Personalized Atrial Fibrillation Ablation with Ablation Index Adapted to Left Atrial Wall Thickness: The Ablate-by-LAW Study.

TRIAL LOCAL IDENTIFIER: Ablation-by-LAW

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PROTOCOL VERSION: 2.3 (June 25th 2020)

Protocol Version	Date of change	Description and comments	Control
1.2	June 18th 2019	Fused LAWT + Single-catheter, clinical FU added	CT + BJ
1.3	September 16th 2019	Anesthesia protocol (Appendix 4) + sample size calculation + peri-procedural TEE addendum + new investigators added	BJ
1.4	September 23rd 2019	Figures added (Appendix 5) + minor text corrections	BJ
1.5	October 1st 2019	Principal investigators' minor change	BJ
1.6	October 16th 2019	Minor text changes + split protocols (retrospective and prospective)	BJ
1.7	October 21st 2019	Minor text changes	BJ
1.8	November 27th 2019	Minor text changes + ADAS-3D list of collaborators + minor data collection sheet changes	BJ
1.9	December 27th 2019	Final participating centers & investigators + format optimization for international centers + English informed consent + minor text changes	BJ
2.0	January 6th 2020	ClinicalTrials.gov ID added	BJ
2.1	February 12th 2020	Minor text changes	BJ
2.2	February 26th 2020	Personalized ablation concept + new diagram, further explanation on esophagus segmentation using MDCT, CARTO data management by the core-lab, anesthetic protocol changes	BJ
2.3	June 25th 2020	Text changes and other centers' queries solved. Sample size re-calculated	BJ

1. INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia and constitutes an important public health burden, being a source of high morbidity and mortality. [1] Circumferential pulmonary vein isolation (PVI) has become a mainstay in the treatment of AF, particularly in symptomatic patients with paroxysmal AF (PAF) intolerant or refractory to medical treatment. [2] Dormant conduction and pulmonary vein reconnections are responsible for AF/atrial tachycardia (AT) recurrences owing to incomplete non-transmural ablation lesions that generate gaps on ablation lines. [3–5]

Local electrogram attenuation, catheter-tip temperature and impedance drop have been used as surrogates for lesion formation. Nevertheless, they correlate badly with contact force and therefore constitute bad predictors of lesion size [6]. Radiofrequency (RF) power, duration of RF energy delivery, baseline impedance and contact force (CF) have been proven to be determinants of lesion formation. [7–9]

More complex formulae have been developed to assess real-time effect of RF delivery and predict threshold values that must be reached to reduce reconnections and achieve permanent PVI. Namely, Force-Time Integral (FTI) which is calculated in grams second (gs) and represents the area under the CF/time curve [10,11]; and Ablation Index (AI) which is a complex weighed formula that integrates CF, RF time and RF power [12,13]. In order to minimize PVI reconnection, FTI and AI threshold values have been studied. In general, these values must be higher in the roof and anterior wall as compared to the inferior and posterior wall probably related to a lower wall thickness. [14]

The CLOSE study [15] analyzed the utility of AI for the reduction of AF recurrences with 91.3% of the patients free from AF/AT/atrial flutter (AFL) at 12 months follow-up. The CLOSE protocol targeted an inter-lesion distance of 6 mm and AI ≥ 400 at the posterior wall and ≥ 550 at the anterior wall. Nonetheless, in over 40% of patients, the target AI of 400 was not attained on the posterior wall owing to chest pain and/or intraesophageal temperature rise (IQR: 378–425 AU). The same 550 and 400 AI target values where used in a retrospective study comparing AI vs. CF-guided ablation resulting in significantly lower AT/AF recurrences on the AI arm. [13] Such targets where chosen based on a previous study that retrospectively analyzed the ablation settings at first AF ablation of patients having redo ablation. Mean AI and mean FTI being statistically lower for reconnected segments [mean AI: 395 (350–429) vs. 422 (380–464), p=0.002; mean FTI: 311 (225–373) vs. 371 (260–502) gs, p=0.003]. [12]

The left atrial wall is a thin structure with heterogeneous thickness, ranging from < 1mm to > 5 mm, with an important inter and intra-patient variability. [16] This variability in wall thickness is the result of a complex array of three-dimensional muscular strands. [17–19] A prospective study already showed that first pass PVI was limited by inability to create

transmural lesions in certain anatomical sites where left atrial wall thickness (LAWT) had been described as being higher in ex-vivo hearts. [18,20] LAWT was an independent predictor of reconnection, [21] dormant conduction [22] and AF recurrence after 12 months follow-up, [23] and it might even be a predictor of transition from paroxysmal to chronic AF. [24]

The relationship between FTI and AI values, LAWT and gap formation on the ablation line after PAF ablation was already studied in two small retrospective studies that used single-point LAWT measurements. Nevertheless, the anatomical location of the measured points in the multidetector cardiac tomography (MDCT) may have not corresponded exactly to the real-time catheter position as seen with the CARTO Merge® (Biosense Webster, Diamond Bar, CA, USA) module. These studies showed that FTI/wall thickness and AI/wall thickness indexes have demonstrated to predict gaps on PVI lines. [25] Although this relationship might also be explained by the fact that the anatomical regions where tissue is thickest are also regions where catheter stability is more difficult to obtain. Therefore, AI is the most suitable index to look at since it also takes stability on account.

Even though many limitations have been described on MDCT atrial wall thickness measurement for previous generations of scanners, modern machines allow for sub-millimetric resolution. In fact, MDCT-derived LAWT measurements have been reliably validated on a porcine model. [26] 3D LAWT maps have already been generated from contrast-enhanced MDCT images, [27] although their integration on a 3D anatomical mapping system for clinical use has not been described yet.

Of all the determinants of lesion creation, LAWT is one key element that has been evaluated in some retrospective analysis but is not yet used as per procedure to dose the radiofrequency delivery. Adapting AI to local LAWT would be very useful in standardizing the ablation procedure with parameters fitted to each patient, enabling the development of a personalized approach that will both: i) increase efficacy by performing transmural lesions to prevent the formation of conduction gaps in the initial lesion set, and ii) increase safety by preventing excessive RF delivery on thin wall areas which can lead to complications, like cardiac perforation or atrio-esophageal fistula.

