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New insights in atrial fibrillation mechanisms, electrogram analysis and alternative therapeutic approaches

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New insights in atrial fibrillation mechanisms, electrogram analysis and alternative therapeutic approaches

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DECLARACIÓN DEL AUTOR/A DE LA TESIS

D./Dña. **Miguel Valderrábano-Vázquez**

Título de la tesis: **New insights in atrial fibrillation mechanisms, electrogram analysis and alternative therapeutic approaches**

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"NEW INSIGHTS IN ATRIAL FIBRILLATION MECHANISMS, ELECTROGRAM ANALYSIS AND ALTERNATIVE THERAPEUTIC APPROACHES"

D. José Ramón González-Juanatey
D. Moisés Rodríguez-Mañero

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Que la presente tesis, se corresponde con el trabajo realizado por D/Dª. Miguel Valderrábano-Vázquez, bajo nuestra dirección / tutorización, y autorizamos su presentación, considerando que reúne los requisitos exigidos en el Reglamento de Estudios de Doctorado de la USC, y que como director de esta no incurre en las causas de abstención establecidas en la Ley 40/2015.

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CONFLICTOS DE INTERÉS

El doctorando declara no tener ningún conflicto de interés en relación con la tesis doctoral titulada "**New insights in atrial fibrillation mechanisms, electrogram analysis and alternative therapeutic approaches**"

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Fdo. Miguel Valderrábano-Vázquez

"Para aprender a enseñar
hay que aprender a aprender"
(A. Einstein)

A Moisés Rodríguez-Mañero,
por su empuje para llevar este proyecto a cabo

A Ana, Laura, Lucía, y Nicolás,
por mostrar lo que de verdad importa

A mis mentores, Peng-Sheng Chen,
James N Weiss y tantos otros

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INTRODUCTION

1. INTRODUCTION

Atrial fibrillation (AF) affects up to 5 million people in the United States, and data suggest that as the population ages, the incidence will continue to increase.[1,2] The rate of ischemic stroke among patients with nonvalvular AF averages 5% per year.[3] The rate of death among patients with AF is about double that among patients with normal sinus rhythm.[3] The overall cost of treating recurrent AF has been estimated to be more than 6.5 billion (dollars) per year.[4] Importantly, as we will discuss later, it seems, that not only prevalence of AF is progressively increasing but also the risk profile of patients with AF.

AF is usually a progressive disease. The natural history often begins with infrequent episodes of limited duration termed paroxysmal AF (often defined as episodes that terminate spontaneously within 1 week). Such episodes then tend to become more frequent and longer in duration, progressing to persistent AF (which fails to terminate spontaneously within 7 days and may require cardioversion) or longstanging persistent AF (if the arrhythmia lasts continuously for more than 1 year. Symptoms include palpitations, shortness of breath, and fatigue; particularly for symptomatic patients, AF has adverse effects on quality of life.[3] Remarkably, AF confers a 5-fold risk of stroke, and one in five of all strokes are attributed to this arrhythmia. In this regard, the identification of various stroke clinical risk factors has led to the publication of various stroke risk schemes[3].

Most have (artificially) categorized stroke risk into ‘high’, ‘moderate’, and ‘low’ risk strata. The simplest risk assessment scheme is the $CHADS_2$ score. The $CHADS_2$ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] risk index evolved from the *AF Investigators and Stroke Prevention in AF (SPAF) Investigators criteria*, and is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age ≥ 75 years, a history of hypertension, diabetes, or recent cardiac failure. Thus, the $CHADS_2$ stroke risk stratification scheme should be used as an initial, rapid, and easy-to-remember means of assessing stroke risk. In patients with a $CHADS_2$ score ≥2, chronic OAC therapy with a VKA is recommended in a dose-adjusted approach to achieve an international normalized ratio target of 2.5. Recently, in the last guidelines for the management of AF other ‘clinically relevant non-major’ risk factors (previously referred to as ‘less validated risk factors’) include female sex, age 65 – 74 years, and vascular disease (specifically, myocardial infarction, complex aortic plaque and periferical artery disease). Note that risk factors are cumulative, and the simultaneous presence of two or more ‘clinically relevant non-major’ risk factors would justify a stroke risk that is high enough to require anticoagulation. This risk factor-based approach for patients with non-valvular AF can also be expressed as an acronym, CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 – 74, and sex category (female)]. This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease

(myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or angiographic evidence of PAD, etc.), and female sex. Thus, this acronym (CHA_2DS_2-VASc) extends the $CHADS_2$ scheme by considering additional stroke risk factors that may influence a decision whether or not to anticoagulate.

Mechanism

The electrophysiological basis of AF requires both a trigger that initiates the dysrhythmia and a substrate that can sustain it.[5,6] Although AF can be precipitated by associated pathologies as we will discuss later on (channelopathiesas, slow auriculoventricular nodal tachycardia, etc), the most common triggers of AF are ectopic atrial beats that arise from the muscle sleeves of the pulmonary veins[7,8]. These triggers may be provoked by the intrinsic activity of cardiac ganglionic plexuses, which are clustered in the vicinity of the pulmonary vein–left atrial junction.[9,10] The pulmonary vein–left atrial junction and an enlarged atrium harboring fibrosis and inflammation serve as the substrate for sustaining wavelets of AF. With persistence of AF, a further electrophysiological change in the atria - namely, shortening of the refractory period of the atrial muscle - occurs and predisposes to the development of other triggers and wavelets. This process results in perpetuation of AF and in a greater predisposition to AF. Out of all potential causes, obstructive sleep apnea (OSA) is one of the leading factors associated with AF. OSA is the most common clinically significant breathing abnormality during sleep. The precise mechanisms of apnea-induced susceptibility to AF are unclear. Numerous possible mechanisms responsible for this association have

been proposed including autonomic dysfunction but delineation of this interaction is currently deficient. Subsequently, in the present work we sought to delineate the autonomic response to apnea, its hemodynamic and electrophysiological correlates, and to test the effects of chemical ablation of cardiac epicardial ganglionated plexi (GP) sensory neurons (Aim 1).

AF treatment; Antiarrhythmic drugs and ablation

Maintenance of sinus rhythm can reverse these changes and mechanisms. Hence, AF begets atrial fibrillation, and sinus rhythm begets sinus rhythm.[11-13] Whether to restore and maintain sinus rhythm ("rhythm control") or allow AF to continue while controlling ventricular rate ("rate control") remains a key decision steeped in controversy. Given the poor outcomes associated with AF,[3] rhythm control makes intuitive sense. However, it remains unclear whether AF causes death or is simply a marker of risk. Despite the association of AF with excess morbidity and mortality, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial and multiple other studies failed to demonstrate reduction in death, stroke, or hospitalization with rhythm control compared with rate control, assuming appropriate anticoagulation as part of either strategy.[14-18] Even in patients with systolic dysfunction and clinical heart failure, in whom AF is a predictor of death and frequent cause of decompensation, the Atrial Fibrillation and Congestive Heart Failure trial identified no difference in overall survival, cardiovascular death, worsened heart failure, or stroke at 37 months with rhythm control.[19] The apparent discrepancy between the poor outcomes associated with AF in epidemiologic studies and the failure of multiple trials to

demonstrate a substantial benefit from a rhythm-control strategy reflect the limited efficacy and adverse effects of the available antiarrhythmic medications used in these studies to maintain sinus rhythm. The proportion of patients actually achieving sinus rhythm with antiarrhythmic drugs in randomized trials, ranging from 26% to 63%,[14-18] illustrates this limited efficacy. Nearly all antiarrhythmic medications carry a risk of ventricular proarrhythmic toxicity. In addition, the predominant antiarrhythmic drug in these studies, amiodarone (used in 62.8% of patients in the rhythm control arm of AFFIRM[14] and in 82% of patients in Atrial Fibrillation and Congestive Heart Failure[19]), has substantial extracardiac toxicity, including pulmonary and hepatic toxicity, thyroid dysfunction, and bradycardia. Furthermore, because the "rate versus rhythm control" trials generally involved older patients with comorbidities, the results cannot be extrapolated to younger, healthier patients who would face the consequences of AF for longer periods with a rate-control strategy. The results of these studies should therefore not be interpreted as a lack of benefit of restoring sinus rhythm, but rather that the toxicity and limited efficacy of available antiarrhythmic medications make their routine use no better than rate control to achieve freedom from stroke and death. In support of this concept, a post hoc analysis of AFFIRM demonstrated that sinus rhythm was associated with a lower risk of death independently of the medications used compared with the presence of AF, and after adjustment for the rhythm, antiarrhythmic medications increased mortality.[20]

Antiarrhythmic drugs are considered the first-line treatment for maintenance of sinus rhythm. However, the efficacy of these agents is not favorable, with only 50% of patients so treated maintaining sinus

rhythm after 1 year of follow-up.[21,22] In addition, as we pointed out previously, the side effects of antiarrhythmic drugs are not trivial. In a recent meta-analysis, these side effects included treatment-related death in 0.5% of patients, torsades de pointes in 0.7%, neuropathy in 5.0%, and thyroid dysfunction in 3.3%.[23] Less serious side effects such as gastrointestinal symptoms occur more frequently and may have a substantial effect on quality of life.

Catheter ablation is indicated to prevent the recurrence of symptomatic AF in patients in whom medical therapy has been ineffective. AF ablation is a therapeutic technique that uses radiofrequency energy or freezing to destroy atrial tissue that is involved in the propagation of the dysrhythmia. Radiofrequency ablation generates an alternating electrical current that passes through myocardial tissue, creating heat energy that conducts to deeper tissue layers. At temperatures of 50°C or higher, most tissues undergo irreversible coagulation necrosis and then evolve into nonconducting myocardial scar tissue.[24,25] Cryoablation destroys tissue by freezing. The principal objective of AF ablation is the electrical disconnection of the pulmonary-vein triggers from the atrial substrate (often called "pulmonary-vein isolation").[26,27] To achieve this goal, ablation is performed around the pulmonary-vein orifice. Ablation of sites beyond the pulmonary vein–left atrial junction in the atrial substrate itself, targeting so-called complex fractionated electrograms, is not necessary in paroxysmal AF but may be very important in patients with persistent AF.[27] Several randomized trials have shown superior outcomes for radiofrequency ablation as compared with antiarrhythmic drug therapy.[28-35] For example, in one trial, 198 patients with paroxysmal AF in whom antiarrhythmic drug therapy

had previously failed were randomly assigned to either radiofrequency ablation or antiarrhythmic drug therapy with other agents.[32] Patients assigned to catheter ablation received antiarrhythmic drug therapy for the first 6 weeks after treatment, and recurrences during this interval were not included in the primary trial end point (a so-called blanking period to allow healing of the atrial myocardium after the procedure). At 1 year, 86% of the patients assigned to catheter ablation and 22% of those assigned to antiarrhythmic drug therapy had not had a recurrent atrial tachyarrhythmia ($P<0.001$). Hospitalizations for cardiovascular disease were also less frequent in the ablation group. In another trial, 167 patients with drug-resistant paroxysmal AF were randomly assigned to ablation or another antiarrhythmic drug.[33] In contrast, the results for ablation of persistent AF are less convincing.

Strategies for persistent AF ablation; approaches and limitations

While isolation of the PVs is firmly established as effective treatment for the majority of paroxysmal AF patients, there is recognition that patients with persistent AF have substrate for perpetuation of arrhythmia existing outside of the pulmonary veins. Various computational approaches have been used to identify targets for effective ablation of persistent AF. Various analyses of electrogram characteristics have been performed with this aim. In the following lines we discuss the clinical aspects of computational approaches that seek to identify critical sites for ablation in the treatment of persistent AF.

1. Complex fractionated atrial electrograms

Electrophysiologists skilled in ablation of arrhythmias have sought to look for characteristics of electrograms that might identify critical sites for ablation. The elimination of complex fractionated atrial electrograms (CFAE) has been shown in some studies to be an effective strategy of catheter ablation.[34,35] Fractionated or prolonged electrograms have been demonstrated to identify areas acting as pivot points, slowed conduction, anisotropy, localized circuits or rotors, all of which are capable of sustaining re-entry.[36] Accurately identifying such electrograms may allow targeted ablation to halt wavelet re-entry and prevent the perpetuation of AF.

