REVIEW ARTICLE

Translational Approach for Percutaneous Interventions for the Treatment of Cardiac Arrhythmias

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Abstract

New translational concepts on cellular and tissue substrate of cardiac arrhythmias have been responsible for the development of non-pharmacological interventions, with important achievements compared to the conventional approach with antiarrhythmic drugs. In addition, the increasing knowledge of anatomical and electrophysiological studies, sophisticated mapping methods, special catheters, and controlled clinical trials have favored the progression of ablation of tachyarrhythmias, particularly of ventricular tachyarrhythmias and atrial fibrillation.

Introduction

Cardiac arrhythmias and conduction disturbances occur in any region of the heart and are caused by critical changes in the electrical activity of myocytes.[1] Electrophysiological studies have been developed in the last fifty years, with translational clinical and experimental models, and favored the development of non-pharmacological interventions for the treatment of arrhythmias. Sophisticated mapping methods, special catheters, and new energy sources have introduced new techniques for ablation of ventricular tachyarrhythmias and atrial fibrillation (AF).

In the 1960s, since the introduction of direct current defibrillators by Lown, other contributions have provided support for the continued development of techniques for the percutaneous treatment of arrhythmias, including the recording of His bundle activity by Scherlag et al.,[2] the electrical stimulation of the heart by Wellens,[3] anatomical surgical ablation of the accessory tracts by Cobb et al.,[4] and, finally, the catheter-induced ablation with initial direct current by Scheinman et al.,[5]

During this same period, the Cardiac Arrhythmia Suppression Trial[6] demonstrated that flecainide and encainide, two potent antiarrhythmic drugs, suppressed ventricular arrhythmias but, paradoxically, increased death in patients, thereby changing completely the paradigm of antiarrhythmic drug therapy. Additionally, no effective drugs for atrial arrhythmias acting on specific channels such as the potassium channel, were available. Then, the introduction in the 1990s of radiofrequency-induced ablation techniques in the United States, Europe[7] and in Brazil[8] followed pathophysiological and translational concepts.

Biophysical Concepts

Catheter interventions to destroy the arrhythmogenic tissues have mostly used heating with direct current, microwave, ultrasound, laser, and radiofrequency. The most used form of energy has been radiofrequency, a form of alternating electric current of 500–1000 kHz. When unipolar energy is applied between the distal pole of the catheter and a surface, it affects the cell membrane, cytoskeleton, nucleus, and cellular metabolism, including the microvascular inflammatory response. After reaching a temperature of 50°C, well-defined and irreversible heating lesions develop because of the sarcolemma lesion and intracellular calcium overload. Temperature monitoring

Keywords

Arrhythmias, Cardiac/physiopathology; Catheter Ablation; Anti-Arrhythmia Agents; Cryosurgery/methods; Translational Medical Research; Atrioventricular Node; Echocardiography/methods; Tomography, X-Ray Computed/methods.

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prevents excessive heating at the catheter tip (which can also be avoided with the use of irrigated catheters), formation of blood clots, and increase in impedance.

Another thermal mechanism is cryoablation, in which pressurized liquid nitrogen is used to freeze and crystallize the structures in contact with a balloon catheter, reversibly (up to -40°C) or irreversibly (<-40°C) compromising the cardiac structures that are in direct contact with the freezing source. More recently, pulse field ablation, a unique investigational tissue-selective nonthermal cardiac ablation modality that creates nanopores with tissue electroporation, may change the future of ablation in the coming years.

Anatomical and Electrophysiological Concepts

Automatism

Myocyte depolarization is dependent on intracellular and extracellular ion concentrations and mediated mainly by the influx/efflux of sodium and potassium. This ion movement is controlled by multiple channels (Figure 1A) and normally, automatically depolarized. These automatic cells act in heart rate control, from structures hierarchically arranged preferably in the sinus node, atrioventricular node (AVN) and in the His-Purkinje (HP) system.