Further on, with regards to procedural safety, a recent study by Pambrun et al. [28] recruited 100 patients with symptomatic, drug-refractory AF that underwent standard wide antral circumferential ablation to achieve PVI, divided into two groups: i) Control group, corresponding to 50 consecutive patients that followed a standard, two-catheter approach (CF ablation catheter plus circular mapping catheter); and ii) study group, conformed by 50 consecutive patients that followed a single-catheter approach (without the need for a circular mapping catheter) to achieve PVI. The rationale for the use of this approach was based on prior studies that showed that the complete loss of pace capture directly along the circumferential ablation line correlates with entrance block in 95% of PV and can be

achieved without circular mapping catheter guidance. [29,30] Moreover, pacing for unexcitability along the ablation line can identify potential sites with dormant conduction, and even excitable sites that would not have been identified using adenosine, [31] which, on the other hand, has not been able to improve the long-term success after AF ablation. [32] The study by Pambrun et al. [28] showed that antral exit block validated with a CF-sensing ablation catheter successfully predicts PVI, and it was demonstrated that this single-catheter approach for achieving PVI is feasible, cost-saving and non-inferior in terms of AF recurrences in the mid-term. However, the study was conducted only in patients with PAF, normal LA volumes and no prior AF ablation procedures. Thus, the potential usefulness of this cost-saving approach in a broader, 'real life' population is still unknown. We hypothesize that a single-catheter approach for RF-based PVI may be feasible, cost-saving and at least as safe and effective as the standard approach when used in all patients referred for AF ablation.

Finally, one key element regarding procedural safety is the avoidance of a dreaded complication, the atrio-esophagueal fistula. [33] It is estimated to occur in <0.1% to 0.25% of AF ablation procedures, but, among causes of death after AF ablation, atrio-esophagueal fistula is the second most common along with stroke. [34] The relationship of the esophagus to the LA posterior wall and pulmonary veins is variable. It tends to be located farthest from the right superior pulmonary vein, but it can be close to any of the others, depending on its course, and may be within a few millimeters at the point of closest proximity. [35] Imaging of the esophagus may be performed as a component of an imaging study that is primarily designed to evaluate extraesophageal anatomy, such as during a cardiac MDCT. In a similar way as for LAWT measurements using MDCT, the distance (i.e. 'tissue thickness') between the posterior wall of the LA and the esophagus can be measured.

We sought to evaluate the feasibility, safety, efficacy and reproducibility of performing atrial fibrillation ablation procedures with a fully personalized protocol that includes: i) the use of MDCT-derived LAWT information to select tailored point-by-point AI targets; ii) the use of a single-catheter strategy to minimize vascular-related complications; and iii) the integration of a MDCT-derived 'fingerprinted' esophagus image to modify the ablation lines to avoid too close proximity of RF applications. The study will be single-catheter-based, hypothesizing that this simplified and personalized approach is feasible, cost-saving and at least as safe and effective as the standard approach when used in all patients referred for AF ablation.

2. HYPOTHESIS AND OBJECTIVES

2.1 Research hypothesis

Personalized AF ablation using the *'ablation-by-LAW'* protocol that uses point-by-point adapted AI values according to the local MDCT-derived LAWT, is feasible, safe and at least as effective as the current AF ablation standards.

Ablation-by-LAW involves the use of tailored point-by-point AI values according to the local MDCT-derived LAWT, the use of a single-catheter strategy, and the integration of a MDCT-derived 'fingerprinted' esophagus image to modify the ablation lines aiming to avoid too close RF applications, while performing the procedures using general anesthesia and a high-rate, low-volume ventilation protocol. The following diagram constitutes a general overview of the protocol:
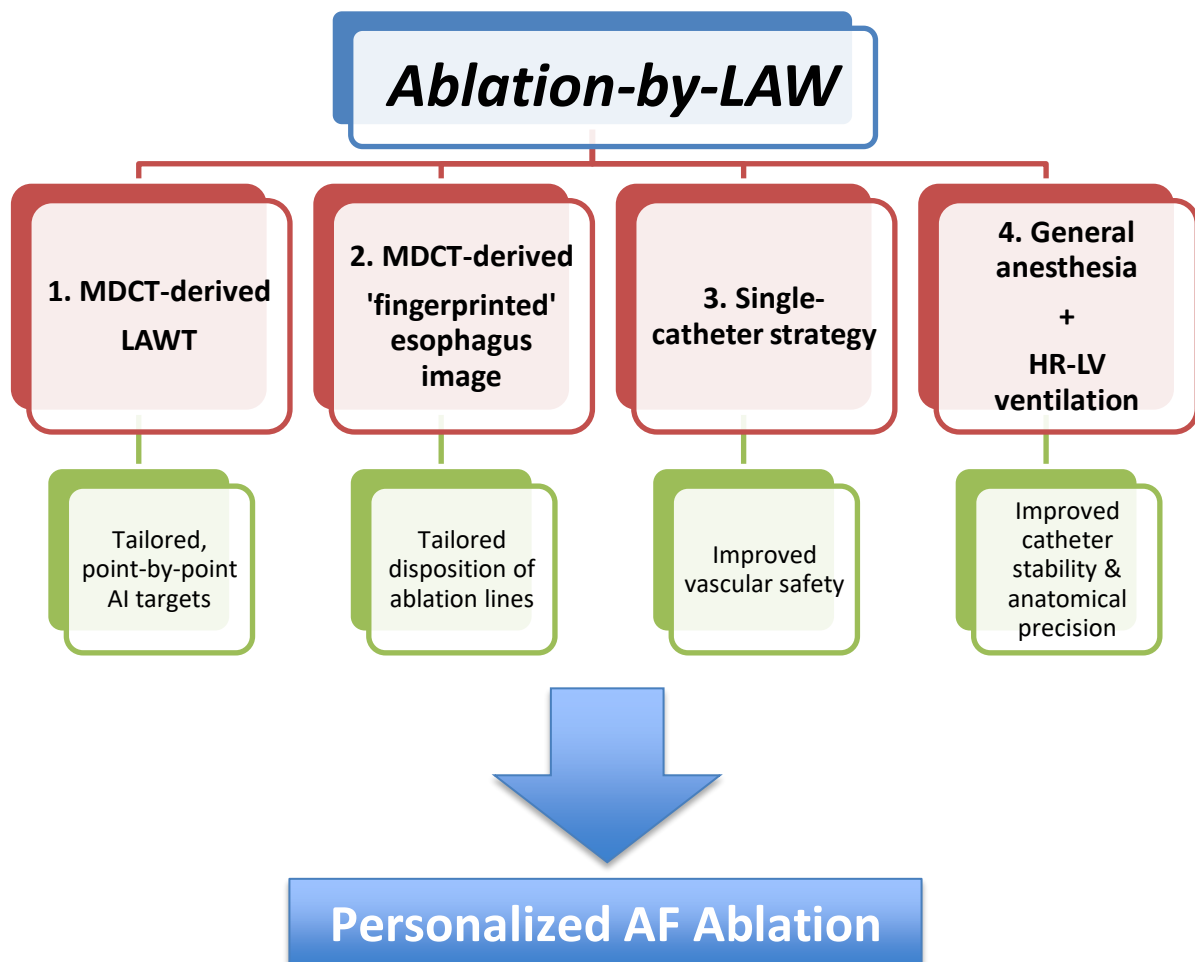
2.2 Study objectives

2.2.1 Primary objective

To determine if the proposed *ablation-by-LAW* protocol is non-inferior in terms of long-term clinical outcomes when compared to other AF ablation protocols using higher AI targets, not adapted to the LAWT.

