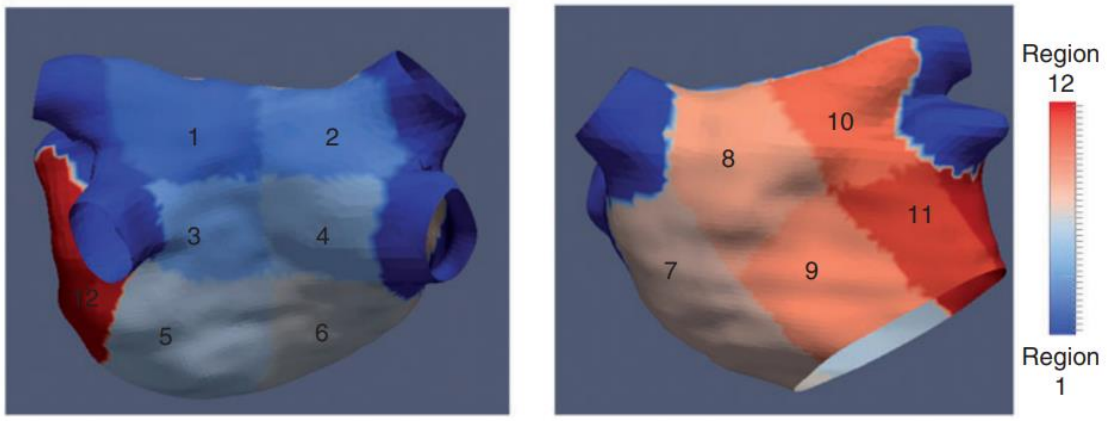


Figure 17. Left atrium twelve proposed segments to perform a regionalized analysis of the atrial substrate

(1) Posterior superior left
(2) Posterior superior right
(3) Posterior middle left
(4) Posterior middle right
(5) Posterior inferior left
(6) Posterior inferior right
(7) Septal wall of the left atrium
(8) Anterior superior left
(9) Anterior inferior left
(10) Anterior superior right
(11) Anterior inferior right
(12) Lateral wall of the left atrium

For the right atrium seven regions are used, based on relevant anatomical structures from the RA them being:

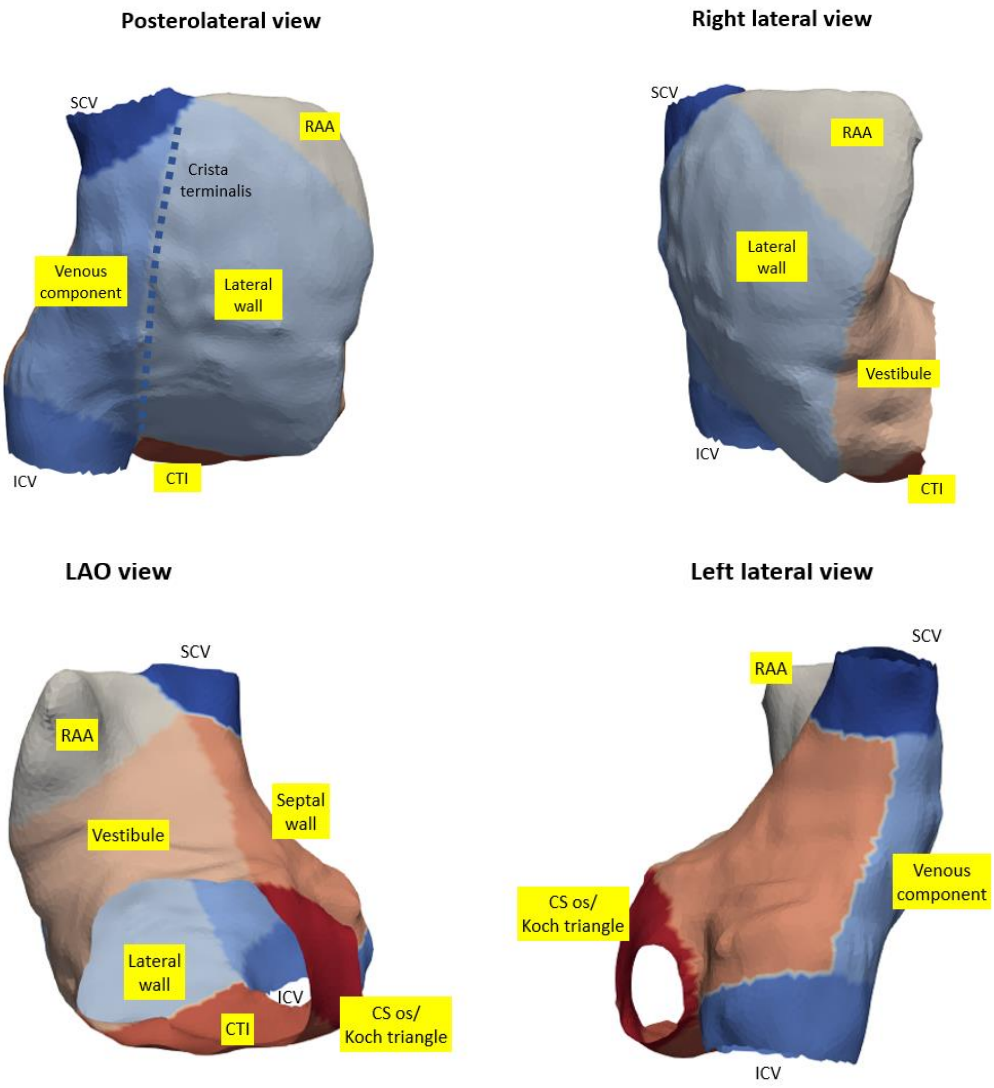


Figure 18. Right atrium seven proposed segments to perform a regionalized analysis of the atrial substrate

(13)Venous component

(14)Lateral wall of the right atrium

(15)Right atrial appendage (RAA)

(16)Cavotricuspid isthmus (CTI)

(17)Vestibule

(18)Septal wall of the right atrium

(19)Coronary sinus ostium

For each of the 38 patients, these regions were drawn to the corresponding object obtained from Matlab using Meshmixer, obtaining as a result another object file with the 19 regions of the atria.