Initially, CFAE were defined as fractionated electrograms composed of ≥2 deflections, perturbation of the baseline with continuous deflection of a prolonged activation complex, or atrial electrograms with a cycle length ≤ 120 ms.[37] However, as this method of ablation became more widespread, a more consistent definition of ablation targets was desired, particularly if one wanted to perform a multi-center trial where standardization across hospitals was paramount. Hence, computer algorithms were designed to provide consistent definitions of CFAE, independent of the operator's discretion. These included the CFAE software module (CARTO, Biosense Webster, CA, USA) and the CFE-mean tool (NavX, Abbott, CA, USA). The recently published STAR AF 2 trial (*Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial*) compared initial stand-alone PVI to PVI with additional ablation of complex fractionated atrial electrograms (CFAEs) or additional linear ablation and could not demonstrate a superior outcome for the additional ablation strategies.[38] The prospective and randomized Alster-Lost-AF

study sought to assess, in patients with persistent and long-standing persistent AF, the midterm outcomes after stand-alone PVI versus a stepwise approach of PVI followed by CFAE ablation and linear ablation.[39] In this study, no significant difference was observed in 12-month freedom from atrial tachyarrhythmias between an index ablative approach of stand-alone PVI and a stepwise approach of PVI plus complex fractionated atrial electrogram and linear ablation. Important to highlight and line with previous studies, results of the ablation were suboptimal: in the substrate-modification group patients, recurrence after a single ablation procedure was of 54% (95% CI 43%-68%) in the PVI-only and 57% (95% CI, 46%-72%) in the Substrate-modification group (p=0.86). The CHASE-AF trial produced similar conclusions, where no benefit from the addition of a CFAE-based ablation strategy over non-CFAE ablation was seen.[40] A recent meta-analysis confirmed that the addition of extra-pulmonary substrate ablation such as that of CFAE in persistent AF patients, was associated with declining efficacy as compared to PVI ablation alone.[41]

2. Dominant frequency

Dominant frequency (DF) analysis aims to distill the local activation frequency from highly complex electrograms. This utilizes computer algorithms (usually fast fourier transform) to assign a fundamental frequency of electrical activation. The DF can then be displayed on a 3D map to guide the ablator to sites of high DF thought to be driving the AF (focal source or rotor). The aim of such analysis is to detect sites of high frequency that have been hypothesized to "drive" the fibrillation process.[42] These sites have been shown by

retrospective analysis to identify effective ablation areas.[43] In an elegant animal study by Kalifa et al, areas of fractionation were demonstrated at the periphery of areas of high dominant frequency.[44] The proximity of high DF and CFAE sites has also been demonstrated in high-density mapping of human AF.[45] Of note, most studies examining DF guided ablation have used off-line analysis, although real-time analysis has also been reported albeit without incremental outcome.[46] In a systematic review of DF-based approaches, Gadenz et al concluded that DF-based approaches are a useful marker of ablation outcome; however, direct intervention targeting DF sites appears premature with mixed results and too few studies.[47] A more recent study using a novel frequency analysis algorithm and longer duration of AF electrograms in search for temporally stable AF drivers has shown some promise.[48]

3. Panoramic mapping of AF mechanisms

Over the last decade, the field has progressed from electrogram-based AF mapping to focus on activation and phase mapping to detect AF drivers in the form of rotational ("rotors") and ectopic focal ("foci") activations. First descriptions of rotational activations were from studies that undertook sequential mapping with multi-polar spiral catheter.[49] The Focal Impulse and Rotor Modulation (FIRM) guided technique was the first panoramic mapping study that showed high success rates with ablating AF drivers.[50] Other panoramic mapping techniques included body surface potentials mapping with inverse-solution electrocardiographic imaging (ECGI)[51] mapping of wavefront propagation using intracardiac multipolar catheter

(CARTOFINDER)[52] and non-contact mapping using a multielectrode array catheter (ENSITE).[53]

Thus, mapping systems developed to identify sites with focal activations (FoA) and/or rotational activations assumed these sites to be mechanistically relevant to the maintenance of AF and consequently suggested as ablation targets to eliminate AF. Because local propagation patterns are influenced by myofiber ar- chitecture, areas of unidirectional block and apparent re-entry may arise during AF; such apparent spurious re-entry may not bear mechanistic relevance, and yet may be identified as relevant by mapping system algorithms. Similarly, apparent focal propagation patterns may be identified when a restricted area is mapped away from a remote source of propagation. Fibrillatory conduction (FC), characterized by intermittent unidirectional block, arises in areas of anatomical heterogeneity and generates fibrillatory electrograms during rapid pacing in the absence of true, self-sustained AF, as shown by Berenfeld et al.[54] in isolated sheep atria. This phenomenon permits testing of the performance of mapping systems in a "negative control" condition where no true, self-sustained AF exists, and any RoA or FoA detected away from the pacing site(s) is, by definition, epiphenomenal. Systems to map propagation patterns in AF, like Topera (Abbott, St. Paul, Minnesota) or Cartofinder (Biosense Webster, Irvine, California), have been developed but have never been studied in such an experimental model of FC.

Along this thesis we aim to explore the mechanistic relevance of roatational and focal activity and to assess the ability of algorithms to detect such activity during in vivo canine models of pacing-induced FC and induced AF (Aim 2).

4. Targeting atrial fibrosis

Targeting low voltage zones (LVZs) beyond PVI as part of a substrate modification strategy has been recently adopted as an ablation strategy. The STABLE-SR (*Electrophysiological Substrate Ablation in the Left Atrium During Sinus Rhythm*) to compare the efficacy of non paroxysmal AF ablation between PVI plus sinus rhythm substrate modification and a conventional STEPWISE ablation approach. At 18 months, 74.0% of the patients in the STABLE-SR group and 71.5% in the STEPWISE group (hazard ratio, 0.78; 95% CI, 0.47– 1.29; p=0.325) achieved success according to intention-to-treat analysis. However, less procedure time (186.8±52.7 versus 210.5±48.0 minutes, p<0.001), reduced post-CPVI fluoroscopic time (11.0±7.8 versus 13.7±8.9 minutes, p=0.006), and shorter energy delivery time (60.1±25.1 versus 75.0±24.3 minutes, p<0.001) were observed in the STABLE-SR group compared with the STEPWISE group.[55] Remarkably, there remain multiple unresolved issues with low voltage area-guided substrate modification. Although some studies have showed that measured voltages are higher during SR than during AF, none have studied voltages in other atrial arrhythmias, such as atrial flutter (AFL). Furthermore, it is unclear if bipolar voltage cutoffs should be adjusted depending on the rhythm, catheter type (electrode size and interelectrode distance), and/or anatomic area being mapped. Most studies have used cutoffs in sinus rhythm using an ablation catheter (3.5-mm tip), but the corresponding thresholds in AF are not known. Finally, there are no data regarding the reproducibility of LVA mapping in AF. Subsequently, we aimed to determine the voltage correlation between sinus rhythm and AF/atrial flutter (AFL) using multielectrode fast automated mapping

and to identify a bipolar voltage cutoff for scar and/ or low voltage areas (Aim 3).

5. Alcohol ablation in the vein of Marshall

The ligament and vein of Marshall (VOM) can be a source of ectopic beats leading to AF and of dual sympathetic and parasympathetic innervation that have been implicated in the genesis and maintenance of AF.[56-58] Additionally, the VOM anatomical location – connecting the coronary sinus with the PVs - coincides with the location of the posterior mitral isthmus, commonly ablated to treat perimitral flutter. VOM ethanol infusion leads to ablation of the VOM and its intrinsic electrical activity,[59,60] as well as the neighboring myocardium, its associated PV connections,[61] the mitral isthmus,[62] and the associated parasympathetic innervation.[63] The VENUS trial - study initiated by our group in Houston Methodist Hospital- demostranted that among patients with persistent AF, addition of VOM ethanol infusion to catheter ablation, compared with catheter ablation alone, increased the likelihood of remaining free of AF or atrial tachycardia at 6 and 12 months.[64] Of the 12 secondary outcomes, 9 were not significantly different, but AF burden (zero burden in 78.3% vs 67.9%; difference, 10.4% [95% CI, 2.9%-17.9%]; p = 0.01), freedom from AF after multiple procedures (65.2% vs 53.8%; difference, 11.4% [95% CI, 0.6%-22.2%]; p=0.04), and success achieving perimitral block (80.6% vs 51.3%; difference, 29.3% [95% CI, 19.3%-39.3%]; p < .001) were significantly improved in VOM-treated patients. For alcohol ablation in the VOM is of utmost importance to describe the anatomical variations of the LA venous drainage as a framework for venous endovascular therapies

targeting the LA. Prior anatomical descriptions of the VOM and other veins have involved pathological necropsy specimens, meanwhile human data is missing. For this reason, this constitutes one aim of the present stud: we aim to catalogued the human venous left atrium circulation system and the ablative effects of ethanol in different branches (Aim 4).

2. HYPOTHESIS

2. HYPOTHESIS

- We hypothesized that apnea induces a complex response of the autonomic nervous system coinciding with heart rate and blood pressure oscillations. Chemical ablation of ganglionated plexi sensory neurons with resiniferatoxin, a neurotoxic TRPV1 (transient receptor potential vanilloid 1) agonist, might decreases ganglionated plexi and stellate ganglion activity, abolishes apnea's electrophysiological response, and inhibits AF induction.

- Mapping algorithms are not reliable to detect pacing sites as true drivers of fibrillatory conduction and to detect epiphenomenal rotational or focal activity.

- It is possible to determine a reliable bipolar voltage cutoff for scar and low voltage area using small sized closely spaced multielectrode during AF and atrial flutter, values thar are rhythm dependent. We also postulated that LA voltage map in AF is reproducible.

- There are remarkable anatomical variations of the left atrial venous drainage among patients. Importantly the venous system can be employed as a vascular route to target the left atrium

3. OBJECTIVES

3. OBJECTIVES

- To delineate the autonomic response to apnea and to test the effects of ablation of cardiac sensory neurons with resiniferatoxin (RTX), a neurotoxic TRPV1 (transient receptor potential vanilloid 1) agonist.

- To explore the mechanistic relevance of focal activations and/or rotational activations and to assess the ability of authomatic algorithms to detect such activity during in vivo canine models of pacing-induced fibrillatory conduction and induced AF.

- To determine the bipolar voltage cutoff for scar and/or low voltage areas using small sized, closely spaced multielectrode fast automated mapping during AF and atrial flutter that corresponds to a sinus bipolar voltage of 0.5 mV. In this aim we also will try to determine the voltage correlation between sinus rhythm and AF and/or atrial flutter; and finally, to examine the reproducibility of leaf atril voltage mapping in AF.

- To describe the anatomical variations of the LA venous drainage as a framework for venous endovascular therapies targeting the LA.

4. METHODS

Aim 1. *"Cardiac Afferent Denervation Abolishes Ganglionated Plexi and Sympathetic Responses to Apnea".*

The animal protocol used was approved by the Institutional Animal Care and Use Committee of the Houston Methodist Hospital (attached in the addendum section). A total of 16 mongrel dogs were intubated and ventilated (Harvard Apparatus Co, Natick, MA) under general anesthesia. Apnea was induced by disconnecting the ventilator tube at end expiration until oxygen saturation (Sao2) dropped at least to 80%.

Protocol 1

Under continuous electrocardiographic and hemodynamic monitoring, after median cervical incision and sternotomy, the anesthesia agent was switched to alpha-chloralose. Bilateral vagal, left stellate ganglion, and anterior right GP (ARGP) nerve recordings were obtained (n=7) before and during apnea episodes, before and after local resiniferatoxin (RTX) injection in the ARGP.

Epicardial fat pads known to contain the anterior right, right and left inferior, and left superior GPs were sampled and the following histological studies were performed: hematoxylin and eosin staining and TRPV1 and CGRP immunohistochemical staining. Terminal

deoxynucleotidyl transferase dUTP-mediated nick end labeling (TUNEL) assay was also performed to detect apoptotic cells.

Protocol 2

Left atrium geometry maps were performed after a transseptal puncture using NavX guidance. A subxiphoid pericardial puncture was performed and a sheath inserted in the oblique sinus. Effective refractory period measurements were measured in 3 sites in the left atrium before and during apnea, before and after intrapericardial RTX injection

Aim 2. *"Epiphenomenal Re-Entry and Spurious Focal Activation Detection by Atrial Fibrillation Mapping Algorithms".*

Healthy mongrel dogs (n = 17) were subjected to general anesthesia. Vascular access was obtained using the right femoral and internal jugular veins. A duodecapolar catheter was positioned so the 10 distal poles were in the coronary sinus (CS) and the 10 proximal poles in the right atrium. Two transseptal punctures were performed: one for a decapolar catheter inserted in the right superior pulmonary vein (RSPV), and the other for the mapping catheter. The protocol was approved by the Houston Methodist Research Institute Institutional Animal Care and Use Committee (attached in the addendum section).