2.2.2 Secondary objectives

- To determine if the *ablation-by-LAW* approach permits to be more efficient in terms of procedure time, RF time, and fluoroscopy time.

- To evaluate the rate of complications using the *ablation-by-LAW* approach.

- To analyze the reasons for not obtaining a first-pass isolation using the *ablation-by-LAW* approach.

3. METHODS

3.1 Study design

Single-arm, international, multicenter, prospective study.

3.2 Study setting

Tertiary hospitals with an electrophysiology team of qualified investigators with proven experience in performing atrial fibrillation ablation.

3.3 Eligibility criteria

Patients will only be recruited if they fulfill the following inclusion criteria:

- Age > 18 years.
- Indication for paroxysmal atrial fibrillation ablation.
- Signed informed consent.

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

- Age < 18 years.
- Pregnancy.
- Previous AF REDO procedure.
- Impossibility to perform a MDCT scan.
- Concomitant investigation treatments.
- Medical, geographical and social factors that make study participation impractical, and inability to give written informed consent. Patient's refusal to participate in the study.

3.4 Interventions

3.4.1 Pre-procedure MDCT scan

A pre-procedural multi-detector cardiac tomography (MDCT) will have to be performed in all participant subjects and centers. In the case of Teknon Medical Center, this will be done using a Revolution^{TM} CT scanner (General Electric Healthcare). The images will be acquired during an inspiratory breath-hold using retrospective ECG-gating technique with tube current modulation set between 50% and 100 % of the cardiac cycle. CT angiographic images will be acquired during the injection of a 70 mL bolus of Iopromide 370 mg I/mL (Ultravist, Bayer Hispania, Barcelona, Spain) at a rate of 3mL/s. Other contrast agents or acquisition protocols will be permitted, according to the usual practice of the corresponding centers. Similar acquisition protocols will be adapted to the local practice and available CT scanner of each participant center. All the data will be transmitted to the core-lab (see section 3.4.2) for

post-processing and will be reconstructed into axial images with a slice thickness of 0.625 mm.

3.4.2 Image processing

MDCT images of all centers will be anonymously sent using a secure data transfer server (eCRD platform developed by the contract research organization –CRO– Xolomon SL) and analyzed by the following core-lab: ADAS 3D Medical SL headquarters (Barcelona, Spain). The ADAS 3D LA™ software (ADAS 3D Medical SL, Barcelona, Spain) will be used to obtain 3D atrial wall thickness maps. All the images obtained in the remaining participating centers will be submitted to the core-lab using a secure server. In order to obtain the atrial wall thickness a 3-step algorithm will be applied: i) the endocardial layer is defined by means of a semi-automatic segmentation based on pixel intensity thresholds; ii) the epicardial layer is defined by a manually delineation in few slices followed by an interpolation in the missing slices; iii) Finally, the wall thickness at each endocardial point is computed as the distance between each endocardial point and its projection to the epicardial shell. These three steps result in a 3D thickness map that can be introduced into CARTO® navigation system (Biosense Webster, Diamond Bar, California, US). The color map uses a color scale to depict a range of thickness red being the thinnest (< 1 mm) and purple being the thickest (> 4 mm). Yellow, green and blue will be considered the intermediate values.

The same post-processing protocol will be applied to compute the distance between each LA epicardial point and the boundaries of the esophagus, thus calculating the soft tissue thickness (i.e. separation in mm) between these two anatomic structures. The tissue thickness at each point will be color-coded in a similar way as for LAWT, and the 'fingerprinted' esophagus image with the tissue thickness information will be also exported into CARTO® navigation system (Biosense Webster, Diamond Bar, California, US). Figure 3 in Appendix 4 shows an example of this fingerprinted esophagus, projected onto the LA posterior wall.

3.4.3 Catheter-based radiofrequency ablation

Procedures should be performed on uninterrupted oral anticoagulation and under general anesthesia aiming to complete neuromuscular relaxation (see Appendix 3), with hemodynamic monitoring using a radial arterial line. Single venous femoral access will be mandatory. Peri-procedural anticoagulation will be performed according to local protocols but always aiming to achieve an intraprocedural activated clotting time (ACT) of 300–350 seconds.

Transeptal puncture will be preferably guided by peri-procedural transesophageal echocardiography (TOE), which does not require for an additional venous puncture. Other imaging techniques, such as intracardiac echo, will be allowed to guide the puncture for those centers without TOE availability (it will have to be collected in the data collection sheet). After the puncture, the TOE probe must be removed from the esophagus to avoid tissue overheating during RF applications. The use of a transesophageal temperature probe will be allowed at operator's discretion. PVI will be performed point-by-point, aiming to

complete a RF circle around the PV ostia (nephroid shape) on the 3-dimensional geometry using a Thermocool SmartTouch 3.5-mm irrigated tip contact force-sensing RF ablation catheter (Biosense Webster, Inc.). In case of a common ipsilateral vein ostium, the line must be drawn around the trunk. PVI will be started in all cases at the right PVs; PV isolation initiated from the right anterior ganglionated plexi (located at the supero-anterior area of the RSPV antrum) could effectively inhibit vagal response occurrence during subsequent RF applications by increasing the basal heart rate. [36] RF lines will be manually traced, aiming to avoid, if possible, the 'fingerprinted' image of the esophagus, projected on the LA posterior wall (see Appendix 4). Maximal interlesion distance will be 6 mm. VisiTag settings will be as follows: catheter position stability: minimum time 3 s, maximum range 4 mm; force over time: 25%, minimum force 3 g; lesion tag size: 3 mm. The irrigation flow rate must be set to 2 ml/min during mapping and 17-30 ml/ min during ablation. AI targets are defined by local AWT on the thickness color map, as follows: Thickness < 1 mm (red): 300; 1-2 mm (yellow): 350; 2-3 mm (green): 400; 3-4 mm (blue): 450; > 4 mm (purple): 500. The recommended power settings to reach these AI values will be, in general, 35W for the posterior wall and 40W for the anterior wall. Wherever local AWT is > 3 mm (green and blue colors), an increased RF power (50W) will be permitted to reach the AI target faster, particularly if the catheter is placed in an unstable place. If the targeted AI value is not reached, another lesion reaching the target must be applied.