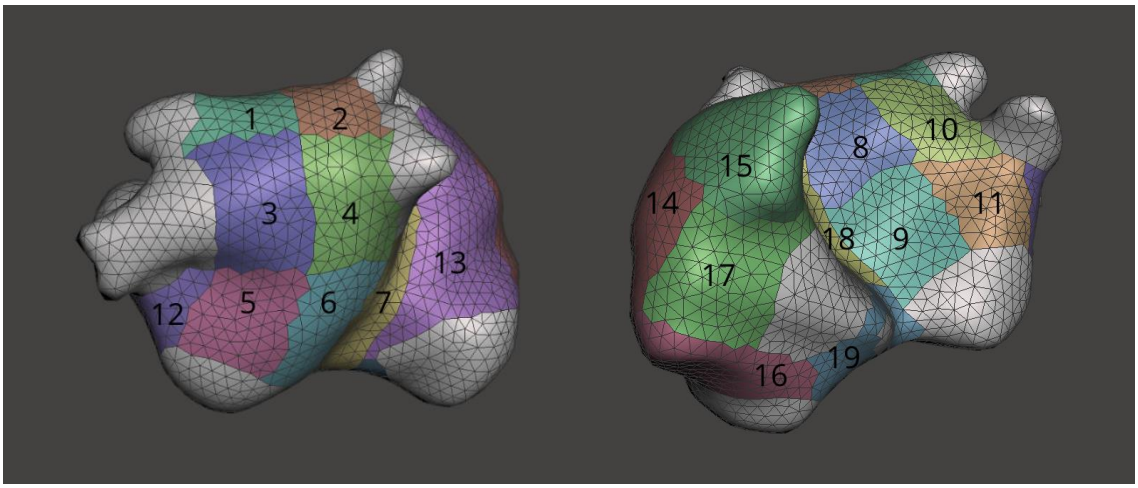
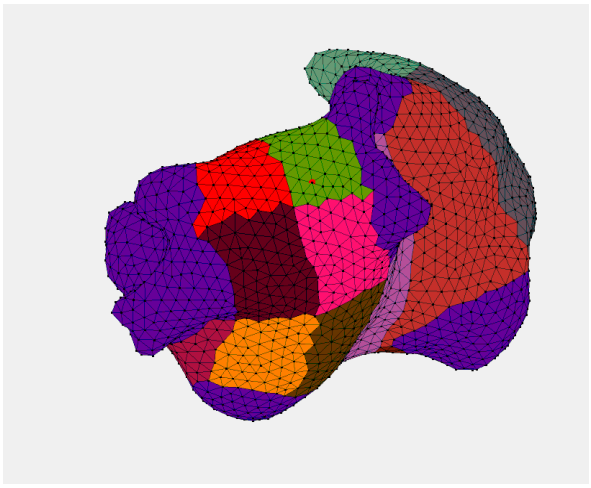


Figure 19. Atria regionalization using Meshmixer

Then, using another Matlab program, information is extracted considering the different regions. In this program, a point must be selected for each of the regions drawn in Meshmixer.

Once a point is selected, which must be in one of the nodes visible to ensure that the point belongs to the region, it is used to label the whole region. The program gives a list of all the possible regions where the selected point could belong to, and the number of the corresponding that specific region is introduced. This process is repeated for the 19 regions previously described. In this case, an additional region is considered, region 20, which corresponds to all those nodes that do not belong to any of the other 19 regions.



```
========================================================================
                    Please select one of the options
Which section is the one selected?
1:  Area 1 - Posterior - superior - left
2:  Area 2 - Posterior - superior - right
3:  Area 3 - Posterior - middle - left
4:  Area 4 - Posterior - middle - right
5:  Area 5 - Posterior - inferior - left
6:  Area 6 - Posterior - inferior - right
7:  Area 7 - Septal wall
8:  Area 8 - Anterior - superior - left
9:  Area 9 - Anterior - inferior - left
10: Area 10 - Anterior - superior - right
11: Area 11 - Anterior - inferior - right
12: Area 12 - Lateral wall LA
13: Area 13 - Venous component
14: Area 14 - Lateral wall RA
15: Area 15 - RAA
16: Area 16 - CTI
17: Area 17 - Vestibule
18: Area 18 - Septal wall
19: Area 19 - CS osteum
20: Area 20 - Non-assigned nodes
========================================================================

2
Continuar trazado? Y/N [Y]: Y
```

Figure 20. Labeling of the 19 regions of the atria in Matlab

As a result, of this process, five .csv files are obtained for each patient containing information about the conduction velocity (CV) and the local activation times (LATs). However, since this project aims

to gather information as localized as possible to be able to compare it to localized fibrosis, it only uses CV data.

6.2.2. LGE-CMR

Prior to the ablation procedure, a LGE-CMR was taken for each patient. From these images, a segmentation is done for both LA and RA using ADAS3D.

The segmentation procedure consists of manually tracing the atrial wall on the different layers of the resonance taken. It is not necessary to do this tracing in all layers since the software does an interpolation between the ones that have been traces. Moreover, the program allows adjustments to ensure that the line traced properly delimitates the atrial wall. From this process, the end result is a 3D representation of the atria as the one in Figure 21.

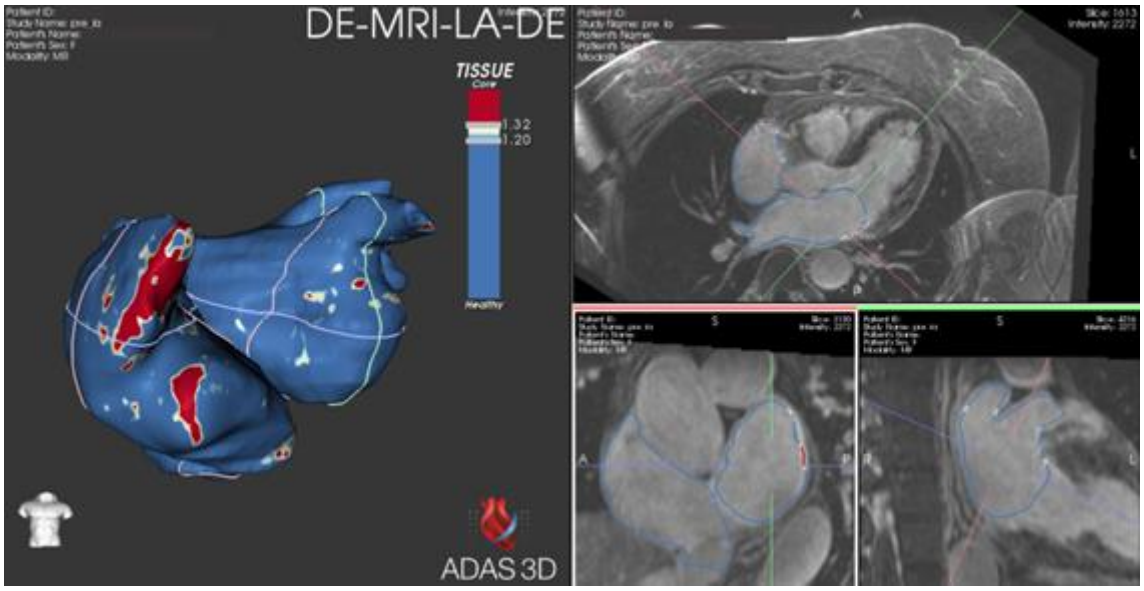


Figure 21. 3D representation of the atria resulting from the LGE-CMR segmentation

Once again, we are interested in regionalizing the atria, and in this case the methodology followed for the left atria is different than the one used for the right.

For left atria, ADAS3D has developed a tool capable of automatically drawing the twelve regions mentioned in the previous section. To do so, the main left atrial characteristic structures have to be selected and labeled. These are the pulmonary veins: left superior (LSPV), left inferior (LIPV), right superior (RSPV) and right inferior (RIPV), the mitral valve (MITRAL) and the left atrial appendage (LAA), and for those patients having a common trunk instead of the two separate PV: left common trunk (LCPV) or right common trunk (RCPV).