Bipolar pacing was performed using electrodes from RSPV, distal CS, or both simultaneously until fibrillatory conduction (FC) was observed. Dual-site, dual-pacing cycle length facilitated induction

of FC. Induced AF was defined as fibrillation sustained for at least 30 s after cessation of pacing. Maps and analyses of AF were conducted during self-sustained AF without pacing. Discrimination of pacing-induced FC versus underlying AF while pacing was performed by the absence of self-sustained AF after pacing. Electrograms were collected with a Bard recording system (Labsystem PRO, Boston Scientific, Marlborough, Massachusetts) at 4 kHz, and were exported for offline analysis. Panoramic basket catheter mapping (n = 5 with Topera, n = 6 with Cartofinder) or sequential OctaRay (Cartofinder, n = 6) was performed, identifying rotational activations (RoA) or focal activations (FoA) with their respective algorithms

Aim 3. ***"Validating Left Atrial Low Voltage Areas During Atrial Fibrillation and Atrial Flutter Using Multielectrode Automated Electroanatomic Mapping".***

For this aim we design a multicenter prospective study, performed in 3 hospitals with experience in the field of AF mapping and ablation. The certificate from the Institutional Review Board (IRB) is added in the addendum section. Patient demographics, clinical characteristics, and medications were exported from patient records. All participants provided written, informed consent for both the ablation procedure and inclusion in medical research at the time of procedure.

High-density atrial mapping

Patients with AF who underwent first or repeat ablation also underwent sequential mapping of the LA using a PentaRay catheter (Biosense Webster, Diamond Bar, California), which contains 5

splines with 4 electrodes each (1 mm, spaced 2-6-2 mm apart). In sinus, atrial electrograms were captured by setting the window of interest from − 50 to − 350 ms, preceding the sharp component of each ventricular QRS complex as a reference. High-density bipolar voltage mapping of the left atrium was performed with an equal distribution of points using a fill threshold of 5 to 7 mm, with a minimum of 1,000 points in each left atrial map. Low-voltage zones were defined as 0.1 to 0.49 mV (peak-to-peak bipolar voltage) and transitional zones were considered ≥0.5 to 1.4 mV. If the patient was in AF, the patient was cardioverted at the beginning of the study to obtain the first map in sinus rhythm (hence, avoiding map displacement after the cardioversion). Afterward, AF and/or atrial flutter was induced by atrial burst pacing from the distal or mid-coronary sinus at a cycle of 250 to 180 ms. In those patients in whom the 2 maps were performed during AF, a 10-min waiting period was performed (2 obtained maps called AF1 and AF2).

In addition, high-density mapping was added at sites where low voltage areas (LVAs) were recorded to exactly delineate the extent of the LVA. Stability was selected at 5 mm. To avoid poor contact points, we set the interior and exterior projection distance filtering to 5 mm from the geometry surface. In sinus, points that did not conform to the surface electrocardiogram P-wave morphology or 75% of the maximum voltage of the preceding electrogram were excluded. Signals were filtered at 30 to 400 Hz and displayed at 100 mm/s. The electrogram at each point acquired on the LA shell was manually reviewed to exclude noise or a pacing artefact before being accepted. We included 7 segments (septum, anterior wall, floor inferior, lateral wall, posterior wall, roof, and pulmonary veins). Each left

atrium−pulmonary vein junction was defined as the region that extended 5 mm proximal to the pulmonary vein ostia circumferentially and that documented an impedance rise of 10 ohms compared with the left atrium.

Two separate left atrium shells (bipolar voltage maps) were created for each patient in 2 different clinical rhythms or in AF at different times. To compare local bipolar voltages from each site in different rhythms, each map was tagged in a separate color before being combined on a new map. Complete transparency was used to manually review points obtained in the same location on each mapping procedure and/or left atrium shell. Only those point pairs with a distance of <1 mm between them were analyzed. Once the 2 points were compared, they were tagged in a different color to avoid duplication.

Aim 4. ***"The Human Left Atrial Venous Circulation as a Vascular Route for Atrial Pharmacological Therapies".***

Patient population

Patients undergoing catheter ablation of AF gave written consent to participate in pilot mechanistic studies or the on-going VENUS-AF (Vein of marshall EthaNol for Unablated perSistent atrial fibrillation) or MARS-AF (vein of Marshall ethanol (VOM) for Recurrent perSistent atrial fibrillation) clinical trials (NCT01898221), or they underwent VOM ethanol infusion as part of their clinical treatment. The protocols were approved by the Institutional Review Board. The certificate from the IRB is added in the addendum section.

The procedure was aimed at cannulating the VOM for ethanol infusion, but occlusion VOM venograms allowed us to visualize the atrial venous anatomy described herein. It was attempted in 235 patients. We inserted a 9-F sheath through the right internal jugular vein (n = 232), the left subclavian vein (n = 2), or the right femoral vein (n = 1), through which the CS was engaged, using commercially available sheaths for left ventricle lead delivery, most commonly a CPS (St. Jude Medical, St. Paul, Minnesota) or a Preface sheath (Biosense Webster, Diamond Bar, California). Then, a left internal mammary angioplasty guide catheter was inserted through the CS sheath and used for contrast injection. To aim for the VOM, the left internal mammary guide tip was directed superiorly and posteriorly in the CS while contrast was injected to identify the VOM or other branches. The VOM was identified as a branch of the CS directed posteriorly and superiorly, immediately distal (toward the CS ostium) to the valve of Vieussens. When the VOM was not amenable to cannulation, other atrial veins were attempted. Once a vein engagement was obtained, an angioplasty wire (Balance Middle Weight [BMW]; Abbott, Abbott Park, Illinois) was advanced. A pre-loaded angioplasty balloon (8-mm length, 2-mm nominal diameter, or 1.5 mm by 6 mmm) was then advanced into the vein for selective venograms. Vein size, branching, and collateral circulation and other opacified atrial veins were catalogued in all patients included in this study. Measurements and digital subtractions were made using OsiriX DICOM (digital imaging and communications in medicine) format viewer (version 8.0.1, Pixmeo Sarl, Geneva, Switzerland), calibrated to known interelectrode distances on the CS decapolar catheter.

5. RESULTS

5. RESULTS

5.1. *"Cardiac Afferent Denervation Abolishes Ganglionated Plexi and Sympathetic Responses to Apnea".*

Circ Arrhythm Electrophysiol. 2019 Jun;12(6):e006942.

DOI: 10.1161/CIRCEP.118.006942. Epub 2019 Jun 5.

Specific contribution in the publication:

Conceptualization, methodology and research: approach and development of animal experiments. Data acquisition and analysis. Writing of the original manuscript.

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Authorization of the journal:

The journal where it has been published allows the reuse of the article by the author as part of the thesis and fulfils the "Fair Use of Copyrighted Materials" (section 107, title 17, US Code; https://www.ahajournals.org/permissions-rights)

5.2. "Epiphenomenal Re-Entry and Spurious Focal Activation Detection by Atrial Fibrillation Mapping Algorithms".

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5.3. "Validating Left Atrial Low Voltage Areas During Atrial Fibrillation and Atrial Flutter Using Multielectrode Automated Electroanatomic Mapping".

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Quality indices:

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Authorization of the journal:

The journal where it has been published allows the reuse of the article by the author as part of the thesis.

5.4. *"The Human Left Atrial Venous Circulation as a Vascular Route for Atrial Pharmacological Therapies".*

JACC Clin Electrophysiol. 2017 Sep;3(9):1020-1032.

DOI: 10.1016/j.jacep.2017.02.022.

Specific contribution in the publication:

Conceptualization, methodology and research: approach and development of clinical studies. Data acquisition and analysis. Writing of the original manuscript.

Quality indices:

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The journal where it has been published allows the reuse of the article by the author as part of the thesis.

6. DISCUSSION

6. DISCUSSION

Atrial fibrillation is the most common sustained cardiac arrhythmia in clinical practice.[1,2] What was defined in the past as a simple arrhythmia characterized by irregularly irregular heartbeats is now accepted as a common and rapidly growing clinical problem and as a disease entity. As a matter of fact, it has generated a wide range of research in the last years, particularly in the last two decades. Nevertheless, as we have tried to reflect through the course of this thesis, there are still lots of gaps of knowledge that deserve further investigation.

First of all, we focused on a mechanistic aspect of AF, specifically the role of apnea (in an attempt to simulate OSA). Based on animal study we delineate the integrated autonomic response to apnea, which includes a consistent sequence of events on oxygen desaturation, including: (1) increases in GP activity; (2) progressively increasing phasic bursts of vagal activity, which closely correlate with HR and BP oscillations; and (3) tonic increase in sympathetic activity, which correlates with steady increases in HR and systolic BP. Second, we correlate these autonomic changes with electrophysiological changes, namely ERP shortening and consistent AF induction with single extrastimulation during apnea. Third, we show the acute effects of RTX administration, both locally as well as intrapericardially, which are characterized by a dramatic increase in ARGP activity and

BP, and increases in HR. Such sympathetic afferent activation, along with its associated hemodynamic effects, can lead to additional electrophysiological changes, including spontaneous ventricular fibrillation but is characteristically transient, and followed by recovery to a baseline physiological state. Fourth, we show that apnea post-RTX lacked ARGP activation, and lacked the increased SG and rebound BP associated with deoxygenation. Additionally, RTX eliminated both apnea-induced AERP shortening and AF inducibility; and after RTX treatment, apnea led to prolonged AERP. These results are consistent with a fundamental role of the cardiac ANS mediating the electrophysiological responses of the atrial myocardium to apnea and suggest the cardiac afferents as a possible therapeutic target for autonomic modulation.

In our second and third aim we focused on atrial electrograms and atrial processing. In the second study ww found that: 1) fibrillatory signals arose in the RA during rapid in vivo LA pacing despite 1:1 propagation in the LA and without induction of AF; 2) spatial distribution of DF and its regularity index during pacing with FC with and without AF induction and during ongoing AF are similar; 3) panoramic mapping with the basket catheter most commonly led to uninterpretable data; 4) RoA during FC or AF was rare, and occurred more commonly in RA than LA (OR: 3.5) and during pacing from distal CS than from RSPV (OR: 6.63); 5) crista terminalis and RAA harbored the majority of RoA detected in the RA, and these locations match the locations of DF break-down during pacing with FC; and 6) FoA detection algorithms were unable to localize true focal sources during pacing. With these results we can conclude that the mechanisms of AF remain still elusive. Without denying FoA or RoA

as mechanisms, the detection of epiphenomenal re-entry and spurious focal sources during FC questions the algorithms approach. Under our point of view, algorithm refinement beyond phenomenological findings of RoA and FoA is needed before its incorporation into clincal practice.

Following, we to aimed determine the voltage correlation between SR and AF/atrial flutter using multielectrode fast automated mapping, to identify a bipolar voltage cutoff for scar and/ or low voltage areas and finally to examine the reproducibility of voltage mapping in AF. Our main findings were: 1) there were significant differences in global and regional voltage distribution when we compared different areas during the same rhythm or different rhythms in the same area; 2) despite a difference in voltage between rhythms, it was possible to establish new cutoffs for AF and AFL with acceptable validity in predicting a sinus voltage <0.5 mV; and 3) multielectrode fast auto- mated electroanatomic bipolar mapping with closely spaced (2 mm) small electrodes (1 mm) in AF seems to be reliable and reproducible when classifying low voltage zones. From our perspective, this study has important clincal implications: voltage mapping in the LA to guide AF ablation depends on the accuracy of each mapping technique and the underlying rhythm. This is particularly important, because recent publications that described success with substrate-based AF ablation approaches were highly dependent on accurate identification and interpretation of LA scar. Our present study suggested that there might be differences in ideal voltage thresholds according to the underlying rhythm. This must be taken into account when mapping during non-sinus clinical rhythms or when designing future studies on the subject. For example, this is

critical awareness of low voltage distribution is critical for instance when conversion of AF to sinus rhythm fails or when it is not desired to perform a cardioversion in those cases when mechanism-based AF mapping is attempted. We showed that mapping using an adjusted lower LVA detection cutoff might produce valid and reliable results that could identify areas with a voltage of <0.5 mV in SR.

Finally, in our last study we intended to catalogue the human venous left atrium circulation system along with the ablative effects of ethanol in different branches. For this aim, patients undergoing ethanol infusion in the VOM as adjunctive therapy to AF catheter ablation were included in this study. Balloon occlusion venograms of the VOM and other LA veins were obtained in 218 patients, the largest human atlas performed so far. This work includes anatomical demonstration of the in vivo entire venous circulation of the LA in humans. Besides the known anatomical locations of atrial veins, abundant interconnections are unveiled, for example, delineation of a percutaneous technique to deliver therapeutic agents to the LA in different regions beyond the VOM and delineation of the regional ablative effects of ethanol in each venous territory. Therefore, this study provides the procedural and anatomical foundation to use retrograde venous approaches to target atrial tissue. Although currently used for ablative purposes in the context of AF treatment, the approach presented herein could be used to selectively reach atrial myocardium for pharmacological or cellular therapies.