Acute PVI will be confirmed after *first pass* with the single catheter method of demonstrating entry and exit block with the ablation catheter placed sequentially in each of the PVs or trunks. There is a minimum waiting time of 10 min after isolation of each ipsilateral PV pair; additional RF applications must be performed at reconnection sites until PVI is achieved. A carina line will have to be always performed for the right pulmonary veins, since there is anatomical [37] and electrophysiological evidence [38–40] for the presence of interconnections of the ipsilateral veins in up to of ⅔ of the patients referred for AF ablation. [41] Additional substrate ablation to create left atrial linear lesions or any extra PV-trigger ablation like CFAE is not permitted. Atrial fibrillation that persists after PVI must be terminated with electrical cardioversion. In case other substrates have to be addressed in the same procedure (i.e. right atrial arrhythmias), the additional time, vascular accesses or catheters employed after PVI will not be taken into account for the purpose of the present study.

Of note is that complete PVI will not be considered unless a second evaluating operator confirms the absence of 'visual gaps' along the ablation lines. This second operator may be any experienced professional involved in the procedure (nurse, engineer, technician, etc.) that is able to assess the presence of gaps in a reliable manner. The visual gaps will be defined as any solution of continuity between two RF lesions tagged using the VisiTag settings previously described and a 3-mm tag size. This confirmation will have to be indicated in ALL cases in the data collection sheet. Its absence will be a reason to exclude the case from the study.

3.5 Outcomes

3.5.1 Primary endpoint

The primary endpoint will be survival free of any atrial arrhythmia at 1-year follow-up. From this endpoint, important definitions must be taken into account:

- AF recurrence will be considered only after the 3-month 'blanking period' (see below), whenever the patient refers clear symptoms of recurrence (fast, recurrent palpitations with abrupt onset and termination, lasting for several minutes or hours), if AF is documented in an electrocardiogram (ECG), or whether it is recorded in a Holter registry (> 30 seconds).
- The 'blanking period' refers to the first 3-month period after the PVI procedure, where a transient increased risk of post-procedural atrial tachyarrhythmias is expected to occur due to pro-arrhythmogenic inflammatory changes after creating tissue RF lesions.

3.5.2 Secondary endpoints

3.5.2.1 Acute procedural outcomes

- Procedure time (skin to skin)
- Radiofrequency time
- Number of applications (total/per RF line/per segment)
- Fluoroscopy time
- First-pass isolation rate
- Early PV reconnections

3.5.2.2 Peri-procedural complications

The following procedure-related complications will be collected:

- Death
- Myocardial infarction
- Diaphragmatic paralysis
- Stroke or transient ischemic attack (TIA)
- Other thromboembolic events
- Cardiac perforation or tamponade
- Vascular complications
- Prolonged or repeat hospitalization
- Heart block
- PV stenosis >70% (as measured by cardiac CT)
- Atrio-esophageal fistula
- Pericarditis requiring intervention
- Pneumothorax
- Pulmonary edema

3.6 Variables

3.6.1 Enrollment evaluation
A complete evaluation will be performed in each patient at enrollment, including:
1. Patient demographic data
2. Clinical evaluation with a physical examination
3. Medical and cardiovascular history
4. NYHA functional class
1. Medication list
2. 12-Lead ECG
3. Transthoracic echocardiography with
    a. LA diameter
    b. LVEF (biplane Simpson's method) (%)
4. Trans-esophageal echocardiography/Intra-cardiac echocardiography.

3.6.2 Procedural evaluation
5. MDCT wall thickness variables
    5.1. Mean LAWT (all of the atrial measures)
    5.2. Mean PVI RF line WT (only around the PV line)
    5.3. Normalized PVI RF line WT (point thickness/maximum PVI RF line thickness)
    5.4. Reconnection point mean WT (mean thickness on a 3mm radium around the point)
    5.5. Reconnection segment mean WT (mean thickness in each segment)
    5.6. Coefficient of variation of wall thickness on each segment (CV-WT) standard deviation of the wall thickness/mean WT
    5.7. Gaussian curvature (to have an idea of the heterogeneity of tissue)
6. Procedural data of the first PVI
    6.1. PV anatomy (presence or absence of common vein ostia)
    6.2. RF time
    6.3. Acute reconnection sites
7. Procedural data of the re-do intervention
    7.1.   Reconnection sites according to an 8-segment model where the antral region of the PVs is divided into segments
    7.2. RF time
    7.3. EGM attenuation time

3.7 Follow-up
Clinical follow-up (FU) will include outpatient clinic visits at 3, 6 and 12 months after the ablation procedure. If no other contraindications, all antiarrhythmic drugs should be stopped at the 3-month FU visit (end of the 'blanking period'; see 'Outcomes' section before). 12-lead ECG and 24-hour ambulatory Holter monitoring will be performed in every scheduled

appointment. Successful ablation will be defined as the absence of clinical symptoms suggestive of AF recurrence, as well as the absence of documented AF in ECGs and/or Holter.

3.8 Study timeline

VISIT / PROCEDURE	Enrollment	Baseline	Ablation	1 month	6 months	12 months
Eligibility screen	✔					
Informed consent	✔					
Demographic Data		✔				
Medical History		✔				
Medication		✔		✔	✔	✔
NYHA Class		✔		✔	✔	✔
12-lead ECG		✔		✔	✔	✔
24-h Holter		(*)		✔	✔	✔
TTE		✔				✔
TOE			✔			
Allocation						
Ablation data			✔			
Protocol Deviation	✔ (*)	✔ (*)	✔ (*)	✔ (*)	✔ (*)	✔ (*)
Adverse event	✔ (*)	✔ (*)	✔ (*)	✔ (*)	✔ (*)	✔ (*)
Termination	✔ (*)	✔ (*)	✔ (*)	✔ (*)	✔ (*)	✔ (*)

3.9 Recruitment and agenda

All participant centers are tertiary referral centers for AF ablation within their health care network. All patients who give consent for participation and fulfill the inclusion eligibility criteria will be consecutively enrolled. First patient will be included after approval of the protocol by ethics committee. We expect to include all the patients within a year period. The

12-month follow-up information of the last included patient should be available approximately 2 years after the first inclusion.

3.10 Document and data control

The principal investigator or delegate is responsible of the data collection on the electronic Case Report Forms (eCRFs). This eCRFs will be introduced using an electronic clinical research data capture (eCRD) platform developed by the contract research organization (CRO) Xolomon SL. The principal investigator will review all the data on the eCRFs and will sign to verify he has reviewed the data collected. Original anonymized paper support forms will be stored in a secure place and manner at each participating center. Anonymization codes will be stored in a safely manner by the local principal investigator. Access to the online study data (eCRFs) will be restricted through passwords. In addition, center coordinators will only have access to their own center's data. Paper files will be physically stored until 5 years after the completion of the study.