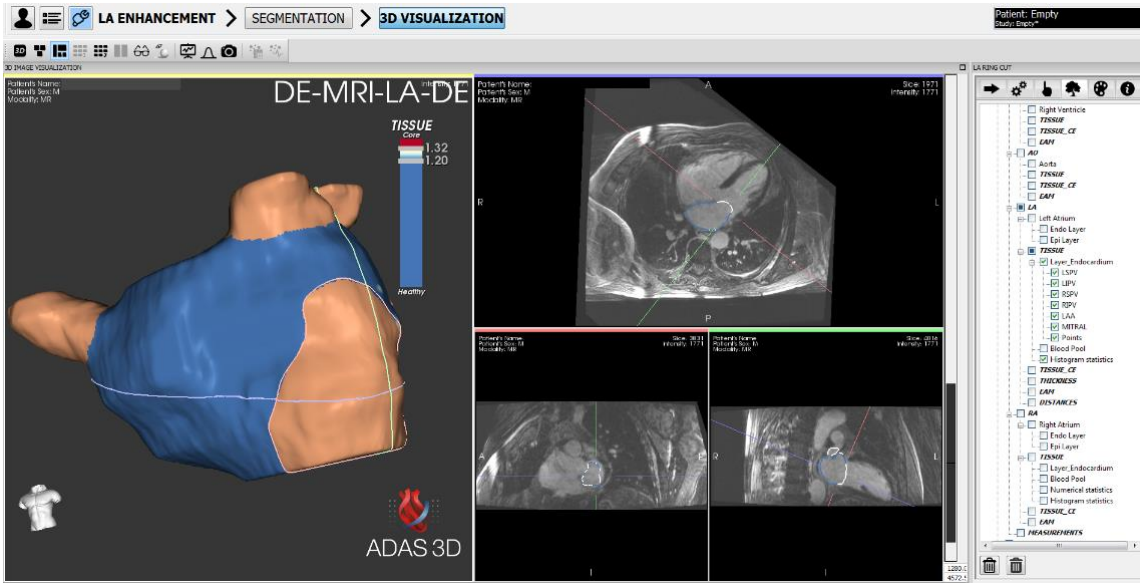


Figure 22. Selection of one of the main left atrial characteristic structures, the mitral valve, using “Ring Cut” tool

The selection of these structures has to be manually performed using the “Ring Cut” tool. Once all the beforementioned structures have been selected and labeled, the “Atrium Segments” tool is used, and the twelve regions are automatically obtained. Once the regionalization of the left atrium is achieved, the program allows to directly obtain its corresponding statistics.

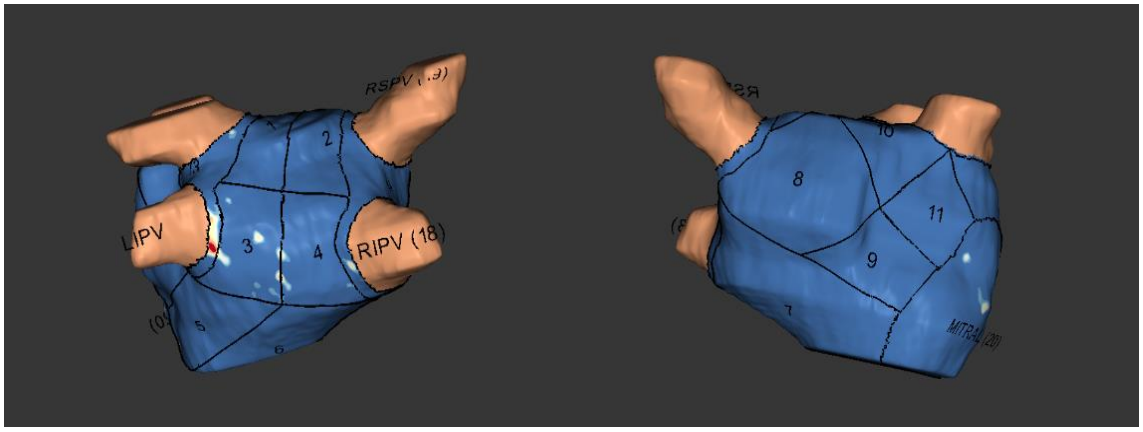


Figure 23. Left atrium with the twelve regions automatically generated

However, for right atria the process is different, since the tool that automatically regionalize the atria is not fully developed yet for the seven regions corresponding to the right atrium. Therefore, the regions are drawn manually. Once the seven regions are drawn, the statistics are obtained.

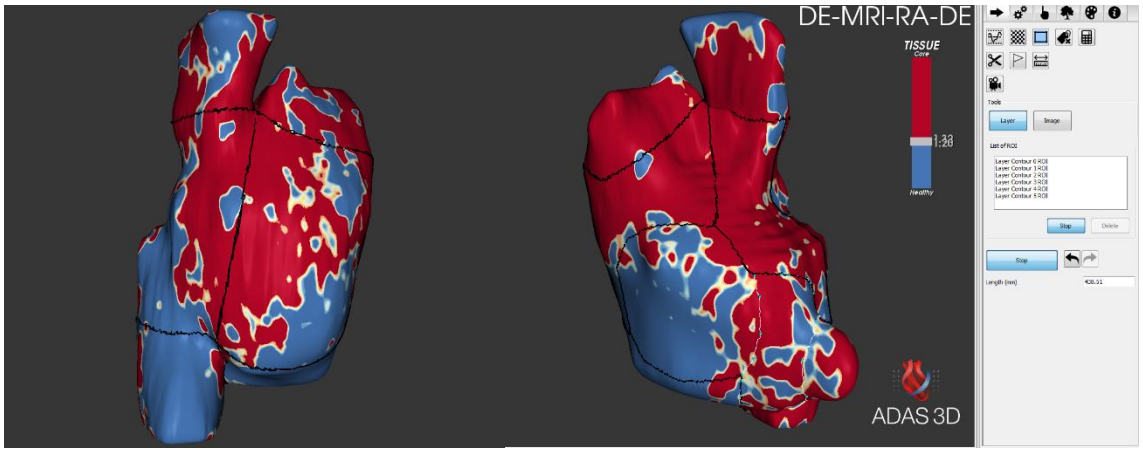


Figure 24. Right atrium manual regionalization

The result of these section was obtaining four .csv files containing left atrium information and two .csv files containing information of the right, for each patient.