Through automatism or triggered activity (early or late depolarizations), there is an increased depolarization of cells, with faster rhythms in areas like sinus node, AV node and HP system, in the right heart (junction with the superior vena cava, terminal ridge, and right ventricular outflow tract [RVOT]) or in the left heart (pulmonary veins, left vena cava, left atrial appendage, left ventricular outflow tract [LVOT], and papillary muscles) (Figure 1B).

The ionic basis of late post-depolarization is related to the overload of calcium in the myoplasma and sarcoplasmic reticulum, and to the secondary release of the calcium ion after repolarization, especially in the presence of catecholamines or cyclic AMP. Generally, these are focal rhythms, and their early activation allows establishing the source focus and mapping for the arrhythmia ablation, if percutaneously accessible.

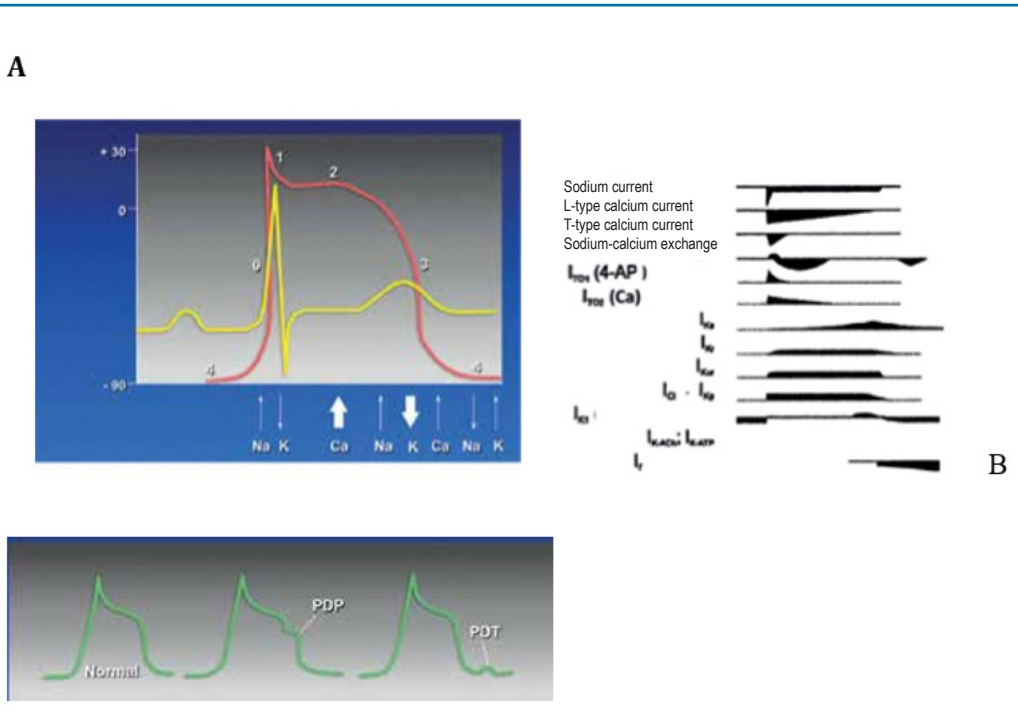

Figure 1 – (A) Ionic currents determining the action potential: inward currents are directed from outside to inside the cell; and outward currents come from within the cell and are directed to the extracellular environment; (B) Automatic cells, with oscillations in their action potential by early and late ionic fluxes PDP: early post-depolarizations, PDT: late post-depolarizations.

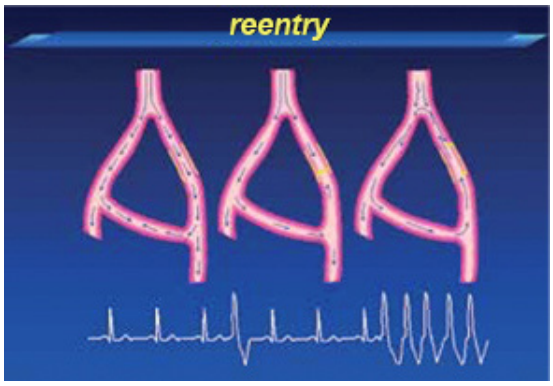

Figure 2 – (A) Tissue with a structural or functional change in conduction without impairing passage in the stimulus under normal conditions. (B) In the presence of an ectopia, there is a bidirectional block. (C) During a precocious ectopia, there is a unidirectional anterograde block and, due to the delayed conduction, there is time to enable retrograde activation and triggering of arrhythmia.