3.10.1 Traceability of documents and data

The investigator shall ensure accuracy, completeness, legibility and timeliness of the data reported to the principal investigator on the eCRFs and in all required reports. When copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

3.10.2 Recording data

Source documents shall be created and maintained by the investigation site team throughout the clinical investigation. The data reported on the eCRFs shall be derived from, and be consistent with, these source documents, and any discrepancies shall be explained in writing. The eCRFs shall be signed and dated by the principal investigator or a delegated investigator. Any change or correction to data reported on a paper CRF shall be dated, initialed and explained if necessary, and shall not obscure the original entry.

3.10.3 CARTO® data management

CARTO® (Biosense Webster, Diamond Bar, California, US) studies of all centers will be exported and anonymously sent using a secure data transfer server (eCRD platform developed by CRO Xolomon SL) and analyzed by the following core-lab: ADAS 3D Medical SL headquarters (Barcelona, Spain). Ablation settings and RF applications will be thoroughly reviewed by an expert operator of the core-lab, to ensure compliance with the LAWT protocol. Any violation of this protocol will be considered enough reason to exclude the case from further analysis.

3.10.4 Review of data

The clinical investigation will be monitored by reviewing the eCRF submitted by the investigators. The following activities will occur:
- All eCRFs will be reviewed for completeness and accuracy upon receipt by the principal investigator.
- The investigator (co-investigator) and/or delegate will be contacted by the principal investigator regarding any missing or unclear data.

3.11 Statistical analysis

3.11.1 Sample size
The sample size calculation has been based on the assumption that the proposed ablation protocol ('LAWT') is an acceptable alternative to the CLOSE protocol[15] (non-inferiority), with the advantage of less radiofrequency applied and likely lower risk for complications. A non-inferiority margin of 10% of clinical success (arrhythmia-free survival one year after the ablation procedure) will be considered to be the largest difference that is acceptable

between both protocols for LAWT to be adopted in clinical practice. Recruiting n = 106 participants will be required to confer 90% power to reject the inferiority null hypothesis, that is, that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of −0.05, indicating no difference between the arms. A drop-out rate of 10% is estimated, and included in the sample size calculation.

3.11.2 Statistical methods

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level. Continuous variables will be reported as mean ± standard deviation, or median (range or interquartile range if data are skewed) if not normally distributed; these variables will be compared using Student's t-test if normally distributed or Mann-Whitney U test if not normally distributed. Categorical variables will be expressed as total number (percentage) and will be compared by chi-squared test. For the primary endpoint, survival free from atrial arrhythmia, we will use the Kaplan-Meier survival analysis. A multivariable Cox proportional hazards model will be performed to investigate the effects of baseline characteristics in predicting ablation results, an adjustment will also be done by recruiting center. A receiver operating curve analysis will be performed to determine optimal cutoff LAWT values for predicting AF recurrence after ablation. All efforts will be done to limit missing data on outcome. Nevertheless, missing data will be reported on the final manuscript and, as much as possible, the reasons why data are missing will be documented. If missing, a simple imputation method will be applied and reported.

3.12 Protocol deviation

A protocol deviation is defined as a situation in which there is a non-compliance with the protocol. The following situations are considered protocol deviations and must be appropriately documented:
1. Utilization of another method for guiding the ablation.
2. Ablation of extra PV substrate.

Investigators will be required to adhere to the investigational plan, signed investigator's agreement, applicable national or local, laws and regulations, and any conditions required by the appropriate Ethics Committees or applicable regulatory authorities. The reporting of all the deviations will be performed through the eCRF application. In the event of repeated protocol deviation as determined by the principal investigator, a clinical research associate or clinical representative will attempt to secure compliance by one or more of the following actions: i) contacting the investigator by telephone, or ii) contacting the investigator in writing.

3.13 Harms

Since all included patients must have an indication for AF ablation, no specific harms are expected in the context of the trial, as AI targets will be decreased at those ablation points with lower LAWT values. In fact, in a single-center, prospective series of 80 patients, whose results will be presented at the EHRA 2020 Congress, there were no procedure-related complications using this approach. All complications will be documented as secondary endpoints.

4. STUDY INVESTIGATORS AND PARTICIPATING CENTERS

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4.1 Coordinating clinical investigator

This will be the principal investigator of the study and the person who will take the decision to submit the report for publication, and will have ultimate authority over all the activities:

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4.2 Responsibilities of the coordinating center

The Heart Institute at Teknon Medical Center (Barcelona, Spain) is the coordinating center that will manage the data and perform statistical analysis.

5. ETHICS AND DISSEMINATION

5.1 Research ethics approval
This protocol must be reviewed and approved by the local institutional review board (IRB) of each center.

5.2 Risks
There are no particular risks related to study participation. Nevertheless, there are risks related to the procedure itself, which is explained on the informed consent sheet.

5.3 Protocol amendments
Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment must be approved by the IRB.

5.4 Consent or assent
Operators will introduce the trial to patients on the pre-operatory outpatient visit. Information sheets and consent forms will be provided to all screened patients at the time of the visit and consents will be collected at the time of hospitalization.

5.5 Confidentiality
All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID [identification] number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems.

5.6 Access to data
Project Principal Investigators will have direct access to their own site's data sets, and will have access to other sites data by request. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

5.7 Dissemination policy
The study results will be released to the participating physicians, referring physicians, patients and the general medical community.

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APPENDIX 1: Informed consent material

ENGLISH VERSION

PATIENT INFORMATION SHEET AND INFORMED CONSENT FOR A RESEARCH STUDY.

Study title: *Personalized Atrial Fibrillation Ablation with Ablation Index Adapted to Left Atrial Wall Thickness: The Ablate-by-LAW Study*
Name of the principal investigator: Antonio Berruezo, MD, PhD.
Coordinating research center address: Teknon Medical Center (Barcelona, Spain)
Número de teléfono de contacto: (+34) 93 290 62 51