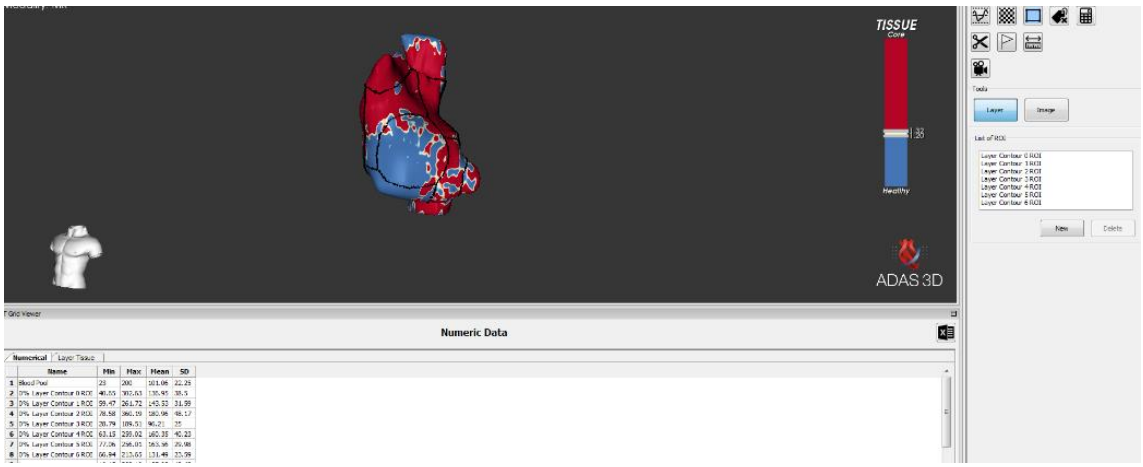


Figure 25. Statistics obtained for the right atrium regionalization

6.2.3. SPSS data base filling

Once information was obtained using the non-invasive methodologies just mentioned, the data is used to fill a database in SPSS.

In the case of the data that initially came from the ECGI, for each patient the following data is filled:

- First, the average conduction velocity of each of the 19 regions and the average conduction velocity when it is saturated at 70. Meaning that for this second column, a value of 70 is given to all conduction velocities with a value higher than 70.

- Secondly, the percentages of low conduction velocity within each region are given. For each column a different threshold value is used to stablish what is considered to be low conduction velocity, the values being lower than 150,100, 90, 80, 70, 60, 50, 40, 30 and 20, respectively.

- Then, some statistical measures of the conduction velocity heterogeneity are given, them being the standard deviation, the interquartile range, the variance and the 75, 50 and 25 quantities, respectively.

- Regarding the LATs, the information filled are the range of local activation times for each region, the local activation time on the right atrium, the local activation time of the left atrium, and the range of local activation times for the whole area.

CV_AVG	CV_AVG_07	LOWCV15_PERC	LOWCV10_PERC	LOWCV09_PERC	LOWCV08_PERC	LOWCV07_PERC	LOWCV06_PERC	LOWCV05_PERC	LOWCV04_PERC	LOWCV03_PERC	LOWCV02_PERC
200,00	70,00	,00	,00	,00	,00	,00	,00	,00	,00	,00	,00
192,35	68,96	5,45	3,64	3,64	3,64	3,64	3,64	3,64	,00	,00	,00
93,96	46,19	63,64	63,64	61,82	60,00	60,00	56,36	56,36	50,91	32,73	14,55
53,12	41,79	95,92	87,76	85,71	83,67	79,59	77,55	69,39	57,14	38,78	2,04
190,77	67,90	4,76	4,76	4,76	4,76	4,76	4,76	4,76	4,76	3,17	1,59
150,04	65,13	36,67	30,00	30,00	30,00	23,33	15,00	15,00	6,67	,00	,00
124,73	63,44	54,43	48,10	46,84	44,30	41,77	22,78	11,39	7,59	,00	,00
89,91	51,46	75,68	64,86	62,16	59,46	54,05	54,05	48,65	32,43	24,32	,00
151,12	69,87	44,44	22,22	16,67	16,67	2,78	,00	,00	,00	,00	,00
112,17	52,91	52,50	50,00	47,50	47,50	45,00	42,50	37,50	35,00	27,50	7,50
141,77	68,08	48,84	25,58	23,26	18,60	9,30	6,98	6,98	,00	,00	,00
136,39	58,37	38,71	32,26	32,26	30,65	30,65	30,65	25,81	20,97	17,74	4,84
152,52	65,42	38,24	25,49	21,57	21,57	21,57	16,67	12,75	5,88	,00	,00
141,54	69,01	53,94	26,77	20,08	12,20	6,30	4,72	1,57	,39	,00	,00
128,45	64,43	56,91	39,36	36,17	31,38	27,66	19,68	11,17	7,98	3,72	,00
125,69	70,00	67,50	46,25	30,00	17,50	,00	,00	,00	,00	,00	,00
122,41	63,09	68,60	37,21	29,07	23,26	19,77	19,77	17,44	13,95	8,14	,00
107,61	59,00	69,84	52,38	50,79	44,44	33,33	30,16	30,16	23,81	11,11	,00
200,00	70,00	,00	,00	,00	,00	,00	,00	,00	,00	,00	,00

SD_CV	IQ_RANG_CV	VAR_CV	PERC_3RDQUART	PERC_2NDQUART	PERC_1STQUART
,00	,00	,00	,00	,00	,00
31,60	,00	998,87	9,09	9,09	9,09
81,72	174,03	6678,73	67,27	49,09	25,45
43,68	30,25	1908,32	75,51	48,98	24,49
37,56	,00	1411,03	7,94	7,94	7,94
67,15	127,97	4508,99	40,00	40,00	25,00
68,30	139,21	4664,91	60,76	49,37	25,32
69,02	126,53	4763,32	75,68	48,65	24,32
48,44	92,90	2346,05	63,89	50,00	25,00
79,04	171,48	6247,37	65,00	50,00	25,00
50,30	96,70	2529,62	74,42	48,84	25,58
73,44	154,64	5392,84	64,52	50,00	24,19
62,85	100,24	3949,87	43,14	43,14	24,51
49,02	98,07	2403,25	74,80	50,00	24,80
62,28	134,95	3879,15	70,74	50,00	25,00
47,80	89,20	2285,26	75,00	50,00	25,00
59,62	115,34	3554,00	73,26	50,00	24,42
65,37	150,70	4273,52	74,60	49,21	25,40
,00	,00	,00	,00	,00	,00

LAT_RANG_AREA	LAT_RA	LAT_LA	LAT_RANG
5,00	69,00	75,00	77,00
9,00	69,00	75,00	77,00
61,00	69,00	75,00	77,00
64,00	69,00	75,00	77,00
5,00	69,00	75,00	77,00
34,00	69,00	75,00	77,00
61,00	69,00	75,00	77,00
45,00	69,00	75,00	77,00
13,00	69,00	75,00	77,00
48,00	69,00	75,00	77,00
19,00	69,00	75,00	77,00
32,00	69,00	75,00	77,00
42,00	69,00	75,00	77,00
40,00	69,00	75,00	77,00
41,00	69,00	75,00	77,00
19,00	69,00	75,00	77,00
45,00	69,00	75,00	77,00
61,00	69,00	75,00	77,00
7,00	69,00	75,00	77,00

Figure 26. SPSS columns filled with data initially coming from ECGI

For the data initially obtained from the resonance, the data filled is the following:

- Image intensity ratio average of the region with respect to the blood pool of the left atrium in the twelve left atrium regions, and with respect to the right atrium blood pool for the seven regions of the right atrium. And, image intensity ratio average LA, which is the same as previously but in this case with respect to the left atrium blood pool for all atria regions.