Reentry

In the presence of conduction abnormalities, the activated electric current flows through tissues with different conduction and refractory properties. Thus, it is possible that a stimulus conduction is perpetuated by its passage through an adjacent tissue that functions as a conduction circuit with heterogeneous refractory periods, unlike in normal tissue. This phenomenon (Figure 2) of reentry can be reproduced in the laboratory as nodal, atrioventricular (AV), and ventricular monomorphic tachyarrhythmias, which may be related to normal or pathological tissues, the latter being represented by scars in the atria and ventricles, due to ischemia or degenerative processes.

The most frequent sustained arrhythmias with reentrant mechanisms were the first to be treated with catheter ablation, notably nodal, AV and ventricular reentrant tachycardia, which will be described below. Subsequently, automatic arrhythmias were also managed using this technique.

Atrioventricular Nodal Reentrant Tachycardias (AVNRT)

The AV node is the natural filter to slow the conduction of the impulse through the atrioventricular junction, ensuring the physiological contractile sequence and protection of the ventricle from fast atrial rhythms such as AF. This slower conduction velocity is determined by the small diameters of the nodal myocytes, the interposition of connective tissue, and, mostly, by the failure of continuity determined by the connexins. Thus, optical, histological mapping, and immunological assays, along with action potential recording, can detect the coexistence of rapid (transitional tissue) and slow (lower nodal extensions) nodal pathways, marked by high and low expression of the connexins Cx40 and Cx43, respectively. In 20% of individuals, slower pathways (Figure 3) with a short refractory period are found in the vicinity of the AVN and may, in special circumstances, trigger AVNRT.

AVN reentry can occur because of functional differences in groups of cells that compose the AV node. There are some evidences of the presence of two major slow pathways participating in AVNRT: right inferior extensions (RIE) and left inferior extensions (LIE), both of which connecting the right atrium to the left atrium through the proximal coronary sinus (Figure 4). Both RIE and LIE can participate in AVNRT and serve as either the antegrade or retrograde limb of the reentrant circuit.

The positioning of catheters and ablation of the slow pathway of patients with AVNRT is generally simple, with a success rate of 95%; it consists of the radioscopic topographic localization (Figure 3D) and electrophysiological evaluation of the potential of the slow pathway for application of radiofrequency energy (30-50 W, 1 min, temperature 40-50°C). Complications are related to poor vascular access (1% of deep venous thrombosis) and proximity of the AVN (1% of total AV block), with a one-year recurrence of 5%.