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

1. WHAT IS THE OBJECTIVE OF THE STUDY?
You are asked to participate in this study because you have a cardiac arrhythmia called atrial fibrillation (AF). Your medical team, according to the Arrhythmia Unit, believes that the best treatment for your disease is to conduct an electrophysiological study to ablate (eliminate) the arrhythmia by applying radiofrequency energy. Radiofrequency ablation of AF is a procedure that, by means of a catheter, seeks to apply radiofrequency energy in the junction areas ("ostia") of the pulmonary veins with the left atrium until they are "electrically isolated". This procedure has been routinely performed for more than 20 years, when it was described the origin of this arrhythmia at the ostia of the pulmonary veins. The effectiveness of an ablation procedure, per year, is around 80% for paroxysmal AF, in some cases requiring a second ablation procedure to isolate any point/s that could have reconnected any of the pulmonary veins with the atrium.
Our objective, with the present study, is to demonstrate, on the one hand, that it is possible to adapt the level of radiofrequency energy applied at each point of the "ostia" of the pulmonary veins according to the thickness of the tissue, previously measured in a cardiac tomography (CT). Up to date, a series of standard parameters have been established with which radiofrequency is applied systematically but, just as not all patients do have the same body surface, e.g., they also do not have the same atria in terms of wall thickness. Applying standard parameters implies, in some cases, assuming a risk (very small, but present) of potentially lethal complications (e.g. perforation, atrio-esophageal fistula) and, in others, not providing maximum benefit in terms of definitive electrical isolation of the pulmonary veins (and, therefore, assuming a higher recurrence rate).
On the other hand, the study aims to achieve the same clinical benefits after ablation, minimizing the risk of complications by using only a single catheter (a procedure that we could consider "minimally invasive") to apply radiofrequency and check the effective electrical isolation of the pulmonary veins. Among the risks of complications that are described for this type of procedure, and that could be minimized, are: Slight discomfort in the puncture area, or the appearance of a bruise that will almost always be reabsorbed spontaneously; less frequent there are other complications (phlebitis, venous

or arterial thrombosis, hemorrhage that requires transfusion, cardiac perforation with tamponade, pulmonary or systemic embolism, narrowing of the orifice opening of one of the pulmonary veins, diaphragmatic paralysis due to phrenic nerve injury or formation of a communication -fistula- between the left atrium and the esophagus), although some of them are serious and require urgent action (< 1 per 100); the risk of death is exceptional (< 1 per 1,000).

2. WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?
If you decide not to participate in this research study, you will undergo the same tests and planned ablation procedure as it is routinely done in the hospital.

3. WHAT ARE THE POSSIBLE BENEFITS OF PARTICIPATION IN THIS STUDY?
The research team thinks that the participation in the study and, therefore, undergoing a personalized and minimally invasive AF ablation procedure, performed in a center with great experience and a very high number of procedures performed annually (> 350), in addition to not involving any additional risk, it will allow to report very useful information about the proposed protocol, permitting to evaluate the long-term efficacy of the ablation and, eventually, facilitating its future implementation by other Arrhythmia Units as a standard to benefit to other patients like you.

4. IS PARTICIPATION IN THIS STUDY VOLUNTARY?
Yes. Participation in this research study is voluntary. You can decide not to participate and you can also change your mind later and leave the study at any time, without affecting your clinical care.

5. IF I PARTICIPATE IN THIS RESEARCH STUDY, HOW WILL MY PRIVACY BE PROTECTED?
Access to your medical history and data derived from the procedure:
The doctors, nurses and other center staff involved in this study will need to access your medical history, including medical records or previous results for the purposes of this study. By signing this consent form, you authorize them to this access and, if necessary, they can contact your GP or other health professionals to access your medical history during the study. In accordance with current regulations on data protection, you expressly consent to the access of your medical record data, as well as those resulting from your participation in the study in a personal data file under the responsibility of the Center. Access to your personal information will be restricted to the study doctor and his collaborators, health authorities and the Research Ethics Committee. By signing this consent, you consent to the use of the (previously anonymized) data derived from the pre-procedural CT, in order to optimize the software used during the post-processing of the images (ADAS 3D LA™; ADAS 3D Medical SL, Barcelona, Spain), as well as to be able to develop a software platform that allows the automatization and standardization of the image post-processing.
Confidentiality of information about your health:
Your health information regarding the trial will be included in a database, but you will not be referred to by name or identified in any report or publication.
Withdrawal from the study:
If you decide to leave the study, tell your study doctor. In this case, the study staff will not collect new information about you. However, the information already collected may continue to be used as described above. If you have any questions about this topic, we recommend that you discuss it with your study doctor.
Compliance with current legislation regarding confidentiality of your health information:

The research team is committed to ensuring compliance with the principles established in the local laws on Biomedical Research and on Protection of Personal Data and Guarantee of Digital Rights. Finally, the research team undertakes to facilitate the exercise by you of the rights of access, rectification, cancellation and opposition provided for the local Laws of Personal Data Protection and Guarantee of Digital Rights. The processing, communication and transfer of personal data of the participants will be in accordance with the provisions of the local Data Protection Regulations. If you have any questions about the handling of your data, you should contact your doctor at ………..……………………….. In addition to the rights you already know (access, modification, opposition and cancellation of data) you can also limit the processing of data that is incorrect, request a copy or transfer the data that you have provided to the study to a third party (data portability). To exercise your rights, contact the principal investigator of the study. We remind you that the data cannot be deleted, even if you stop participating in the study, to guarantee the validity of the investigation and comply with the legal duties and medication authorization requirements. You also have the right to contact the Data Protection Agency if you are not satisfied.

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

Before signing this document, you should ask everything you do not understand. The study team will answer your questions before, during and after the study. If you think your question has not been fully answered or if you do not understand the answer, keep asking until you are satisfied. If you have any concerns or complaints about this study or the way it is being conducted, do not hesitate to discuss it with the study team. The phone numbers to contact the study team are listed on the first page of this document.

I, _____ (name and surname)

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

PARTICIPATING SUBJECT:

_____   _____   _____
Signature of participant   Date   Time

INVESTIGATOR:

_____   _____   _____
Signature of researcher   Date   Time

APPENDIX 2: Data collection sheet

Name: ……………………………………………………………… **Nº History:** …………………………………

Date of birth: ……………………………………… **Study code:** ……………. **Center** …………………………………

<u>1. PROCEDURE AND PATIENT DATA</u>

FIRST OPERATOR……………………… **Anesthetist**…………………… **EVALUATING OPERATOR**………………………
DATE OF THE PROCEDURE…… /…… /……
HR ventilation Yes/No **Rate** ………… **Tidal vol** …………

Age: ……… **Sex:** Male //Female **CHA$_2$DS$_2$-VASc** = …. **HAS-BLED:**… **Weight** ….. Kg **Height:** …… m
CVRF: none // HBP // Dislipemia // DM-2 // Smoker // OSA // Sport (>4 h/week x 10 y)
Underlying HD: none // Hypertensive // Ischemic // HOCM // Valvular // Other ………………………
Conduction disturbances: none // LBBB // RBBB // LAHB // LPHB // Other: …………….
Treatment: ……………………………………………… **OAC:** ……………………………… Interrupted: Yes // NO // ¿?
TEE LA Size (mm): ………… **LVEF**: ……… **Mitral annulus:** ………… cm **Other:** ……………………………………
PV anatomy: 4 indep. // Left common // Right common // Accessory veins: …………………………………….
LAA Closure: YES // NO **Closure device type and size**: ………………………………………