- The blood pool of the left atrium for the twelve regions and the blood pool of the right atrium for the other seven.

- The core percentage, the core plus border-zone percentage and, the border-zone percentage within the region. The core are those zones where the IIR is higher than 1.32 (the red ones in the ADAS3D platform) and the border zone are those where the IIR is higher than 1.2 and lower than 1.32.

- The total surface of the left atrium and the total surface of the right atrium. Also, the surfaces of each of the nineteen regions, in cm².

- The core, core plus border-zone and border-zone surfaces of the region, in cm².

- The core, the core plus border-zone and border-zone percentages with respect to the total area of the atria.

IIR_AVG	IIR_LA_BP	BLOOD_POOL	CORE_PERC	CORE_BZ_PERC	BZ_PERC	LA_SURF	RA_SURF	REGION_SURF	CORE_SURF	CORE_BZ_SURF	BZ_SURF	CORE_PERC_ATR	COREBZ_PERC_ATR	BZ_PERC_ATR
1,06	1,06	155,75	14,33	19,92	5,59	129,60	131,18	1,91	,27	,38	,11	,21	,29	,08
1,11	1,11	155,75	24,39	31,94	7,55	129,60	131,18	2,35	,57	,75	,18	,44	,58	,14
1,72	1,72	155,75	75,85	86,03	10,18	129,60	131,18	2,90	2,20	2,49	,29	1,70	1,92	,22
1,08	1,08	155,75	1,89	13,53	11,64	129,60	131,18	2,95	,06	,40	,34	,05	,31	,26
1,35	1,35	155,75	34,23	64,24	30,01	129,60	131,18	3,72	1,27	2,39	1,12	,98	1,84	,86
1,05	1,05	155,75	4,13	14,21	10,08	129,60	131,18	6,20	,26	,88	,63	,20	,68	,49
1,16	1,16	155,75	18,16	24,59	6,43	129,60	131,18	5,69	1,03	1,40	,37	,79	1,08	,29
1,23	1,23	155,75	18,91	33,43	14,52	129,60	131,18	6,36	1,20	2,13	,92	,93	1,64	,71
1,12	1,12	155,75	7,61	22,84	15,23	129,60	131,18	3,52	,27	,80	,54	,21	,62	,42
1,15	1,15	155,75	11,74	37,35	25,61	129,60	131,18	3,70	,43	1,38	,95	,33	1,06	,73
1,15	1,15	155,75	5,62	22,86	17,25	129,60	131,18	1,66	,09	,38	,29	,07	,29	,22
1,10	1,10	155,75	1,55	18,27	16,72	129,60	131,18	3,97	,06	,72	,66	,05	,56	,51
1,36	,88	101,06	51,58	64,50	12,93	129,60	131,18	16,17	8,34	10,43	2,09	6,36	7,95	1,60
1,42	,92	101,06	57,71	74,57	16,85	129,60	131,18	19,58	11,30	14,60	3,30	8,62	11,13	2,51
1,79	1,16	101,06	83,07	90,70	7,53	129,60	131,18	10,75	8,93	9,75	,81	6,81	7,43	,62
,95	,62	101,06	6,93	13,39	6,46	129,60	131,18	10,53	,73	1,41	,68	,55	1,08	,52
1,59	1,03	101,06	73,25	81,00	7,75	129,60	131,18	9,16	6,71	7,42	,71	5,11	5,66	,54
1,62	1,05	101,06	84,09	93,68	9,59	129,60	131,18	8,86	7,45	8,30	,85	5,68	6,33	,65
1,30	,84	101,06	49,74	70,82	20,95	129,60	131,18	7,78	3,87	5,51	1,63	2,95	4,20	1,25

Figure 27. SPSS columns filled with data initially coming from LGE-CMR

Once the SPSS database is filled with all these data for each of the 38 patients, it is used to do some analysis and extract the results.

6.3. Results

As previously mentioned, the goal of this project is to characterize non-invasively the atrial substrate using both LGE-CMR and ECGI.

The first thing that was assessed was whether there existed a correlation between the data obtained for both methods. To do so, the data used were the conduction velocities, in the case of ECGI, and for LGE-CMR the IIR average with respect to the LA blood pool.

To determine whether there existed an association within these two variables, the data was fitted into a linear model, using the lmer function. The linear model obtained showed a negative beta coefficient value. Beta coefficients are regression coefficients that are analogous to the slope in a simple correlation. In this case the beta coefficient obtained is -51.489.

The lmer function outputs can be seen in Table 2. The Pr(>|z|) column represents the p-value associated with the value in the z value column, which corresponds to the regression coefficient divided by the standard error. Since the Pr(>|z|) column has values lower than 0.05 the model has proven to be statistically significant.

	Estimate	Std. Error	Z value	Pr(>|z|)
(Intercept) == 0	193.989	2.926	66.30	<2e-16
Average_IIR_ref_LA	-51.489	1.370	-37.57	<2e-16

Table 2. Parameters of the linear model for the association of conduction velocity (ECGI) and IIR average with respect to the LA blood pool

In order to be able to visualize the results obtained, the data obtained from the linear regression model previously mentioned was used to create Figure 28.

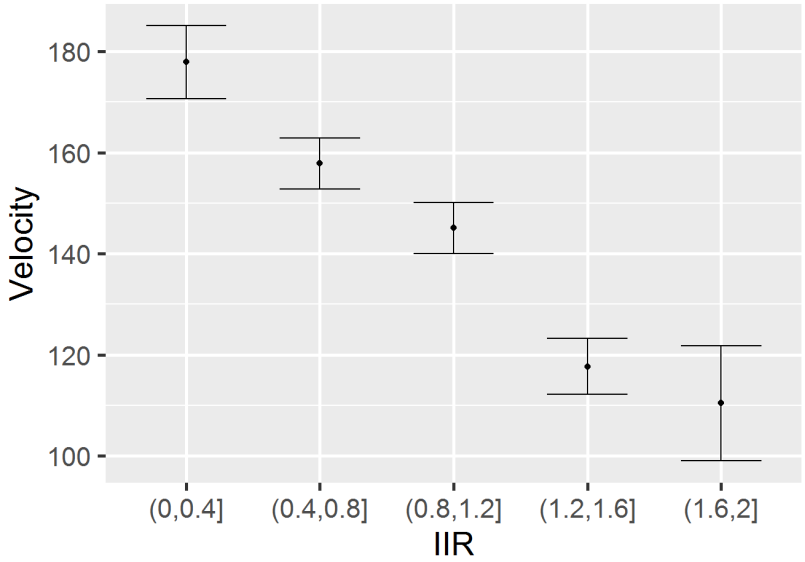


Figure 28. Graphical representation of the linear regression model obtained for the association between conduction velocity (ECGI) and IIR average with respect to the LA blood pool (LGE-CMR)

The second thing addressed was the regionalized analysis to determine in which regions the association between the data from both methods was higher. For this, the function emtrends was used, obtaining the trend of the IIR variable for each region. The trends in this case are used to describe whether the data shows an upward or downward movement when the conduction velocity increases. The results obtained for each region are shown in Table 3. The column SE shows the corresponding standard error and LCL and UCL are the lower and the upper control limits, using a confidence level of 0.95.