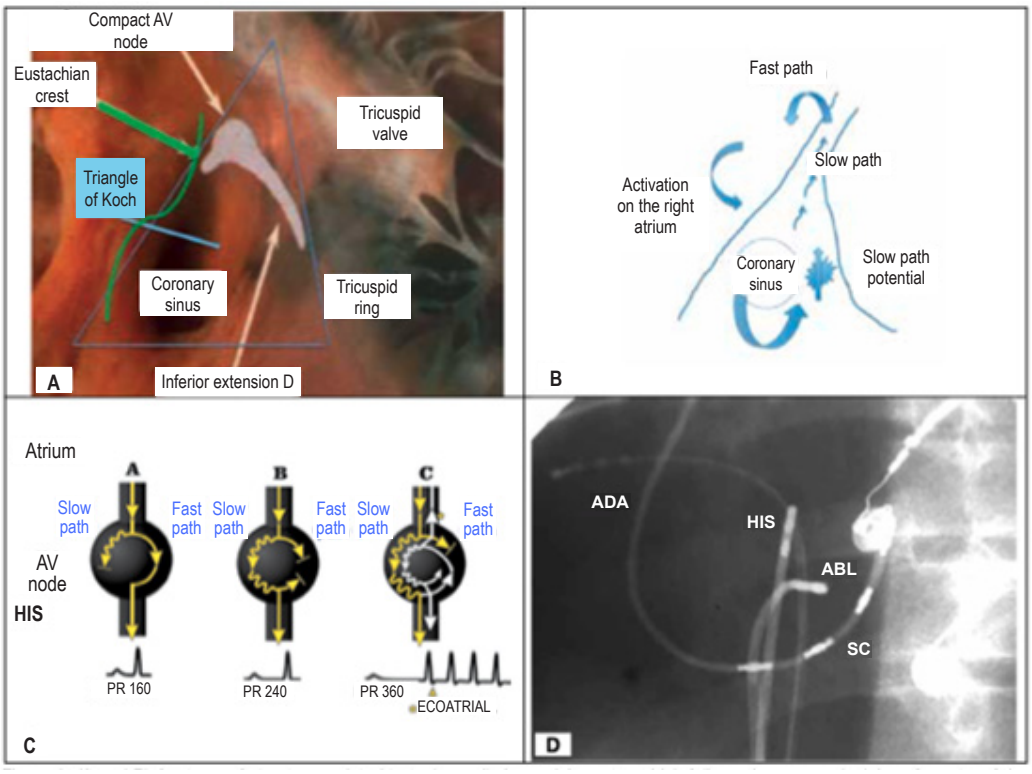

Figure 3 – (A and B) Anatomy of structures related to atrioventricular nodal reentry tachycardia, which follows the same principles of reentry of the electrocardiographic (C) identification of saltatory conduction through the atrioventricular node that precedes tachycardia. (D) Radiographic images of catheters used in the left anterior oblique projection and their positions.
AV: atrioventricular, HRA: high right atrium, H: His, CS: coronary sinus, ABL: ablation catheter. RIE: Right inferior extension, LIE: Left inferior extension. Modified from Inoue.[10]

Atrioventricular Reentrant Tachycardias (AVRT)

The accessory pathway consists of bundles of myocardial cells inserted freely along the mitral annulus (60%), tricuspid (15%), or the right or left septal side of these valves (25%). Rarely, the accessory pathways emerge directly from the atria (atriofascicular), AVN (nodofascicular, nodoventricular), or the His bundle (His-fascicular). They may be multiple (13% of the cases) and, in the presence of Ebstein's disease, accessory pathways are 4-fold more frequent (52%). They may also present decremental conduction such as in the Mahaim fibers, with anterograde conduction, behaving functionally as a duplicated His bundle in the lateral region of the tricuspid ring and inserted distally in the right HP system, near the apex of the right ventricle. Finally, there are also postero-septal fibers with exclusively retrograde decremental conduction, generating Coumel-type tachycardia that, because of its incessantness, can lead to the development of tachycardiomyopathy.

Radiological and electrophysiological techniques seek to define the insertion of pathways along the AV ring, with similar success and clinical outcome of ablation of accessory pathways to those of AVNRTs. There is a greater technical difficulty in the epicardial ablation of pathways, multiple pathways, or when the accessory pathways are associated with complex heart diseases.

Some muscle fibers that involve the coronary sinus and its tributary veins can function as a connecting muscle bridge between atria and ventricles. When there is a need for ablation in this location of limited blood flow, irrigation at the catheter tip is performed; in this way, the lesion will be formed without limiting the increase of impedance and temperature. The proximity of the arteries (mainly the posterior descending artery) with the branches of the venous sinus requires anatomical definition and special care during ablation.

Depending on the anatomical peculiarities of anomalous bundles, sheaths can be used to stabilize the mapping of larger rings such as the tricuspid, for the transeptal access in the left routes and pericardial access for epicardial routes.