Next, we will review in detail te most important ideas of the abovementioned studies:

Cardiac Afferent Denervation Abolishes Ganglionated Plexi and Sympathetic Responses to Apnea. Implications for Atrial Fibrillation

ANS Response to Apnea: Hemodynamic and Electrophysiological Correlates

The consistent sequence of events we detected seems to initiate with slow, steady decreases in HR followed by HR and BP oscillations and later by a BP rebound increase (see the graphic abstract presented in the paper). An initial increase in GP activity subsided to then increase, particularly at the end of apnea. The onset of HR oscillations preceded the onset of phasic bursts of vagal discharges, whose frequency, amplitude, and spike density grew as apnea persisted. The crescendo nature of these bursts was paralleled by an increase in the frequency of HR and BP oscillations, which supports a mechanistic connection. Of note, vagal bursts coincided with the upsloping phase of HR oscillations and the downsloping phase of BP oscillations. The mechanistic origin of such vagal bursts is unclear, but could represent afferent activity[65-80] since most fibers in the vagal nerves are afferent,[80,81] or originate from sympathetic efferents of the vagus leading to HR increases,[82] or be parasympathetic efferents with either primary effects on BP or delayed effects on HR.

Coinciding with the onset of oxygen desaturation, a tonic increase in sympathetic (SG) activity was found, which matched the onset of a steady increase in BP. Subcutaneous nerve activity matched the SG activity, as previously reported.[79] The GP and SG activity and the BP rebound were abolished by RTX injection.

Role of the ANS and Sensory Neurons in the Genesis of AF in Apnea

Previous experimental studies have demonstrated a close mechanistic association between the cardiac ANS and apnea-induced AF, focusing mainly on parasympathetic contributors.[66,83] In a canine model of apnea, Ghias et al[65] documented increases in neural activity within the GP before the initiation of AF. Furthermore, ablation of the aorta superior vena cava ganglionated plexus significantly diminished the inducibility of AF. We expand their findings to show the orchestrated intrinsic (GP) versus extrinsic ANS (vagal and SG) response to apnea and their changes after RTX.

Sensory neurons are an integral part of the GP. GP local sensory neurons are thought to mediate a local neurosensory reflex within the GP.[84] The overall physiological effect of sensory neurons activation is a depolarization of postganglionic parasympathetic neurons,[85,86] thus enhancing GP output and leading to the local release of acetylcholine and the electro- physiological effects that follow (namely ERP shortening). This effect could be occurring at a local GP level. The mechanical and chemical stimuli to which sensory neurons react under physiological conditions is unclear, but it makes physiological sense to hypoth- esize that apnea-induced hypoxia, hypercarbia, acidosis, or mechanical stretch may play a role. Our data support such contention.

We propose a reflex model of apnea-induced AF susceptibility. Apnea directly causes hypoxia, hypercarbia, and acidosis. Either by chemoreceptors sens- ing pH, pO2 or pCO2, or mechanoreceptors sensing increased pressure, sensory neurons would be activated via TRPV1. Sensory neurons have the somata in the dorsal root ganglia,

in the nodose ganglion of the vagus, and in the intrinsic cardiac nervous system themselves.[84] Local intrinsic cardiac nervous system sensory neuron activation could activate post-ganglionic parasympathetic neurons,[85,86] thus form ng a local reflex arc that leads to ERP shortening in neighboring myocardium. Sympathetic afferents enter through the stellate ganglia and the spinal cord and terminate in the nucleus of the solitary tract,[87] leading to increased sympathetic outflow. Both the local effect leading to ERP shortening and AF inducibility, as well as the increased sympathetic outflow, are abolished by RTX-induced sensory neuron ablation. Vagal responses were unchanged. The lack of vagal effects suggests that either parasympathetic afferents were not affected, or perhaps more likely, that they are mediated by non-GP afferents, either pulmonary or carotid.

After RTX, apnea-induced prolongation of the ERP rather than shortening. This is consistent with direct myocardial effects of hypoxia, hypercarbia or acidosis, increasing postrepolarization refractoriness, analogous to the myocardial effects of ischemia,[88] which are normally counteracted by the neuronal reflexes described.

Acute RTX Effects

Sensory afferents mediate the cardiac sympathetic afferent reflex, thought to lead to sympathoexcitation in heart failure and acute ischemia.[77] RTX applied to the epicardium in rats can abolish this response,[77,78] and leads to loss of TRPV1-expressing neurons, which in turn has been associated with reduced fibrosis in ischemia-induced heart failure.[78] The acute hemodynamic effects of RTX in vivo have been described.[85] Consistent with transient hyperactivation of cardiac

sympathetic afferents, RTX led to marked GP activity, doubling of the systolic BP, increases in HR, and significant electrocardiographic changes (ST elevation, T-wave inversion, and even ventricular fibrillation). These changes completely subsided and normalized over the course of up to 40 minutes, consistent with the time course from RTX-induced activation followed by neuronal toxicity.

Clinical Implications

Sleep apnea is associated with AF. Multiple mechanisms are involved, but a prominent role of the ANS is suspected. Here, we delineate the integrated autonomic response to apnea, that includes GP, vagal, and SG firings in a consistent manner that leads to hemodynamic and electrophysiological (shortened ERP) changes that culminate in AF inducibility. The GP and SG responses were abolished by sensory neuron ablation with RTX. Sensory neurons mediate the electrophysiological response to apnea and could be a valid therapeutic target to reduce apnea-induced AF.

This study has some limitations that needs to be aknowdledge. OSA-induced AF is multifactorial and is likely to involve a plethora of mechanisms that were not studied here as hypertension, obesity, metabolic syndrome, atrial structural remodeling, among others.[90] The animal model used in this study is merely an acute model, and not an exact replica of OSA as it does not reproduce all events associated with long- term OSA. However, this approach reproduces the hypoxia, hypercarbia, and acidosis of OSA as putative triggers of an autonomic response in an acute model of apnea and eliminates other confounding factors such as obesity, metabolic syndrome, and intrathoracic

pressure dynamics that can confound a mechanistic response of the sensory neurons.

Future studies are needed to investigate the chronic effects of chemical ablation of cardiac GP sensory neurons. Chronically repeated OSA episodes has been shown to cause cardiac remodeling with fibrosis playing a prominent role which contributes to AF promotion.[91] We did not record signals from all GPs as we were limited by anatomic access to the ARGP. Additionally, peripheral blood CO2 and pH were not monitored. Although the mechanistic implications are significant, basic electrophysiological properties, such as action potential duration, and conduction velocity, were beyond the scope of this study. There could be concerns about the specificity of RTX effects. However, it should be highlighted that prior studies have consistently shown the absence of myocardial effects.[77]

To sum up, apnea leads to a complex response of the cardiac ANS including GP firing, phasic vagal bursts coinciding with HR and BP oscillations, and tonic SG firing that led to ERP shortening and increased in AF vulnerability. Chemical ablation of intrinsic cardiac sensory neurons with RTX decreases sympathetic and GP nerve activity, and abolishes the electrophysiological response seen during apnea. A critical role of a neurosensory reflex in apnea-induced AF is suggested and could potentially be therapeutically targeted.

Epiphenomenal Re-Entry and Spurious Focal Activation Detection by Atrial Fibrillation Mapping Algorithms

Spectral characteristics of pacing-induced fibrillatory conduction and induced AF.

Consistent with other studies,[92-104] we found a left-to-right frequency gradient during pacing- induced AF, which has been attributed to the left- to-right inward rectifier potassium current gradients[105-106] and was found to occur in both pacing-induced and spontaneous human AF.[107] We also confirm gradients of organization of fibrillation (as shown by RI gradients) between the LA and RA. We expand these findings by demonstrating that similar spatial gradients of DF and organization occur during pacing with FC both with and without AF induction (see Figure 2D of the paper). The latter observation both points toward a site-specific tissue property as the basis for this variability in organization and shows that gradients in DF and RI occur in the absence of AF inducibility and cannot be considered mechanistically inherent to AF.

Fibrillatory electrograms in the absence of induced AF.

Despite regular 1:1 propagation and regular signals in the LA, the RA showed fibrillatory electrograms. This disruptive conduction, however, did not necessarily induce AF, as evidenced by the disappearance of fibrillatory electrograms and restoration of sinus rhythm post-pacing. The fact that fibrillatory sig- nals exist in the absence of sustained AF is clinically relevant. Fibrillatory electrogram complexity[108] and frequency content[109] have been used to attribute mechanistic relevance to different sites in atrial fibrillation as targets for ablation therapy.[110] We show that the complexity and spectral

characteristics of fibrillatory electrograms in the RA occur in the absence of AF induction (see Figure 2D; paper 2). Although the phenomenon of FC in the RA has been described by Berenfeld et al.[54] in ex vivo tissues, the current study shows that the mere presence of this FC is not sufficient for self-regeneration and sustainment of fibrillation.

Additionally, we show that dual-site, dual-cycle length pacing can induce complex propagation pat- terns with fibrillatory electrograms that, in the absence of AF induction, can lead to complex frequency distribution maps.

RoA during pacing and AF.

The Cartofinder algorithm detected RoA in 4.2% (n = 20 of 479) of the OctaRay maps during rapid pacing with FC. The presence of such RoA—confirmed manually in all cases—did not correlate with the induction of AF. Such apparent RoA arose as propagating wave fronts from the pacing site encountered unidirec- tional block (anatomically determined by local heterogeneities) that led to a local rotation around the site of block. Consistent with Berenfeld et al.[54] and our previous observations in fibrillating ventricles,[111] abrupt fiber orientation changes can lead to the formation of local re-entrant propagation, and as in those studies, such RoA occurs at the very sites (see the central illustration of the paper) of frequency breakdown (see Figure 3B; paper 2). The fact that this RoA exists in the absence of sustained AF proves that algorithm- detected RoA is not sufficient to qualify an RoA as an independent driver of AF—the only true "driver" during LA pacing-induced FC is the pacing stimulus—and

questions the mechanistic relevance of indiscriminately using ablation techniques targeting algorithm-detected RoA.

We found greater incidence of RoA in the RA during CS pacing than during RSPV pacing. Although the specific mechanism for this finding is speculative, the closer proximity of the RSPV to the RA may limit the number of anatomical complexities propagation waves encounter as they reach the RA. The fact that the incidence of RoA in the RA could be modulated by the site of LA pacing—and yet be clustered in the same locations—illustrates the interplay between dynamic and fixed factors. Fixed heterogeneities in the RAA- crista terminalis connection are potential sites of anisotropic unidirectional conduction block and induction of re-entry.[112]

The clinical relevance of our findings is that we show that such re-entry is entirely a passive phenomenon during pacing, and although mapping algorithms can detect it, such RoA cannot be conceived as a driver of self-sustained propagations, let alone ablation targets.

The incidence of RoA was low. It is possible that factors not tested here - such as shortening action potential duration or conduction velocity slowing - may be present in clinical AF and promote RoA to greater incidences than what was found in our study.

Focal activity during pacing and AF

We mapped FC during a known-site pacing to test the ability of the mapping algorithms to identify FoA in a controlled fashion. FoA detection by the mapping system was suboptimal, both failing to identify the pacing site, and erroneously identifying focal sources in areas remote from the pacing sites(s), including the RA, despite pacing from known LA sites only. The algorithm identifies the earliest

QS pattern within 50 ms of a single OctaRay recording. The QS criterion proved to be prone to errors (limited specificity and sensitivity) considering the limited spatial sampling. Among the FoA identified in the RA during pacing from LA sites, the RA septum had the highest FoA detection rate (see supplemental Table 1), suggesting that passive activation from the LA might have been labeled as a focal source in the RA. Thus, the relatively high FoA detection rate in this model repre- sents a failure of the algorithm.

The shortcomings of panoramic mapping.

Panoramic mapping using the basket catheter frequently showed uninterpretable results. The anatomical correlation of Topera maps depends on arbitrary assessments of electrode location. Using Cartofinder, for any given recording, multiple electrograms were discarded due to insufficient proximity to the atrial wall—an unavoidable problem that Topera masks. Although we cannot disprove the reported clinical utility[113-114] or value of other catheter designs, we found the challenge of obtaining meaningful signals from a whole atrial chamber unsurmountable given the anatomical complexities.

This study has some important limitations that need to be kept in mind at the time of data interpretation. FC and pacing-induced AF episodes in healthy, young canines were short and with low incidence of RoA, and they may be mechanisti- cally distinct from clinical AF in humans. Future studies can focus on testing the algorithm in chronic AF models to better mimic persistent AF. Pacing artifacts could have affected our frequency analyses. Although we show that RoA can be

epiphenomenal during FC, we cannot disprove that RoA may contribute to AF maintenance in clinical AF.