<u>2. PROCEDURAL DATA OF PVI:</u>

Number of femoral accesses: 1 / 2 (only 2 permitted in case of ICE use)
Ablation lines adapted to fingerprinted esophagus: YES // NO (why: ……………………………….)
Curve of the ablation catheter (SmartTouch®): Blue // Orange // Black
Procedure time: ………… min **FAM + Merge time**: ………… min **Transeptal time:** ………. min
Transeptal puncture technique: TEE // ICE
Fluoro time: ……… sec **Fluoro dose:** ……… mGy **Fluoro dose (index):** ……… Gy/cm^2
RF power: anterior wall ……… W // posterior wall ……… W
RF time: Right PV ……… s // Left PV ……… s
Number of RF points: Left ……… Right ……..
Electrical cardioversion: Yes // No
Acute complications: ………………………………………………………………….
<u>**Was the procedure evaluated for the absence of gaps by the 2nd operator?:**</u> YES // NO

Select at which segment/s the subjacent rhythm was (entirely or predominantly) AF/AT: This is to assess in the future whether segments where rhythm disturbances are observed could influence catheter stability, quality of RF lesions and, ultimately, be a predictor of reconnections.
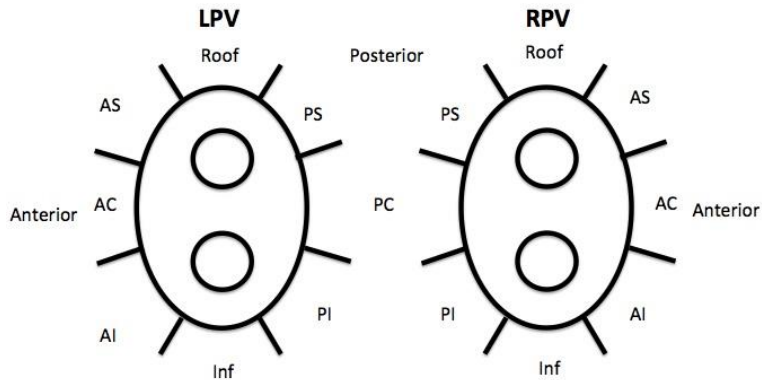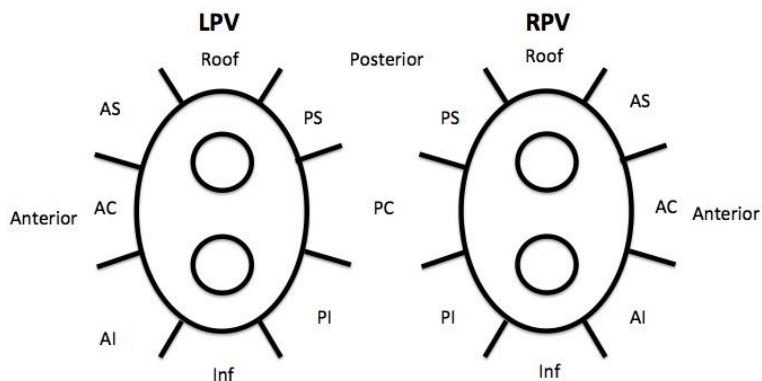

Select at which segment/s _FIRST PASS_ isolation was NOT ACHIEVED, an explain why:
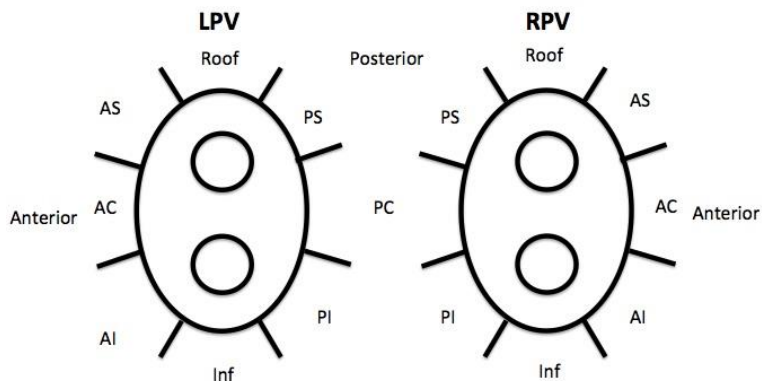
....
....
....
....

Select at which segment/s ACUTE RECONNEXION was observed, an explain why:

....
....
....
....

APPENDIX 3: Anesthetic protocol for ablation

NOTE: This is a recommended anesthetic protocol, which may be adapted to the daily practice of the corresponding participating centers. The only essential requirement that must be met is to achieve a 'high-rate, low-volume' ventilation: <u>respiratory rate > 40 rpm, and a tidal volume adapted to the patient's weight (in general, 3.5-4.0 ml/Kg).</u>

1. Standard Anesthetic Monitoring:

- Non-invasive blood pressure (NIBP) an invasive blood pressure (IBP)
- EKG
- SpO2, inspired and tele-expiratory O_2
- Capnography: $EtCO_2$ and inspired CO_2
- Standard mechanical ventilation monitoring: inspiratory peak pressure, airway plateau pressure, tele-expiratory pressure, tidal volume, respiratory rate, expired volume, pulmonary distensibility curve, arterial gasometry
- Bispectral analysis for anesthetic depth (BIS), neuromuscular relaxation monitoring with train-of-four (TOF-Cuff Monitor®)
- Optional brain Doppler: Peak middle cerebral artery flow (MCA), mean ACM flow and pulsatility index.

2. Anesthetic induction:

Midazolam: 1-2 mg, Fentanyl 2-3 mcg/Kg, Propofol 1.5-2 mg/Kg (holder), Rocuronium bromide: 0.6 mg/kg. It can be considered as anesthetic inducer Etomidate 0.2-0.3 mg/Kg if there is severe ventricular dysfunction or any other reason that contraindicates the use of propofol.

3. Endotracheal intubation:

Once a TOF of 0% is corroborated, endotracheal intubation is performed. It is very important to consider the need to use difficult airway devices (DAV). There is some association between arrhythmias, OSAHS and difficult intubation. On-hand video-laryngoscope (Glidescope®) or similar device for advanced DAV management.

4. Introduction of the Trans-esophageal Echocardiography (ETE) probe:

Standard assessment, corroboration of preoperative data, discard thrombi in left atrial or atrial appendage, left atrial velocity measurement, interatrial septum analysis. Real-time progress guide of catheters and puncture in the appropriate area of the inter-atrial septum. Review of possible complications (rule out hemopericardium, cardiac valvular disease, etc.)