Regions	IIR trend	SE	LCL	UCL
1	-20.204	7.84	-35.56	-4.85
2	5.641	7.50	-9.06	20.35
3	-27.523	6.76	-40.78	-14.27
4	-17.186	7.37	-29.67	-4.70
5	-5.433	8.53	-22.16	11.29
6	-44.988	7.70	-60.08	-29.90

7	-9.329	7.79	-24.60	5.94
8	-29.026	7.85	-44.41	-13.65
9	-7.742	10.36	-28.04	12.56
10	32.221	8.37	15.81	48.63
11	-109.671	9.39	-128.07	-91.27
12	-0.501	6.74	-13.71	12.71
13	-43.883	6.65	-56.91	-30.86
14	17.220	3.53	10.29	24.15
15	12.200	3.67	5.07	19.47
16	-74.435	5.00	-84.24	-64.63
17	-12.200	3.94	-19.93	-4.47
18	-26.062	10.11	-45.88	-6.24
19	-63.028	9.20	-81.07	-44.99

Table 3. Results of the regionalized analysis considering the association between conduction velocity (ECGI) and IIR average with respect to the LA blood pool (LGE-CMR)

Regarding LGE-CMR data, another variable that indicates the existence of unhealthy tissue is the percentage of core and border zone. Thus, the same analysis was performed, but instead of using the IIR variable, the percentage of core and border was used. The results can be observed in Table 4. Here the beta coefficient is -0.25113.

	Estimate	Std. Error	Z value	Pr(>|z|)
(Intercept) == 0	151.16915	2.42405	62.36	<2e-16
Perc_core_BZ	-0.25113	0.01462	-17.18	<2e-16

Table 4. Parameters of the linear model for the association of conduction velocity (ECGI) and percentage of core and border zone (LGE-CMR)

Regarding the analysis per regions, the results obtained are shown in Table 5.

Regions	Perc_core_BZ tend	SE	LCL	UCL
1	0.55578	0.0839	0.39133	0.7202
2	0.50255	0.0768	0.35201	0.6531
3	-0.30638	0.0408	-0.38640	-0.2264
4	-0.11764	0.0457	-0.20720	-0.0281
5	0.03627	0.0641	-0.08945	0.1620
6	0.35540	0.1160	0.12810	0.5827
7	-0.26687	0.1237	-0.50927	-0.0245
8	0.05339	0.0649	-0.07381	0.1806
9	0.00541	0.0899	-0.17071	0.1815
10	0.58787	0.0850	0.42127	0.7545
11	-0.62507	0.0973	-0.81581	-0.4343
12	0.11568	0.0577	0.00262	0.2287
13	-0.83543	0.0801	-0.99242	-0.6784
14	0.41260	0.0408	0.33256	0.4926
15	0.35386	0.0349	0.28541	0.4223

16	-0.89364	0.0583	-1.00792	-0.7794
17	-0.27460	0.0390	-0.35097	-0.1982
18	0.28952	0.0670	0.15815	0.4209
19	0.26616	0.0910	0.08786	0.4445

Table 5. Parameters of the linear model for the association of conduction velocity (ECGI) and percentage of core and border zone (LGE-CMR)

6.4. Discussion

In this section the main conclusions that one can extract from the results obtained are addressed.

As beforementioned, the association between the two non-invasive techniques was assessed, using the conduction velocity variable for the ECGI and the average IIR referred to the LA blood pool for the LGE-CMR. The election of the average IIR referred to the LA blood pool as the variable for the LGE-CMR came from the fact that the whole methodology followed to obtain the data was initially thought for characterizing just the LA. Thus, it was thought that by considering the LA blood pool as reference the data obtained would be more precise.

The linear model obtained once these data were fitted showed a negative beta coefficient of -51.489. Thus, the two variables proved to be associated negatively, meaning that for lower conduction velocities, the IIR was higher. The indicator of unhealthy tissue for the ECGI were low conduction velocity regions, and for the LGE-CMR the fibrotic tissue regions were those with a higher IIR. Therefore, these results show that both methods are capable of characterizing the atrial substrate, since it can be seen that a high IIR in the LGE-CMR, representing fibrotic tissue, is associated with low conduction velocity in the ECGI.

Regarding the regionalized analysis, the region where these variables showed a higher association was region 11, corresponding to the anterior inferior right region within the LA. When taking onto account only the RA regions, the one showing a higher association is region 16, corresponding to the cavotricuspid isthmus. Thus, in these regions, small differences in IIR values suppose higher differences in conduction velocities than in other regions. A possible explanation for the fact that some regions presented a positive association, them being regions 10, 14 and 15, could be that they are close to the atrial appendages (LAA and RAA), and in LGE-CMR it is difficult to characterize fibrosis and obtain good geometries of these structures.

The results also consider taking another variable as the one representing the unhealthy tissue in the LGE-CMR, this variable being the percentage of core and border zone. Thus, the percentage of zones considered to have an IIR > 1.2 (indicator of fibrotic tissue).

Considering this other variable, its association with the conduction velocity was also assessed fitting a linear model. The beta coefficient obtained was -0.25113, which is also negative, indicating that the variables were also negatively associated. Thus, a high percentage of fibrotic tissue proved to be associated with low conduction velocity. The regionalized analysis in this case showed that region where the association between the variables was higher was region 16, the cavotricuspid isthmus. The higher one when considering only the LA was region 11, the anterior inferior right region.

However, the beta coefficient obtained using the percentage of fibrotic tissue had a much lower value than the one achieved when using the average IIR referred to the LA blood pool. This could

potentially indicate that the IIR variable should be the one considered to characterize the atrial substrate when working with LGE-CMR.

The overall conclusion of the results obtained is that it is possible to characterize the pathological atrial substrate functionally with ECGI and structurally with LGE-CMR. Moreover, using both techniques combined could help with AF patient stratification, thus providing the best treatment in each case.

7. Execution chronogram

The temporal organization of the project is explained in this section. Starting by looking into the different tasks performed, and then visualizing them graphically using a GANTT diagram to clearly comprehend the timings followed. An important thing to mention is the fact that some tasks extended their initial expected timing.

7.1. Task definition and timing

The explanation of the tasks and their corresponding timings can be found below.

A) Bibliographic research about AF and the two non-invasive techniques: LGE-CMR and ECGI.
In order to be capable of starting the project development perse, prior knowledge regarding FA, its current treatment, and how the non-invasive techniques that were going to be used in the project worked, was needed. For this, an initial literature review took place.

B) Familiarization with the Acorys software.
Since the prior knowledge on the Acorys software was almost inexistent, some hours were spent learning the different features of the platform and how useful maps could be obtained, in both sinus rhythm and stimulated from the coronary sinus rhythm.