To summarize, in the context of FC without AF induction, where any FoA sites other than the pacing site are spurious and any RoA is epiphenomenal, mapping algorithms failed to localize pacing sites as the true FoA origin, and instead identified spurious FoA sites and epiphenomenal RoA. Thus, phenomenological identification of FoA and RoA by current AF mapping

Validating Left Atrial Low Voltage Areas During Atrial Fibrillation and Atrial Flutter Using Multielectrode Automated Electroanatomic Mapping

Atrial fibrosis and AF

Atrial fibrosis has been observed in greater frequency in patients with AF,[31,115,119]. At the same time, evidence for extensive fibrosis is also associated with a longer standing history of the arrhythmia as well as a lower success rate for PVI.[116,120-129] These findings suggest a possible mechanistic relationship between atrial fibrosis and/or scarring and AF.[120,124] Although reparative fibrosis has been suggested to replace electrically active conductive tissue, thus causing anisotropy and enhancing re-entry, interstitial fibrosis may be more electrically inert.[130] However, substrate manipulation in areas of fibrosis has been suggested to help improve outcomes for selected patients.[131] Wang et al.[129] performed a randomized controlled trial of substrate modification versus a more traditional stepwise ablation approach for patients with long-standing persistent AF. The authors found improved effectiveness after a first procedure in the substrate

modification groups, a lower atrial tachycardia recurrence rate, and a shorter procedure time, but the benefits faded after repeat procedures. Lin et al.[122] showed that rotors involved in AF maintenance exhibited lower voltage than sites without rotors (0.68 ± 0.44 vs. 0.71 ± 0.63). A meta-analysis of similar studies showed a benefit of adding substrate modification targeting areas of scar identified by low voltage compared with traditional PVI only.[55]

It seems that absence of atrial low voltage may identify patients in whom PVI alone is likely to be sufficient, whereas the presence of atrial low voltage may indicate scar tissue and potential alternative sources of the arrhythmia related to a slow conducting substrate.[131]

Identifying fibrotic tissue by means of abnormal electrocardiogram.

Electrophysiologically, atrial fibrosis produces low-amplitude electrograms,[123] electrogram fractionation, conduction heterogeneity, and manifests as abnormal signals that can be identified using electroanatomic mapping during SR.[132-133] A 3-dimensional map may thus show areas of fibrosis to help guide diagnosis or ablation procedures. Several authors already showed that LVAs identified in SR on such electroanatomic maps of the atria correlated well with late gadolinium enhancement seen on cardiac magnetic resonance imaging.[134,135] Nevertheless, some limitations to those studies should be highlighted. First, the use of current magnetic resonance imaging technology to diagnose atrial scarring has several limitations and is not well validated against histological evidence.[55] Second, a low voltage on bipolar electrodes may be related to several factors independent of fibrosis, including direction of conduction vector,

amount of contact, and electrode size and interelectrode distance characteristics.[130]

Voltage differences during different rhythms.

Our finding of higher voltages in SR than AF is in agreement with previous studies in the literature. Yagashita et al.[124] found a linear voltage correlation between SR and AF using an ablation catheter (3.5-mm tip)[124], whereas Masuda et al.[133] found that the correlation was only present if electrograms did not become fractionated during AF. There was a possible mechanistic explanation for the observation of progressively lower voltages in AFL and AF compared with SR. During arrhythmias with shorter cycle lengths, a substantial amount of tissue might not depolarize when it is still refractory, or small pieces of underlying or neighboring tissues might depolarize nonsimultaneously and in opposite directions, which results in low bipolar voltage amplitudes.[133-135] In addition, bipolar voltage was dependent on the direction of wavefront propagation. In AFL, the more organized activation seen in macrore-entries compared with microre-entries in AF could give rise to less beat-to-beat variation and a steadier peak-to-peak deflection.

Ideal cutoff for ablating.

The bipolar voltage of <0.5 mV cutoff was originally based on baseline noise levels in early electroanatomic mapping systems and was only later validated in imaging studies.[134,135] Therefore, the ideal clinical cutoff value was arguably still unknown, but our study findings suggested that such a threshold was likely to be different depending on the rhythm during mapping. Furthermore, only a few studies validated this conventional cutoff when it was used in atrial

mapping during AF.[120] Even more important, most clinical studies of substrate modification procedures performed mapping mostly during SR.[127] Jadidi et al.[131] accomplished mapping in AF with different types of catheters and evaluated the effects of ablating at points with certain electrogram characteristics lying in or near LVAs after PVI. The authors successfully demonstrated improved effectiveness compared with a conventional PVI-only strategy for persistent AF. Although values changed slightly according to the statistical analysis used, we found that a 0.38- mV cutoff in AFL and 0.31-mV cutoff in AF provided a good negative predicted value, positive predicted value, specificity, sensitivity, and accuracy for predicting a voltage of at least 0.5 mV in SR. Moreover, as indicated in Table 3, these cutoffs (by means of Blanda Latman plots)[136-138] could be even further adjusted according to the sampled region[139].

In the study by Yagashita et al.[124], the number of points with LVA in AF, using a bipolar voltage cutoff of 0.5 mV (4.0 ± 2.4) (using a 3.5-mm tip ablation catheter), was significantly higher than those used in SR using the same cutoff (1.9 ± 2.1; $p < 0.001$). An adjusted bipolar voltage of 1.5 mV in SR produced a similar area of fibrosis to that of 0.5 mV in AF ($p = 0.125$). In our opinion, there are several limitations to that approach for defining cutoffs.[140] First, because a sinus voltage of 0.5 mV is the most studied, we believe it is most important to define the thresholds in AF and AFL that predict such a voltage in SR and not the inverse. Second, the total area of low voltage depends on the number of points sampled in each particular segment.[141] Derivations based on the area of low voltage may thus be biased by the interpolation created at the time of the electroanatomical map. In our study, we derived thresholds from an analysis based on a

point-by-point comparison and were able to prove great accuracy for predicting a sinus voltage < 0.5 mV. Our study also derived threshold values for AFL and studied the reproducibility of LVAs in AF patients.

Reliability of mapping in AF.

Bipolar voltage is measured in a single window as the maximum peak- to-peak voltage of 2 to 3 consecutive AF beats, and may be subject to temporal variation and quality of contact. For this reason, we attempted to use a widened window of 400 ms. Remarkably, despite the beat-to-beat variation seen in AF, we proved good reproducibility of the AF voltage maps and confirmed the reliability of LVA mapping during this rhythm.

Clinical implications.

Voltage mapping in the LA to guide AF ablation depends on the accuracy of each mapping technique and the underlying rhythm. This is particularly important, because recent publications that described success with substrate-based AF ablation approaches were highly dependent on accurate identification and interpretation of LA scar.[108,127-144] Our present study suggested that there might be differences in ideal voltage thresholds according to the underlying rhythm. This must be taken into account when mapping during nonsinus clinical rhythms or when designing future studies on the subject. For example, this is critical awareness of low voltage distribution is critical for instance when conversion of AF to sinus rhythm fails or when it is not desired to perform a cardioversion in those cases when mechanism-based AF mapping is attempted. We showed that mapping using an adjusted lower LVA detection cutoff

might produce valid and reliable results that could identify areas with a voltage of <0.5 mV in SR.

Concerning the limitations of our study it needs to be hoghlieted some points. Our analysis could have been affected by undetected map shifts. We attempted to minimize this by performing well-distributed electroanatomic voltage mapping using CARTO3 system (Biosense Webster, Diamond Bar, California) and strict analysis, including only adjacent points that were <1 mm apart. Furthermore, we cardioverted patients with AF at the beginning of the study, so that the first mapping procedure was obtained in SR, thus avoiding any significant map shifts during cardioversion. We had nearly identical LA volumes in SR and AF maps that we believe add credence to the reliability of the mapping obtained. However, despite the fact of having nearly identical LA volumes in SR and AF maps, as it is well known that LA volume can be different between SR and AF because volume loading is different with different rhythms. We tried to overcome this limitation by taking stables references and comparing them along the course of the procedure (coronary sinus, His location, and the PV antrum) and by excluding those cases in which a cardioversion was needed. For all these reasons, this is the reason why it should not have significantly altered the conclu- sions of the present study. In some patients, we might have underestimated the voltage due to possible stunned myocardium. We used CARTO3 for electroanatomic voltage mapping and 1-mm electrodes with 2-mm interelectrode spacing; therefore, our findings might not be applicable to other mapping systems and catheters. Because we do not currently perform pre-ablation cardiac magnetic resonance routinely on patients undergoing repeat AF ablation, we were unable to make comparisons

between electroanatomic mapping-derived scar versus LA scar as seen on cardiac magnetic resonance in this patient series. [145,146]

With this information we can conclude that there are further implications in non-AF studies as well. For example, "fine tune" scar recognition and subsequent ablation is extremely important during AFL ablation. In this situation, interruption of AFL might be undesirable to avoid difficulty with inducing it afterwards. Hence, activation mapping and electroanatomical mapping, both performed during on- going AFL or AF, could help delineate the re-entry or focal site, and the substrate without interrupting the rhythm.

The Human Left Atrial Venous Circulation as a Vascular Route for Atrial Pharmacological Therapies Effects of Ethanol Infusion

Left atrial venous circulation.

Descriptions of the human left atrial veins are scarce.[147-151] von Lüdinghousen et al.[152] studied 100 post-mortem human hearts and their left atrial veins. They described 3 groups of veins. The first group included veins that drained directly into the right atrium. These included inferoseptal veins, with ostia in the neighborhood of the CS, and anteroseptal veins draining close to the SVC.[153] The former had been originally described by Bochdalek,[154] connecting to the right atrium as sinusoids separate from the CS. We show that selective cannulation of inferoseptal veins can be achieved from the CS itself and that they can connect with right inferior pulmonary veins. Additionally, septal veins can be opacified through collateral flow during injection in other veins. The anteroseptal veins draining into

the SVC-RA junction described by von Lüdinghousen et al.[152] would correspond to the veins we define as “roof veins,” which, in our experience, were only visualized through collateral flow and did not have CS connections. In some cases, the roof veins did not drain in the RA but seemed to drain into the LA, close to the right superior pulmonary vein.

A second, larger and more consistent venous system consisted of veins that were branches of the CS and great cardiac vein. These included inferior veins, lateral veins, the VOM, appendage veins, and anterior veins. We confirmed this overall pattern but show substantial variability in the individual vein size, shape, branching patterns, and connection to one another. The VOM is the most consistent LA vein. Von Lüdinghousen et al.[152] found it in 99% of their speci- mens. In a study of 100 patients undergoing CS venograms, the VOM was present in 73% of patients.[155] In that study, 75% of patients with a VOM had a poorly developed VOM as described by the authors (it did not reach the roof of the left atrium).[155] However, asshown here, selective venograms of the VOM, compared to nonselective venograms through the CS, may be able to better visualize the entire length of the VOM and the presence of collaterals veins.

In one of the larger descriptions of the VOM from a group of 275 anatomical specimens, the VOM was present in 84% of specimens, with a mean length of 2 to 3 cm and an average diameter of 1 mm.[153] In other studies, the presence of a VOM has been variable, ranging from 34% in a study of 38 patients undergoing multislice cardiac computed tomography scanning[156] to 87% in a study of 23 pathologic specimens.[157] Our own success at cannulating the VOM was 86.2%, but the VOM was visualized using collateral flow of other

venograms. Despite its consistent presence, the VOM was significantly varied in size, branching patterns, and capillary content.

The third venous system included true thebesian veins, named "proper" atrial veins,[152] that were located in the posterior wall, drained into the left atrium itself, and had frequent connections with mediastinal veins.

Our work confirms these anatomical features in vivo and describes the potential clinical utility of percutaneous cannulation of these veins.

Interconnections of the venous system.

The value of in vivo cannulation and venograms, as opposed to post-mortem studies, is that we were able to show the abundant interconnections among different venous branches. Contrast injection in the septal veins commonly led to opacification of neighboring veins through capillaries, including inferior vein, posterior veins, and roof veins and even back to the VOM. Contrast injection in the VOM could opacify septal and inferior veins, but most commonly the VOM communicated with LAA veins and roof veins. Roof veins could only be demon- strated through collateral flow, from either the VOM, the LAA veins, or anterior veins. [157] Communication between the atrial veins and the PVs was unexpected but probably represents the PVs' own wall vasa vasorum venous drainage connecting to LA veins.

Ethanol-induced ablation.

The VOM has been mechanistically related to the genesis of AF (for a review. see reference 158), both as a source of focal ectopic beats that trigger AF[159] and as an AF substrate linked to its abundant

parasympathetic[160] and sympathetic[161] innervations that modulate electrical properties of atrial tissue and contribute to AF maintenance.[162] These properties have made the VOM an attractive target during ablation of AF.

The therapeutic validity of ethanol infusion in the VOM seems to be clear for difficult cases of perimitral flutter,[163] or occasional cases of VOM atrial tachycardia.61 Only the aforementioned VENUS-AF clinical trials have established its role for the general AF ablation patient population.[64] The use of ethanol in other veins is less established mechanistically. Because, by definition, CS-cannulated atrial veins are annular, the use of ethanol can be justified if seeking mitral annular conduction block. It is of interest that ethanol infusion in the anterior LA vein led to an ablation lesion strik- ingly similar to that of an anterior mitral line (see Figure 8F; aim 4).[164,165] Lesions obtained by ethanol injection in LAA veins lead to a low-voltage scar in the LAA base that can be used to obtain mitral annular conduction block as well. Other lesions created by inferior and septal lines can contribute to the larger lesion sets occasionally sought in long-standing persistent AF ablation. Generally, the extent of ethanol infusion reflected the size and capillary network of the cannulated vein and served here to illustrate the myocardial regions that can be targeted for cannulating each vein branch. Future therapies targeting atrial myocardium, for therapeutic purposes beyond mere chemical destruction with ethanol, can be based on the anatomical depictions and technical basis shown in our work.