5. Super-Protective Mechanical Ventilation Protocol with Short-Term Permissive Hypercapnia:

Once the patient is intubated, mechanical ventilation is established at Tidal Volume (V_t) of 8 mL/Kg and Respiratory Rate (RR) at 12-15 resp/min, FiO_2 0.5 (oxygen/air) at 1 L/min for 10 min. Alveolar recruitment maneuvers are performed. Then change to the Super-Protective Pattern consisting of V_t 3.5-4.0 mL/Kg and RR 45-55 resp/min; with FiO_2 0.4, I:E relationship 1:1.5, and PEEP 0 mmHg. Systemic blood pressure and pulmonary systolic pressure, RV and LV function, tricuspid valve are evaluated. If there are no changes greater than 10% of baseline values, continue with Super-Protective protocol. If $PaCO_2$ greater than 60 mmHg is documented, a high flow of fresh gases (O_2/FiO_2 air 0,5 to 4 L/min) is administered to increase CO_2 washing of the anatomical dead space. At the end of the Super-Protective protocol, alveolar recruitment maneuvers are performed before anesthetic awakening.

Pre-operative relative contraindications to initiate the Super-Protective protocol:
- Severe LV or RV dysfunction
- Severe pulmonary hypertension
- Moderate or severe CPOD with evidence of self-PEEP
- Severe asthma
- Chronic or severe metabolic acidosis
- Hypercalcemia
- Past history of severe migraines, neuralgia of trigeminal or atypical facial pain, hydrocephalus, patients with ventricular-peritoneal shunt valves, Parkinson's, epilepsy, vertigo, Ménière syndrome, narrow angle glaucoma, or stroke with considerable neurological sequelae.

6. Maintenance of general anesthesia:

Mixture of O_2/air to FiO_2 0.4 to 4 L/min, Sevoflurane 1-1.5Vol% or propofol 2 mcg/mL TCI (Schnider Model), Remifentanil 1.5-2.0 ng/mL TCI (Model Minto), Rocuronium 0.2 mg/Kg every 30 minutes.

If PAIV decreases more than 20% with respect to the anesthetic pre-induction value, vasopressor boluses such as: Ephedrine 5-10mg, Phenylephrine 25-50 mcg or Norepinephrine 2.5-5 mcg can be used.

It may be advisable to prepare phenylephrine perfusion at 0.1-0.5 mcg/Kg/min (10 mg in 100 mL of 0.9% sol) to maintain perfusion pressure in case of hypotension. Alternatively, very diluted Noradrenaline ("Baby-Nora": 4 mg/250 mL) infusion of 0.02-0.08 mcg/Kg/min can be used.

7. Anesthetic weaning:

After the TEE is removed (according to echocardiography protocol, after complications of interventional cardiological procedures or other types of incidence have been ruled out), gleras are gently aspirated and a state of residual muscle relaxation is corroborated. The safety target for reversal of neuromuscular relaxation is a 100% TOF, in case the patient presents TOF-ratio less than 80%, Sugammadex 2 mg/Kg is administered. If TOF-ratio is greater than 80% and less than 100% it can be considered to use Sugammadex or neostigmine at 50 mcg/Kg. Paracetamol 1 g, dexketoprofen 50 mg and ondansetron 4 mg is given.

Once the patient has spontaneous breathing, adequate Vt and RR, SpO2 above 98% and BIS above 80-90, is extinguished. It is transferred to a Semi-Critical Care Unit monitored or with nasal cannulas with FiO2 0.3 at 2 L/min.

APPENDIX 4: Representative figures

Figure 1. Aspect of the left atrial (LA) anterior wall after MDCT imaging segmentation. An analysis of the LA wall thickness (LAWT) has been performed. The color map uses a color scale to depict a range of thickness; red being the thinnest (< 1 mm) and purple being the thickest (> 4 mm). Yellow (1-2 mm), green (2-3 mm) and blue (3-4 mm) will be considered the intermediate values. The full-range color-coded LAWT map (*left image*) can be simplified using an adaptative binarization algorithm (*right image*) that helps selection the proper Ablation Index (AI) targets for each zone.
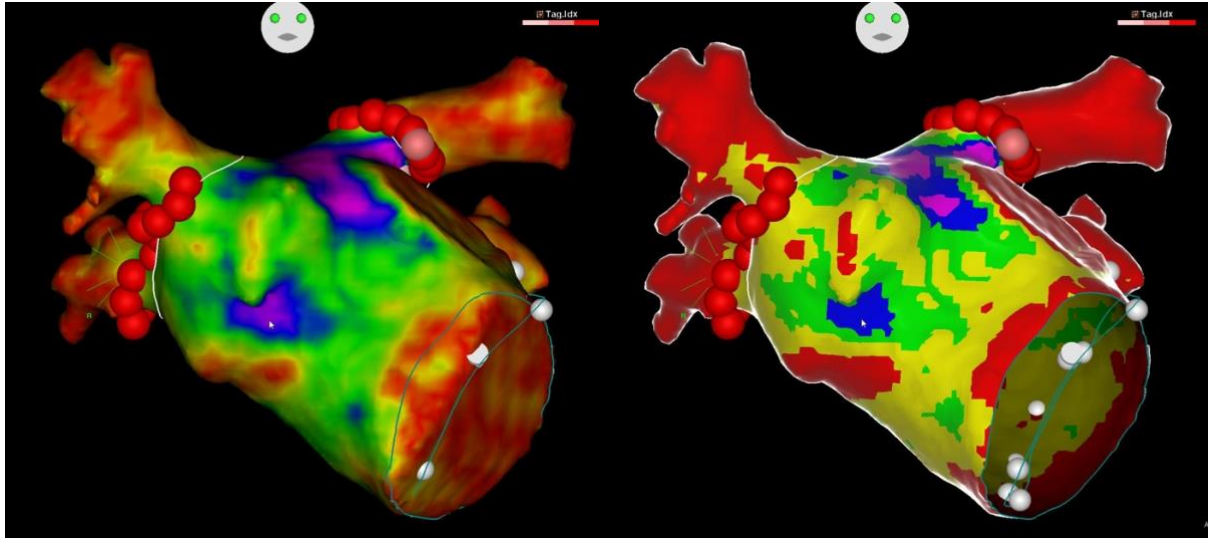

Figure 2. Aspect of the LA posterior wall after MDCT imaging segmentation. *Right image*: Full-range color-coded LAWT map as seen in CARTO. *Left image*: Binarized color-coded LAWT map integrated in CARTO.

Figure 3. Integration of the anatomical position of the esophagus with respect to the LA posterior wall. The esophagus is segmented using the MDCT and its anatomical position is then integrated in CARTO, along with the LA anatomy (*left image*). The point-by-point distance between the esophagus body and the corresponding LA posterior wall is also calculated, color-coded and exported (*right image*), an information that can help selecting safer AI targets in this area. *Lower image*: The color-coded distance map can be visualized in a semi-transparent mode that helps during RF applications.