C) ECGI map obtention of the 38 patients.
Once understood how the Acorys software worked, the maps were obtained. For each patient the goal was to obtain four maps. Two of the patients in sinus rhythm, one pre and one post the ablation procedure, and two in stimulated rhythm, also pre and post the procedure. Once a map that made sense was obtained in each of the cases, it was exported as an episode.

D) Regionalization of the atria using Meshmixer.
From this point the maps used were only the ones obtained in sinus rhythm prior to the procedure. The maps were obtained in episode format and converted into objects using a MATLAB code. Once the .obj file was obtained, using Meshmixer the nineteen different atria regions were painted for each patient. And another .obj file containing the regionalization was exported for each patient.

E) Data extraction using MATLAB
Using the .obj file containing the atria regionalization a MATLAB program was used to obtain the information considering the different regions.

F) Filling the SPSS database corresponding columns.
The data obtained following this procedure was filled into a database.

G) Regionalization of the atria using ADAS 3D software.
In the case of ADAS 3D no prior familiarization sessions were needed due to an internship carried out during the summer at Arrhythmia's Unit. LA and RA were regionalized separately for each patient, since the methodology is different. For LA, using "Ring Cut" the significant anatomical structures were selected and an automated regionalization

obtained using to “Atrium Segments” tool. Whereas for RA the regions were manually traced.

H) Filling the SPSS database corresponding columns.
The data obtained following this procedure was filled into a database.

I) Data analysis.
Using the filled database some statistical analyses were performed to determine the association of the IIR average, the IIR average referred to the LA and the percentage of core and border zone respect to the conduction velocity of the different regions.

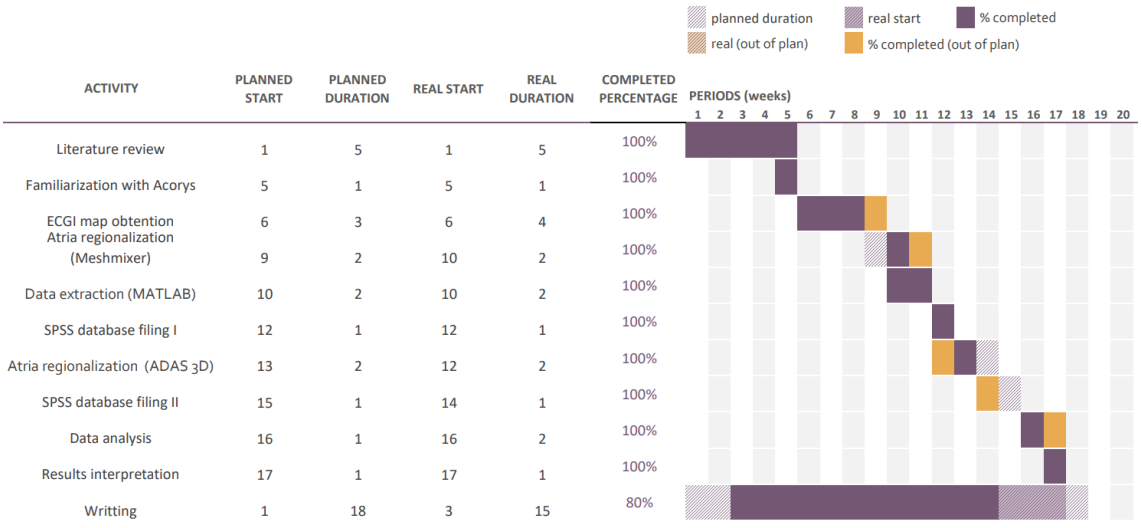
J) Information extraction from the results obtained.
Once the statistical analysis was performed, a critical review of their results was carried out regarding their possible interpretations and implications.

K) Writing the memory of the project.
During the project development a written memory has been elaborated.

7.2. GANTT diagram

A GANTT diagram us a useful tool that allows the display of the project tasks against time. In this case the time is distributed in weeks, number 1 corresponding week 31/01/22-06/02/22 and number 18 being week 30/05/22-05/06/22.

On the left there is the list of the tasks performed during the project. Then, the week were each one of them supposed to start according to the plan and their initial estimated duration. On their right there is the week were the task really started and its real duration. Moreover, in order to track the evolution of the project during its different stages of development, the completed percentage was used. As it can be noticed, at the moment at which this is being written the only task that has not been fully completed is the writing of the memory.



ACTIVITY	PLANNED START	PLANNED DURATION	REAL START	REAL DURATION	COMPLETED PERCENTAGE
Literature review	1	5	1	5	100%
Familiarization with Acorys	5	1	5	1	100%
ECGI map obtention	6	3	6	4	100%
Atria regionalization (Meshmixer)	9	2	10	2	100%
Data extraction (MATLAB)	10	2	10	2	100%
SPSS database filing I	12	1	12	1	100%
Atria regionalization (ADAS 3D)	13	2	12	2	100%
SPSS database filing II	15	1	14	1	100%
Data analysis	16	1	16	2	100%
Results interpretation	17	1	17	1	100%
Writting	1	18	3	15	80%

Figure 29. GANTT analysis

8. Technical viability

In order to get a clearer idea on the technical viability of the project, a SWOT analysis is performed. Both internal and external factors are reviewed. As internal factors, the strengths and weaknesses are considered, and as external factors the threats and opportunities.

Internal factors	
Strengths	Weaknesses
- Part of a bigger project - The technology used is non-invasive - Validation of both non-invasive techniques	- Atria regionalization highly operator dependent - In some patients proper ECGI maps could not be obtained
External factors	
Opportunities	Threats
- Growing market - Promising technology - Few studies regarding LGE-CMR and ECGI	- No evidence of outcome improvement on the ablation procedure when guided by these techniques - Patient authorization and consent

Table 6. SWOT analysis

8.1. Strengths

The main strength of this project is the fact that it is based on non-invasive techniques. By using only, the sinus rhythm pre-ablation ECGI maps and LGE-CMR, all the data is obtained in a completely non-invasive way. Thus, the data obtention process is painless for the patient and its associated discomfort is minimal.

Also, looking at the association between the data obtained from both techniques can lead to their validation. Since if the results concur it can be argued that they are both capable of characterizing the unhealthy atrial tissue properly.

Moreover, this project is a part of a bigger project carried out at the Arrythmia's Unit, which is helpful because both methods have already been used there and thus, the proper methodology to obtain useful the data had already been assessed.

8.2. Weaknesses

Regarding the weaknesses, the main one is the fact that the atria regionalization id highly operator dependent. In the case of LGE-CMR, the regions are defined in the ADAS 3D software. Even though in the case of LA the regions are automatically defined once the characteristic anatomical structures of the LA have been selected, the selection of these structures can vary according to the operator's criteria. Thus, despite the automatic generation of the regions, there is some degree of variability because it uses the selected anatomical structures are used as reference. In the case of RA, the regions are completely dependent on the operator's criteria since they are manually traced.

When working with ECGI, the regionalization of the atria in Meshmixer is also completely manual, thus, there also exists variability between operators.

The other weakness is the fact that in some cases no proper sinus rhythm ECGI map prior to the ablation procedure can be obtained. This can be due to many different factors, including the patient being in AF when the procedure starts or missing recordings at the moment prior to the ablation.