This study also has some limitations that need to be emphasized. Cannulating atrial veins other than the VOM can be difficult due to their small size. Thus, technical reproducibility may be limited. It is

possible that using vasodilatory agents (e.g., nitroglycerin) could have helped expand the venous network to improve visualization. Although we do not believe anatomy should differ, the current data set was obtained in patients with AF and may not be generalizable beyond those patients.

7. CONCLUSIONS

7. CONCLUSIONS

- Apnea increases GP activity, followed by vagal bursts and tonic stellate ganglion firing. RTX decreases sympathetic and GP nerve activity, abolishes apnea's electrophysiological response, and AF inducibility. Sensory neurons play a role in apnea-induced AF.

- Mapping algorithms were unable to detect pacing sites as true drivers of FC, and detected epiphenomenal RoA and FoA sites unrelated to AF induction or maintenance. Algorithm-detected RoA and FoA did not identify true AF drivers.

- It is possible to establish new cutoffs for AFL and/or AF with acceptable validity in predicting a sinus voltage of <0.5 mV. Multielectrode fast automated mapping in AFL and/or AF seems to be reliable and reproducible when classifying LVAs. These observations have clinical implications for left atrial voltage distribution and in procedures in which scar distribution is used to guide pulmonary vein isolation and/or re-isolation.

- The atrial venous anatomy is amenable to selective cannulation. Consistent anatomical patterns are present. Targeting atrial tissues through atrial veins can be used for therapeutic purposes.

CONCLUSIONES

- La apnea aumenta la actividad de los plexos ganglionares (PG), seguida de ráfagas vagales y descarga del ganglio estrellado. La RTX disminuye la actividad simpática y PG, anula la respuesta electrofisiológica de la apnea y la inducibilidad de la fibrilación auricular (FA). Las neuronas sensoriales juegan un papel en la FA inducida por apnea
- Los algoritmos de mapeo no son capces de detectar los puntos de estimulación como verdaderos impulsores de FC y detectaron sitios “epifenómenos” de actividad rotacional y focal no relacionados con la inducción o el mantenimiento de la FA. Los algoritmos de detección de actividad rotacional y no identificaron los verdaderos “drivers”.
- Es posible establecer nuevos puntos de corte para fluter auricular y / o FA con validez aceptable para predecir un voltaje sinusal < 0,5 mV. El mapeo automático rápido de múltiples electrodos en fluter auricular y / o FA parece ser confiable y reproducible al clasificar las áreas de bajo voltaje. Estas observaciones tienen implicaciones clínicas para la distribución de voltaje de la aurícula izquierda y en los procedimientos en los que se utiliza la distribución de cicatrices para guiar el aislamiento y / o el reaislamiento de las venas pulmonares.

- La anatomía venosa auricular es susceptible de canulación selectiva. Se encuentran patrones anatómicos consistentes. Abordar el tejido auricular através del sistema venoso representa una estrategia factible.

8. SUMMARY

8. SUMMARY - RESUMEN

En la presente tesis se intentan evaluar aspectos importantes a nuestro parecer referentes al manejo integral de los pacientes con fibrilación auricular (FA), desde aspectos mecanísticos hasta técnicos relativos a la hora de mapeo de la FA en el momento de la ablación y finalmente nuevas rutas terapeúticas que podrían ser utlizadas como de rescate en pacientes con arritmias refractarias al tratamiento convencional.

En primer lugar, se abordan los mecanismos precisos de la asociación entre la apnea obstructiva del sueño y la FA pues estos no están del todo claro en el momento actual, pero si se sospecha un papel destacado del sistema nervioso autónomo en base a estudios previos. Además, se sabe que la ablación por radiofrecuencia del sistema nervioso autónomo cardíaco intrínseco (plexo ganglionado (PG) cardíaco intrínseco) inhibe la FA inducida por apnea. Nuestro estudio ahonda el papel de la apnea como promotor de una respuesta compleja del sistema nervioso autónomo que incluye una marcada descarga de los plexos ganglionares, respuestas vagales bifásicas que coinciden con las oscilaciones de la frecuencia cardíaca y de la presión arterial, y descarga del ganglio estrellado que conduce a un acortamiento del período refractario efectivo auricular, así como a un aumento de la inducibilidad de la FA. Además, la ablación química de las neuronas sensoriales de PG con resiniferatoxina, un agonista neurotóxico de

TRPV1 (receptor de potencial transitorio vanilloide 1), disminuye la actividad de PG y del ganglio estrellado, eliminando la respuesta electrofisiológica de la apnea. Por lo tanto, las neuronas sensoriales situadas a nivel de los PG juegan un papel en la FA inducida por apnea y podrían potencialmente ser dirigidas terapéuticamente.

En segundo lugar, en el presente trabajo se evalua el papel de los sistemas de mapeo que se han desarrollado en los últimos años destinados a identificar sitios con activaciones focales y / o activaciones rotacionales durante la FA (Topera (Abbott, St. Paul, Minnesota) o Cartofinder (Bio- sense Webster, Irvine, California)). Se ha asumido que estos sitios son mecánicamente relevantes para el mantenimiento de la FA y, en consecuencia, se sugirieron como objetivos de ablación para eliminar la FA. Sin embargo, estos sistemas nunca se han evaluado ni comparado en un modelo simulador de actividad fibrilatoria. Para este objetivo se plantea un estudio en modelo canino en el que se realiza estimulación desde la aurícula izquierda de cara a crear electrogramas fibrilatorios, con y sin inducción de FA (n = 17). En nuestro modelo, en el contexto de conducción fibrilatoria sin inducción de FA, donde cualquier sitio de activación focal distinto del sitio de estimulación es falso y cualquier actividad rotacional es epifenómeno, los algoritmos de mapeo no pudieron localizar los sitios de estimulación como el verdadero origen de activación focal y, en su lugar, identificaron sitios de activación espurios y regionales con activación rotacional. Por lo tanto, la identificación de estos fenómenos (focal y rotacional) mediante el mapeo actual de FA los algoritmos pueden no ser del todo fiables a la hora de guiar la ablación de la FA. Desde nuestro punto de vista más estudios son necesarios antes de ser incorporados a la práctica clínica habitual.

Tan importante como el desarrollo de sistemas de mapeo capaces de distinguir el mecanismo subyacente de la FA es la validación de estos sistemas a la hora de identificar las zonas de bajo voltaje dependiendo del ritmo subyacente. La fibrosis auricular y/o tejido cicatricial sirven como un sustrato importante para la actividad focal y reentrante. Se ha sugerido el mapeo electroanatómico para delinear áreas de cicatriz. Sin embargo, quedan varios problemas sin resolver, como la correlación de voltaje entre la FA – ritmo sinusal o en flutter auricular, así como la reproducibilidad del mapeo de voltaje en FA. Es este el tercer objetivo de este trabajo. En aquellos pacientes remitidos a ablación de FA, se realizó primero un mapa en ritmo sinusal y a continuación en FA o flutter auricular (inducido). En algunos pacientes, se realizaron 2 mapas durante la FA. Los mapas se combinaron para crear uno nuevo y se analizaron los puntos de < 1 mm de diferencia. Las conclusiones que observamos es que es posible establecer nuevos puntos de corte para FA y flutter auricular con una validez aceptable para predecir un voltaje en ritmo sinusal < 0,5 mV. Además, el mapeo electroanatómico en la FA en los mapas repetidos parecen ser reproducible al clasificar las zonas de bajo voltaje. Desde nuestro punto de vista estos resultados tienen importantes implicaciones clínicas sobre todo en aquellos procedimientos en los que se utiliza la distribución de cicatrices para guiar la estrategia de ablación.

Por último, además de sistemas de mapeo es importante ahondar en estrategias terapéuticas capaces de abolir la FA o disminuir la carga de la misma. En este sentido, en los últimos años se han propuesto, entre ellos nuestro grupo, la ablación alcohólica de la vena de Marshall por ser esta estructura un detonador potencial para iniciar la FA o una estructura clave en su perpetuación. Además, presenta un

recorrido particular correspondiente al istmo mitral, estructura muy temida por los electrofisiólogos por su complejidad de ablación (en caso de arritmias perimitrales por ejemplo). En este contexto es crucial delimitar las variantes anatómicas de esta estructura y resto del sistema venoso. Además, esto podría ser de interés para futuras terapias. Con estos antecedentes como ultimo objetivo del presente trabajo de tesis se realiza una extensa caracterización del sistema circulatorio venoso de la aurícula izquierda humana y los efectos ablativos del etanol en diferentes ramas. Para este objetivo se incluyeron pacientes sometidos a infusión de etanol en el Vena de Marshall como terapia adyuvante a la ablación con catéter de FA. Se obtuvieron venogramas de oclusión con balón de la Vena de Marshall así como de otras venas auricular en 218 pacientes. Tras un minucioso análisis fuimos capaces de crear un preciso atlas definidndo la anatomía venosa. Relevantemente la gran parte de disco sistema venoso es susceptible de canulación selectiva. Además, observamos patrones anatómicos consistentes. Por lo tanto, y como ya se viene utilizando y cada vez de forma más generalizada, las venas auriculares se pueden utilizar con fines terapéuticos en determinados pacientes con arritmias no corregibles mediante ablación convencional.

En suma, en el presente trabajamo hemos intentado evaular de forma integral (mecanística, mapeo y tratamiento) aspectos relevantes para el manejo de pacientes con FA-flutter auricular que desde nuestro punto de vista son relevantes y deben ser tenidas en cuenta por todos aquellos profesionales que traten con pacientes afectos por esta cada vez más prevalente enfermedad.

9. RESUMO

9. RESUMO

A fibrilación auricular (FA) representa a arritmia clínica máis frecuente no noso medio. Os datos actuais apuntan a que a medida que a poboación envellece, a incidencia seguirá aumentando. Esta arritmia supón a primeira causa de ictus na poboación xeral, en concreto, a taxa de ictus isquémico entre os pacientes con FA non valvular é de media do 5% ao ano. Ademais, a taxa de morte entre os pacientes con FA é aproximadamente o dobre que entre os pacientes con ritmo sinusal normal, entre as causas de este incremento da mortalidade atópase fundamentalmente a súa asociación con insuficiencia cardíaca. Por outra parte, o custo total do tratamento da FA recorrente estimouse en máis de 6.500 millón ao ano. É importante destacar que non só aumenta progresivamente a prevalencia da FA, senón que tamén o fai o perfil de risco dos pacientes con FA. A FA é xeralmente unha enfermidade progresiva. A historia natural comeza a miúdo con episodios esporádicos de duración limitada denominado "FA paroxística" (moitas veces definidas como episodios que terminan espontaneamente nunha semana). Estes episodios tenden a ser máis frecuentes e de maior duración, progresando a FA persistente (que non remata espontaneamente en 7 días e pode requirir cardioversión) ou FA persistente de longa duración ("long-standing persistent") (cando a arritmia dura máis de 1 ano). Os síntomas inclúen palpitacións, falta de aire e fatiga, especialmente para pacientes sintomáticos, e ademais, ten importantes efectos adversos sobre a calidade de vida. Neste

sentido, a identificación de varios factores de risco clínico de ictus levou á publicación de varios esquemas de risco de ictus (CHA2DS2-VASc). A base electrofisiolóxica da FA require tanto un disparador para iniciar a arritmia como un substrato para mantela. Aínda que a FA pode precipitarse por patoloxías asociadas (canalopatías, taquicardia auriculoventricular, obesidad, alteracións do tiroides, etc.), os desencadenantes máis frecuentes da FA son latidos auriculares ectópicos que se orixinan nas zonas de unión de aurícula esquerda coas veas pulmonares. Estes desencadenantes poden ser causados pola actividade intrínseca dos plexos ganglionares cardíacos, que se agrupan nas proximidades da unión das veas pulmonares coa aurícula esquerda. A unión da vea pulmonar coa aurícula esquerda e unha aurícula dilatada que alberga fibrose e inflamación serven de substrato para mantener a FA. Coa persistencia da FA, prodúcese outro cambio electrofisiolóxico nas aurículas, o acurtamento do período refractario do músculo auricular, que predispón o desenvolvemento doutros desencadeantes. Este proceso ten como resultado a perpetuación da FA e unha maior predisposición á FA. De toda as posibles causas, a apnea obstrutiva do sono é un dos principais factores asociados á FA. A apnea do sono é a anomalía respiratoria clinicamente significativa máis común durante o sono. Os mecanismos precisos da susceptibilidade á FA inducida pola apnea non están del todo claros. Nos últimos anos propuxéronse numerosos mecanismos posibles responsables desta asociación, entre eles a disfunción autonómica, pero a descrición desta interacción é actualmente deficiente. Respecto ao seu tratamento, aínda que os fármacos antiarrítmicos (AAD) poden influír na actividade eléctrica do corazón, evitando a aparición e perpetuación da arritmia, describiuse que os AAD, como tratamento

único ou en combinación, poden ser efectivos a longo prazo só nun minoría de pacientes con FA. Ademais, a administración crónica é necesaria para manter un ritmo sinusal estable, que adoita estar asociado con efectos secundarios graves ou intolerables que conducen á interrupción do AAD. A ablación percutánea da FA propúxose hai moitos anos como unha alternativa á terapia de FAA a longo prazo. Nos últimos anos, os resultados obtidos en estudos aleatorizados puxeron de manifesto a superioridade a curto prazo da ablación percutánea sobre os AAD convencionais no tratamento de pacientes con FA paroxística ou crónica. En base a estes datos, estableceuse recentemente unha recomendación de clase I para o uso da ablación percutánea, cun nivel de evidencia A para pacientes con FA paroxística sintomática e aurícula esquerda normal ou levemente dilatada. De forma relevante, nos últimos anos cobrou un papel importante no contexto de pacientes con insuficiencia cardíaca, onde a ablación de FA asociouse cunha redución importante na mortalidade (vease entre outros o estudio CASTLE). En doentes con FA persistente, sobre todo aquelos coa forma "long-standing persistent" a indicación ten menos recomendación, debido en parte a que os resultados son máis decepcioantes, con incluso tasa de éxito inferiores ao 50%. Por este motivo, propuxéronse novos enfoques consistentes na creación de liñas na aurícula esquerda, illamento do apéndice auricular esquerdo, a parede posterior, vena cava superior dereita, ablación das áreas de actividade rotatoria e a ablación alcohólica da vea de Marshall (que se aborda especialmente neste traballo), entre outros.

Con estes antecedentes, estes interrogantes, nesta tese, titulada "Novos coñecementos sobre mecanismos de fibrilación auricular,

análise de electrogramas e enfoques terapéuticos alternativos" trátase de avaliar aspectos importantes na nosa opinión respecto ao manexo integral dos pacientes con FA, dende aspectos mecanicistas ata técnicos, relacionados co tempo de mapeo de FA no momento da ablación e, finalmente, novas vías terapéuticas que poderían utilizarse como rescate en pacientes con arritmias refractarias ao tratamento convencional.

En primeiro lugar, abórdanse os mecanismos precisos da asociación entre a mencionada apnea obstrutiva do sono e a FA, xa que neste substrato, os mecanismos non están totalmente claro, pero se se sospeita dun papel destacado do sistema nervioso autónomo en base a estudos previos. Ademais, sábese que a ablación por radiofrecuencia do sistema nervioso autónomo cardíaco intrínseco (plexo ganglionar cardíaco intrínseco (PG)) inhibe a FA inducida pola apnea. O noso estudo en animais afonda no papel da apnea como promotora dunha resposta complexa do sistema nervioso autónomo que inclúe unha marcada descarga dos plexos ganglionares, respostas vagales bifásicas que coinciden coas oscilacións da frecuencia cardíaca e da presión arterial, e a descarga dos ganglios estrelados que conducen a un acurtamento do período refractario efectivo auricular así como un aumento da inducibilidade da FA. Para demostralo, creouse un modelo de FA simulando unha apnea no que tamén puidemos facer rexistros neuronais. Ademais, este traballo non só explora a base mecanicista da FA seno que tamén explora novas dianas terapéuticas. En concreto, a ablación química das neuronas sensoriais PG con resiniferatoxina, un agonista neurotóxico TRPV1 (potencial de receptor transitorio vaniloide 1), diminuíu a actividade do PG e dos ganglios estrelados, eliminando a resposta electrofisiolóxica da apnea.

Polo tanto, as neuronas sensoriais situadas a nivel dos PGs xogan un papel na FA inducida pola apnea e poderían ser dirixidas terapéuticamente. Dende o noso punto de vista, este estudo abre a porta a novas investigacións dirixidas a avaliar o efecto terapéutico sobre as neuronas sensoriais.

En segundo lugar, neste traballo avaliamos o papel dos sistemas de cartografía que se desenvolveron nos últimos anos destinados a identificar sitios con activacións focales e/ou activacións rotacionais durante a FA (Topera (Abbott, St. Paul, Minnesota).) ou Cartofinder (Biosense). Webster, Irvine, California). Suponse que estes sitios son relevantes mecanicamente para o mantemento da FA e, en consecuencia, suxeríronse como obxectivos para a ablación da FA. Aínda que o aislamiento eléctrico das veas pulmonar está firmemente establecido como un tratamento eficaz para a maioría dos pacientes con FA paroxística, recoñécese que os pacientes con FA persistente teñen un substrato para a perpetuación da arritmia existente fora das veas pulmonares. Utilizáronse varios enfoques computacionais para identificar obxectivos para a ablación eficaz da FA persistente. Con este obxectivo, nun estudio independente, varias análises das características dos electrogramas, como as que aquí se comentan. Non obstante, estes sistemas nunca foron avaliados nin comparados nun modelo simulado de actividade fibrilatoria. Para iso, proponse un estudo nun modelo canino no que se realiza a estimulación dende a aurícula esquerda para crear electrogramas fibrilatorios, con e sen indución de FA (n = 17). No noso modelo, no contexto da condución fibrilatoria sen indución de FA, onde calquera sitio de activación focal que non sexa o sitio de estimulación é espurio e calquera actividade de rotación é un epifenómeno, os algoritmos de mapeo non foron capaces

de localizar os sitios de estimulación como a verdadeira orixe do foco de activación e, en cambio, identificou sitios de activación espurios e rexionais con activación rotacional. Polo tanto, a identificación destes fenómenos (focales e rotacionais) mediante os algoritmos actuais de mapeo de FA pode non ser totalmente fiable para guiar a ablación. Dende o noso punto de vista, son necesarios máis estudos antes de incorporarse á práctica clínica habitual.

Tan importante como o desenvolvemento de sistemas de cartografía capaces de distinguir o mecanismo subxacente da FA é a validación destes sistemas na identificación de zonas de baixo voltaxe dependendo do ritmo subxacente. A fibrose auricular e/ou o texido cicatricial serven como un substrato importante para a actividade focal e de reentrada. Propuxéronse cartografías electroanatómicas para delimitar as áreas de baixo voltaxe. Esta cartografía sería a base de estratexias de ablación que teñan como obxectivo abordar as zonas de baixo voltaxe. O estudo STABLE-SR (ablación do substrato electrofisiológico auricular esquerdo durante o ritmo sinusal) comparou a eficacia da ablación da FA non paroxística entre o illamento das venas pulmonares máis a modificación do substrato do ritmo sinusal e un enfoque de ablación "STEPWISE". Aos 18 meses, o 74% dos pacientes do grupo STABLE-SR e o 71% do grupo STEPWISE (hazard ratio de 0,78; IC 95%, 0,47-1,29; p = 0,325) lograron éxito según o análise por intención de tratar. Non obstante, o grupo "STABLE-SR" asociouse cun tempo de procedemento máis curto (186,8±52,7 fronte a 210,5±48,0 minutos; p<0,001), menos tempo de fluoroscopia post-illamento eléctrico nas veas pulmonares (11,0±7,8 fronte a 13,7±8,9 minutos, p=0,006) e menor tempo de radiofrecuencia (60,1±25,1 fronte a 75,0±24,3 minutos, p<0,001) en

comparación co grupo "STEPWISE". No obstante, quedan varios problemas sen resolver coa modificación do substrato guiada por zonas de baixo voltaxe. Aínda que algúns estudos demostraron que os voltaxe son máis altas durante o ritmo sinusal que durante a FA, non está estudiado se o voltaxe e dependente do ritmo de base, como por exemplo en fluter auricular. Ademais, non está claro se os puntos de corte deben axustarse en función do tipo de catéter (tamaño dos electrodos e espazamento dos polos) e/ou da área anatómica que se está mapeando na aurícula esquerda. A maioría dos estudos utilizaron puntos de corte en ritmo sinusal medido con catéter de ablación (3,5 mm), pero descoñécense os limites correspondentes en FA. Finalmente, non hai datos sobre a reproducibilidade do mapeo das zona de baixo voltaxe en FA. Estes foron os obxectivos deste traballo. Para iso deseñouse un estudo no que, naqueles pacientes derivados para ablación de FA, realizouse primeiro un mapa en ritmo sinusal e despois en FA ou flutter auricular (inducido). Se o paciente estaba en FA realizouse cardioversión para deste xeito facer o primeiro mapa de ritmo sinusal, evitando así o desprazamento dos mapas electroanatómicos que poidesen artefactar as medicións. Nalgúns pacientes realizáronse dos mapas durante a FA con un intervalo de tempo de 10 minutos para comparar as diferencias nos dous mapas electroanatómicos. Finalmente, combináronse os mapas (ritmo sinusal co de FA, fluter con FA en os dous mapas de FA entre sí) para crear un novo mapa no que poder analizarse os puntos con unha diferenza de menos de 1 mm. As conclusións que observamos é que é posible establecer novos puntos de corte para a FA e o flutter auricular cunha validez aceptable para predicir voltaxe en ritmo sinusal < 0,5 mV. Ademais, a cartografía electroanatómica en FA nos mapas repetidos

parecen ser reproducible na clasificación das zonas de baixo voltaxe. Neste estudo, tamén se realizou unha caracterización detallada das diferentes zonas da aurícula esquerda que ademais quedou plasmada nunha aplicación online gratuita (https://aurora.shinyapps.io/mashaf/). Desde o noso punto de vista, estes resultados teñen importantes implicacións clínicas, especialmente naqueles procedementos nos que se utiliza a distribución das zonas de baixo voltaxe para guiar a estratexia de ablación (a denominada estratexia "STABLE-SR").

Por último, ademais dos sistemas de cartografía, é importante afondar en estratexias terapéuticas capaces de abolir a FA ou reducir a súa carga. Neste sentido, nos últimos anos propúxose a ablación alcohólica da vea de Marshall, xa que esta estrutura é un potencial desencadéante para iniciar FA ou unha estrutura clave na súa perpetuación. Ademais, presenta un curso particular correspondente ao istmo mitral, unha estrutura moi temida polos electrofisiólogos pola súa complexidade de ablación (no caso das arritmias perimitrais, por exemplo). Neste contexto, é fundamental definir as variantes anatómicas desta estrutura e do resto do sistema venoso. O ensaio VENUS, un estudo iniciado polo noso grupo no Houston Methodist Hospital, mostrou que, entre os pacientes con FA persistente, a adición de infusión de etanol da vea Marshall á ablación convencional con catéter, en comparación coa estratexia convencional, aumentou a probabilidade de permanecer libres de FA ou taquicardia auricular aos 12 meses. Dos 12 criterios de valoración secundarios do estudo, 9 non foron significativamente diferentes, pero a carga de FA (carga "cero") logrouse no 78,3% fronte ao 67,9% dos pacientes; diferenza de 10,4% [IC 95%, 2,9%-17,9%]; P = 0,01), ausencia de FA tras múltiples procedementos (65,2% vs 53,8%; diferencia de 11,4%

[intervalo de confianza (IC) do 95%, 0,6%-22,2%]; p=0,04) e éxito do bloqueo perimitral (80,6% vs. 51,3%; diferencia de 29,3% [IC 95%, 19,3%-39,3%]; p <0,001) melloraron significativamente nos pacientes tratados con ablación alcohólica da vea de Marshall. Importante, se ben este procedemento supón un incremento do procedemento de ablación (co una media de 44 minutos), non se asociou a complicacións maiores derivadas da técnica, si a un lixeiro incremento na taxa de pericarditis e disección venosas. Para conseguir esta adecuada ablación de alcohol na vea de Marshall, é de suma importancia describir as variacións anatómicas da drenaxe venosa de aurícula esquerda como marco para as terapias venosas endovasculares dirixidas a aurícula. As descricións anatómicas previas da vea de Marshall e outras veas implicaron exemplares de necropsia patolóxica, mentres que faltan datos humanos. Por iso, este constitúe un dos obxectivos do presente estudo: catalogar o sistema de circulación venosa auricular esquerda humana e os efectos ablativos do etanol en diferentes ramas. Para este fin, incluíronse pacientes sometidos a infusión de etanol na vea Marshall como terapia adyuvante á ablación con catéter de FA. Obtivéronse venogramas de oclusión con balón da vea de Marshall e doutras veas auriculares en 218 pacientes. Despois dunha análise exhaustiva puidemos crear un atlas preciso que define a anatomía venosa. De forma relevante, gran parte do sistema venoso é susceptible de canulación selectiva. Ademais, observamos patróns anatómicos consistentes. Por outra banda, o valor da canulación e dos venogramas in vivo, a diferenza dos estudos post mortem, é que puidemos mostrar as abundantes interconexións entre as diferentes ramas venosas. A inxección de contraste por exemplo nas veas septais normalmente levou á

opacificación das veas veciñas a través dos capilares, incluíndo a vea inferior, as veas posteriores e as veas do teito e mesmo de volta á vea de Marshall. A inxección de contraste na vea de Marshall podería opacificar as veas septais e inferiores, pero máis comunmente a vea de Marshall comunicaba coas veas do apéndice auricular esquerdo e as veas do teito. As veas do teito só se podían demostrar a través do fluxo colateral, xa sexa desde a vea de Marshall, as veas do apéndice auricular ou as veas anteriores. A comunicación entre as veas auriculares e pulmonares foi inesperada, pero probablemente representa a drenaxe venosa do vaso vasorum da parede das veas pulmonares que se conectan ás veas da aurícula esquerda. Finalmente, estas descargas da anatomía venosa, nunca realizadas con anterioridade, mostraron naqueles pacientes nos que se realizaba a ablación alcohólica da vea de Marshall, as áreas de ablación auricular conseguida en función da anatomía venosa. Por iso, e como xa se está a utilizar cada vez máis, as veas auriculares poden utilizarse con fins terapéuticos en determinados pacientes con arritmias que non se poden corrixir mediante a ablación convencional, é fundamental unha correcta compresión do sistema venoso. Ademais, aínda que non é o obxectivo deste traballo de tese nese atlas se detalla tamén a anatomía venosa ventricular que estase erixindo como unha alternativa de rescate nas ablacións de taquicardia ventriculares refractarias ao tratamento convencional.