8.3. Opportunities

The AF market is currently growing, and it is expected to keep growing in the upcoming years. Thus, more fundings are expected to be directed to this field of research, enabling new studies and clinical trials.

The technology used in this project is relatively new, therefore the fully extend of their possibilities is yet to be determined. Moreover, the number of existing studies involving both LGE-CMR and ECGI is very limited at the moment.

8.4. Threats

The main threat of this project is the need further research, especially in the case of ECGI. Moreover, the results of the studies and trials that have been carried out until now show no evidence of improvement in the ablation procedure when being guided by either LGE-CMR nor ECGI.

Furthermore, consent from the patient is needed to obtain their data and the data acquisition process must follow several regulations and directives to ensure patient's safety. Moreover, when the patient authorizes their data to be used for research purposes, the data is still subjected to regulations and restrictions, for instance, it has to be anonymized.

9. Economic feasibility

In this section the theoretical costs to accomplish this study are presented. They are divided into human resources, software and hardware and fungible products.

This final degree project has an estimated amount of work corresponding to 300 hours. In Spain of a biomedical engineer is considered to be paid 26.35 €/hour. [76] However, since it is the case of a student, the salary is reduced to its 60%, becoming 16 €/hour. This leading to a total of 4.800 €.

When considering the software used, ADAS 3D and Acorys licenses were provided by Hospital Clinics, due to their partnerships. MATLAB and SPSS Statistics licenses were paid by Universitat de Barcelona since they are available for its students. Finally, Meshmixer is a free software platform. Therefore, the software did not add any additional cost.

Regarding the hardware, the LGE-MRI scans and the ECGI analyses were provided by the hospital along with computers containing ADAS 3D and Acorys access. The only additional hardware used was a private computer containing the other beforementioned software. Therefore, as for this project, hardware did not add additional costs.

	Item	Cost (€)
Human Resources	Student	4800 €
Software	ADAS 3D	0 € (Provided by the Hospital Clínic)
	Acorys	0 € (Provided by the Hospital Clínic)
	SPSS Statistics	0 € (University of Barcelona license)
	Meshmixer	0 € (Free download)
	MATLAB	0 € (University of Barcelona license)
Hardware	LGE-CMR scans	0 € (Provided by the Hospital Clínic)
	ECGI analysis	0 € (Provided by the Hospital Clínic)
TOTAL COST		**4800 €**

Table 7. Project development costs

In conclusion, from an economical point of view, the project is completely feasible, since the 4800€ of the total cost correspond to a theoretical salary, and since this project is part of a university course in reality this cost did not exist.

Once the costs of this particular project have been addressed. It is interesting to take a look at the current AF ablation treatment costs.

For each AF patient the inpatient admission mean cost is estimated to be 2328€ in Spain. [77] Each year, according to the Spanish Catheter Ablation Registry, 5164 AF ablation procedures take place. [78] Which leads to a total of approximately 12 million euros per year.

If it was possible to better stratify patients that are indicated to undergo this kind of procedure the cost per year would be reduced. Meaning that if some markers found non-invasively could help determining which patients were not going to benefit from the procedure, due to their high potential tendency to recurrence, less procedures would have to take place. Thus, the total annual cost would be reduced, mainly because the cost of using non-invasive techniques to stratify patients, such as LGE-CMR or ECGI is inferior to that of an ablation procedure.

10. Normative and legal aspects

This project has been carried out using real patients' data that underwent an ablation procedure at Hospital Clinic de Barcelona due to their AF. Thus, the legal requirements considered are those of the Spanish legislation.

The full project development has been don following the General Data Protection Regulation (GSPR) of the European union. [79] Moreover, the information obtained also follows under the scope of the Spanish *Ley Orgánica 3/2018 de Protección de Datos Personales y garantía de los derechos digitales*. [80] This law, among other aspects, stablishes the legislation regarding personal data protection in scientific research and medical trials. [81]

For this matter, prior to the procedure all patients signed an informed consent regarding both LGE-CMR and ECGI studies and the usage of their data. To be able to do the project, all the data was previously anonymized since the clinical data that is used cannot be tracked up to the patient from which it was obtained.

Regarding LGE-CMR, the FDA considers MRI scanners to be class IIa medical devices, since they are considered to be devices with low to moderate risk, mainly because they are radiation-emitting electronic products. [82] There exist many FDA recognized voluntary consensus standards regarding MRI safety, including ISO/TS 10974:2018, which assesses the safety of MRI for patients with an implantable medical device. [83]

Also related to the LGE-CMR, the software used for atrial segmentation and data extraction, ADAS 3D, holds ISO 13485:2016, which specifies the requirements for a quality management system in medical devices. [84] Moreover, this medical software also complies with Medical Device Regulation (EU)2017/745 regarding company quality systems. [85]

When it comes to ECGI, it is also classified as a class II medical device by the FDA. There exist many safety requirements for this type of systems, including IEC 60601-1:2005/A1:2012, which contains the requirements concerning safety and performance for medical electrical equipment. [86] Furthermore, IEC 62304:2006 is the standard that defines the requirements for medical device software, which is also interesting to consider in ECGI systems. [87]

11. Conclusions

The main objective of this project was to characterize non-invasively the atrial substrate with two different approaches, structurally, using LGE-CMR, and functionally, using ECGI. To do so data from 38 patients that underwent a catheter ablation procedure due to their AF at the Arrhythmia's Unit of Hospital Clínic de Barcelona was gathered.

In order to obtain more localized information of the atrial substrate the atria were regionalized into nineteen regions. The goal of this regionalization was to obtain useful information to be capable of properly stratifying patients to be capable to provide the best treatment methodology in each case. The fact that these data could be obtained in a completely non-invasive way would be a key factor to stablish a good stratification strategy, since it would be painless for patients and in its turn, it would also allow saving lots of resources.

To determine whether these two techniques could be used to properly characterize the atrial substrate their association was assessed. The results showed that there exists a negative association between conduction velocities of the ECGI and the variables indicating fibrotic tissue in LGE-CMR, them being the IIR average with respect to the LA blood pool and the percentage of fibrotic tissue (IIR>1.2). This proving that low velocities are associated with the fibrotic areas visible in LGE-CMR images. Moreover, results showed this association to be higher in regions 11 and 16 of the atria, them being the anterior inferior right region of the LA and the cavotricuspid isthmus, respectively.

As a future perspective, more AF markers could be studied, such as the conduction velocities dispersion values. Also, normality values could be defined using healthy people to achieve a clearer definition of pathology in ECGI. Moreover, it would also be interesting to determine the association of these two non-invasive techniques with the current gold standard to characterize atrial substrate, electroanatomic mapping, always keeping in mind that the data obtained in that case would no longer be exclusively non-invasive.

All in all, the results proved the capability of both non-invasive techniques to properly characterize the atrial substrate, in the case of ECGI, functionally, and in the one of LGE-CMR, structurally. Furthermore, their combined usage could be an interesting opportunity for patient stratification, which will become essential in a near future due to the continuous growing of AF prevalence.

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