En resumo, neste estudo intentouse avaliar de xeito exhaustivo (mecanísticos, de cartografía e de tratamento) aspectos relevantes para o manexo dos pacientes con aleteo auricular e FA que, dende o noso punto de vista, son relevantes e deben ser tidos en conta por todos eses profesionais que se ocupan de pacientes afectados por esta

enfermidade cada vez máis prevalente. O noso traballo non remata neste traballo de tese, senón que é o inicio de novas vías de investigación. Cos resultados do primeiro obxectivo propúxose un estudo no contexto da apnea crónica que, como é sabido, produce unha remodelación cardíaca que favorece o desenvolvemento de áreas de fibrose. Ademais, preténdese detallar a actividade eléctrica de cada un dos plexos ganglionares para concretar con exactitude o papel de cada un deles. Para o segundo obxectivo, propúxose probar o papel destes sistemas de cartografía en función da presenza de zonas de baixo voltaxe, xa que o estudo que aquí se presenta no modelo canino ten a limitación de ser aurículas con voltaxes preservados. En relación co terceiro obxectivo deste traballo de tese, propuxémonos validar as diferenzas das áreas de voltaxe con novos eléctrodos de cartografía máis precisos. Ademais, aínda que no momento de realizar este traballo non contabamos coa tecnoloxía necesaria para definir estas zonas de baixa voltaxe en resonancia magnética, a aparición de novos equipos está a permitirnos validar os nosos achados en resonancia magnética cardíaca. Por último, en relación co último obxectivo, estamos a traballar en novas estratexias que nos axuden a mapear o sistema venoso. Ademais, pretendemos mellorar os criterios de selección dos pacientes que poidan beneficiarse da ablación alcohólica na vea de Marshall, podendo así evitar o procedemento naqueles casos nos que non se espera ningún beneficio desta técnica sobre a estratexia convencional. Para resolver estes puntos de investigación previamente mencionados, creouse un grupo de traballo entre o Hospital Clínico Universitario de Santiago de Compostela/Instituto de Investigación Sanitaria (IDIS) e o *Houston Methodist Hospital*, moi activo na actualidade que pretende afondar nestas cuestións nos vindeiros anos.

8. REFERENCES

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11. APPENDIX

HOUSTON Methodist LEADING MEDICINE

NOTIFICATION OF IACUC COMMITTEE DECISION

From: David R. Beers, PhD.
HMRI IACUC Chair

To: Miguel Valderrabano

CC: Sufen Wang

Re: IS00006217 Percutaneous Neuromodulation in Atrial Fibrillation

The above numbered protocol was reviewed by the Institutional Animal Care and Use Committee. The protocol has been **APPROVED** for the following period:

4/19/2021 through 4/18/2024

Renewal of this study is required on an annual basis.

Please note that prior to starting any experiments it is your responsibility to give a copy of this document to all research personnel involved in the project and to discuss the project with each employee. Any changes to the protocol must be approved by the IACUC before the changes can take place.

Sincerely,

David R. Beers, PhD.

If you are logging into MORTI from outside the Houston Methodist system, the above link may not work. Please log into MORTI directly at http://morti.tmhs.org and then navigate to the above referenced project.

Houston Methodist Research Institute
6670 Bertner
Houston, TX 77030

HOUSTON Methodist LEADING MEDICINE

NOTIFICATION OF IACUC COMMITTEE DECISION

From: David R. Beers, PhD.
HMRI IACUC Chair

To: Miguel Valderrabano

CC: Amish Dave

Sufen Wang

Re: IS00005574 Mechanistic Insights Through Signal Processing Algorithms in a Canine Model of Atrial Fibrillation

The above numbered protocol was reviewed by the Institutional Animal Care and Use Committee. The protocol has been **APPROVED** for the following period:

11/13/2019 through 11/12/2022

Renewal of this study is required on an annual basis.

Please note that prior to starting any experiments it is your responsibility to give a copy of this document to all research personnel involved in the project and to discuss the project with each employee. Any changes to the protocol must be approved by the IACUC before the changes can take place.

Sincerely,

David R. Beers, PhD.

If you are logging into MORTI from outside the Houston Methodist system, the above link may not work. Please log into MORTI directly at http://morti.tmhs.org and then navigate to the above referenced project.

Houston Methodist Research Institute
6670 Bertner
Houston, TX 77030

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CONSELLERÍA DE SANIDADE
Secretaría Xeral Técnica

Secretaría Técnica
Comité Autonómico de Ética da Investigación de Galicia
Secretaría Xeral. Consellería de Sanidade
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galicia

DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN DE SANTIAGO-LUGO

Ana Estany Gestal, Secretaria del Comité de Ética de la Investigación de Santiago-Lugo,

CERTIFICA:

Que este Comité evaluó en su reunión del día21 de mayo de 2019 el estudio**:**

Título: Incidencia de presencia de áreas de bajo voltaje en pacientes con fibrilación auricular remitidos para ablación de fibrilación auricular y relevancia clínica
Versión: 2.0
Promotor/a*:* Moisés Rodríguez Mañero
Investigador/a: Moisés Rodríguez Mañero
Código de Registro:2019/216

Y que este Comité, tomando en consideración la pertinencia del estudio, el conocimiento disponible, los requisitos legales aplicables y los Procedimientos Normalizados de Trabajo del Comité, emite un dictamen **FAVORABLE** para la realización del citado estudio.

XUNTA DE GALICIA
CONSELLERÍA DE SANIDADE
Secretaría Xeral Técnica

galicia

Y HACE CONSTAR QUE:

1.- El Comité Territorial de Ética de la Investigación de Santiago-Lugo cumple tanto en su composición como en sus PNTs los requisitos legales vigentes.

2.- La composición actual del Comité Territorial de Ética de la Investigación de Santiago-Lugo es:

Presidente
Juan Manuel Vázquez Lago. Médico especialista en Medicina Preventiva y Salud Pública. Área de Gestión Integrada de Santiago**.**

Vicepresidenta
Pilar Rodríguez Ledo. Médico especialista en Medicina Familiar y Comunitaria. Área de Gestión Integrada de Lugo.

Secretaria
Ana Estany Gestal. Licenciada en Farmacia. Fundación Instituto de Investigación Sanitaria de Santiago de Compostela.

Secretario Suplente
Lorenzo Armenteros del Olmo. Médico especialista en Medicina Familiar y Comunitaria. Área de Gestión Integrada de Lugo.

Vocales
María José Alfaro Águila-Real. Paciente experta. Lugo
Francisco Campos Pérez. Biólogo. Fundación Instituto de Investigación Sanitaria de Santiago de Compostela.
Rosana Castelo Domínguez. Farmacéutica de Atención Primaria. Área de Gestión Integrada de Santiago.
Ricardo García Martínez. Licenciado en Derecho. Área de Gestión Integrada de Lugo.
Jaime Gulín Dávila. Farmacéutico especialista en Farmacia Hospitalaria. Área de Gestión Integrada de Lugo.
Cristina Márquez Riveras. Enfermera. Dirección Xeral de Saúde Pública.
Guillermo José Prada Ramallal Médico especialista en Farmacología Clínica. Área de Gestión Integrada de Santiago. Fundación Instituto de Investigación Sanitaria de Santiago de Compostela.
Jesús Prego Domínguez. Enfermero. Área de Gestión Integrada de Santiago.
María Mercedes Rodicio García. Médico especialista en Pediatría. Área de Gestión Integrada de Lugo.
Carlos Rodríguez Moreno. Médico especialista en Farmacología Clínica. Área de Gestión Integrada de Santiago.
Sandra Vidal Martínez. Enfermera. Área de Gestión Integrada de Santiago

Para que conste donde proceda, y a petición de quien proceda, en Santiago de Compostela,

La Secretaria del Comité Territorial de Ética de la Investigación de Santiago Lugo,

ESTANY GESTAL ANA - 46896853Z

Xacobeo 2021

HOUSTON Methodist LEADING MEDICINE

Full AAHRPP Accreditation

APPROVAL

June 14, 2022

Dear Dr. Miguel Valderrabano:

Type of Review:	Continuing Review
Title:	Catheter Ablation Registry
Investigator:	Miguel Valderrabano
IRB ID:	CR00001379
Funding:	None
Grant Title:	
Grant ID:	None
IND, IDE, or HDE:	None
Documents Reviewed:	None

On **06/13/2022**, the IRB reviewed and approved the above referenced documents and determined that the application qualifies for Expedited status according to 45 CFR 46.110.

Continuing review is no longer required per: 2018 Requirements 45 CFR 46(f). However, an update will be required annually to assure that the study is still active and in compliance on **06/12/2023**.

Expedited Category	(5) Research involving materials (data, documents, records, or specimens) that have been collected for any purpose, or will be collected solely for non-research purposes.
Waiver of Consent (not FDA)	Waiver of Informed Consent (45 CFR 46.116)
Full Waiver of HIPAA Authorization	Waiver of HIPAA Authorization (45 CFR 164.512(i)(1)(i).) The IRB has determined all the specified criteria for a waiver or an alteration. Documentation of approved elements may be required prior to data abstraction.

You will receive an email notice from the IRB Office asking for the current status of your study. If no response wtihin 30 days of the anniversary date, the IRB Office will administratively terminate the protocol.

As the Principal Investigator, you are responsible for oversight of the conduct of this study and must assure compliance with the approved protocol and all applicable

regulations and HMRI Policies and Procedures related to Human Subject Research and Research Protections Good Clinical Practice procedures which can be found by navigating to the MORTI IRB Homepage and HM Policy Tech.

Except for changes made to assure the immediate safety of a research participant, no modifications to this protocol or informed consent may be made without prior IRB review and approval.

The IRB requires prompt reporting of unanticipated problems involving risks to subjects or others; unanticipated adverse device effects; protocol violations that may affect he subject's rights, safety or well-being and / or the completeness, accuracy and reliability of the study data; suspension of enrollment or termination of the study.

If the study is expected to last beyond the approval period, you must request and receive re-approval prior to the expiration date noted above. A report to the IRB is due prior to expiration or at the time the study closes, whichever is earlier. It is recommended that you submit status reports at least 4 weeks prior to your expiration date to avoid lapses in approval.

Sincerely,

HMRI IRB

If you have any questions or comments, please contact the HMRI IRB Offices IRB@houstonmethodist.org or by Phone at: 346-356-1400.

The HMRI IRB is organized, operates, and is registered with the United States Office for Human Research Protections according to the regulations codified in the United States Code of Federal Regulations at 45 CFR 46 and 21 CFR 56. The HMRI IRB operates under the HM Federal Wide Assurance No. FWA00000438, as well as those of hospitals and institutions affiliated with the Institute.

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En la presente tesis se intentan evaluar aspectos importantes referentes al manejo integral de los pacientes con fibrilación auricular, desde aspectos mecanísticos (en concreto el papel del la apnea del sueño en el desarrollo y mantenimiento de la FA) hasta técnicos, relativos a la hora de mapeo de la FA durante el procedimiento de ablación (rentabilidad de los algoritmos automáticos de detección de actividad rotacional y focal además del análisis detallado de los mapas de voltaje en función del ritmo subyacente).

Finalmente se presenta el primer atlas del sistema venoso auricular imprescindible con "estrategias de rescate" tales como la ablación alcohólica de la fibrilación auricular.