Ventricular Reentrant Tachycardias

The scar substrate of sustained ventricular tachycardias (VTs) after myocardial infarction has provided a reproducible reentry model, intensely studied by contemporary electrophysiology. The scar region is composed not only of a dense scar but also of surrounding tissues with myocardial fibrils inserted into the scar, characterized by alterations in CX43, decreased intercellular coupling, slow conduction, and predisposition to reentrant VT. Adaptive changes in the sympathetic and parasympathetic nervous system with increased efferences and decreased neuronal afference of the infarcted area result in greater heterogeneity and multiplicity of the arrhythmogenic substrate circuits, identified by fractional potentials, late potentials, and abnormal localized ventricular activity (Figure 4).

Structural remodeling of the myocardium is associated with the appearance of myofibroblasts, fundamental cells, and the translational biological basis of the VT substrate. Recent animal studies showed that after 6 weeks of experimental infarction, the isthmus of the VT has a very high density of myofibroblasts (an increase of 5 times) and increased vascularity (an increase of 1.7 times) in the border of scars, due to the increase in cellular recruitment or by pro-angiogenic factors of these same myofibroblastic cells. There are also cell bridges between the myofibroblasts and the remaining cardiomyocytes, with organized heterogeneity at the edges of the scar and isolated by collagen septa, with altered tissue heterogeneity and resistance due to the non-uniform heterocellular coupling between the cardiomyocytes.[11] These experimental findings were based on the relationship between electrical heterogeneity and conduction abnormalities and the inducibility of ventricular arrhythmias.

The presence of a stable substrate, characterized by a scar with viable myocardial tissue in its interior, establishes the conditions for the reentry mechanism and, with it, the reproduction of human monomorphic ventricular tachycardia (VT) in the laboratory.

The possibility of mapping of sustained VTs (SVTs) by using electrophysiological techniques has defined locations, with a good correlation with surface electrocardiogram, offering the possibility of non-invasive diagnosis of their origin (Figure 5).

The substrate of SVTs consists of regions of abnormal myocardium where the ventricular muscle is replaced by fibrous tissue, creating regions of slow conduction and the occurrence of reentry, characterized regionally by low local electrical activity and segmental contraction deficit. The response of these regions to programmed electrical stimulation, allowing the reproduction in laboratory of clinical SVT in patients with previous myocardial infarction, has been one of the most important translational milestones for the understanding of the arrhythmogenic mechanisms of modern electrophysiology. Subsequently, the advent of radiofrequency as an energy source enhanced the accuracy of cardiac electrophysiological mapping techniques, increasing the knowledge of important pathophysiologic bases of arrhythmogenesis.

In these patients with heart disease and monomorphic SVTs, the more frequent presence of reentrant macro circuits facilitates the investigation of critical locations for the maintenance of these arrhythmias in the endocardium, epicardium, or intramural region of the ventricles. These circuits are usually made of scars with residual surviving myocytes, constituting true conducting channels (Figure 6). These channels, called isthmuses, are complex structures that form non-excitable anatomical (scar, valve annulus) or functional (blockage of conduction during tachycardia) barriers, that slow the conduction of the electric impulse, thereby preventing wave front penetration and perpetuation of SVTs.

In addition to characterization of the circuits, electrophysiological techniques have enabled the localization and non-pharmacological treatment of SVTs, which has advanced with electroanatomic mapping techniques, towards a more accurate localization of the arrhythmogenic circuits (Figure 7).

The propagation of the electrical impulse to ventricular endocardium is dependent of the high conduction velocity of the Purkinje system. When tachycardia originates from the epicardium, there is slow conduction, longer duration of the QRS complex , absence of initial R and presence of pseudo-delta waves with intrinsicoid deflection in the leads related to the origin of the VT (Figure 8).

It has been emphasized that epicardial ventricular tachycardia is more frequent in cardiomyopathies, mainly in chagasic cardiopathy, accounting for >50% of the cases.

Figure 4 – Surface lead (V6) and ablation catheter electrogram.Fragmented and late potentials in sinus rhythm of the arrythmogenic substrate in patients with sustained ventricular tachycardia, who underwent radiofrequency ablation.

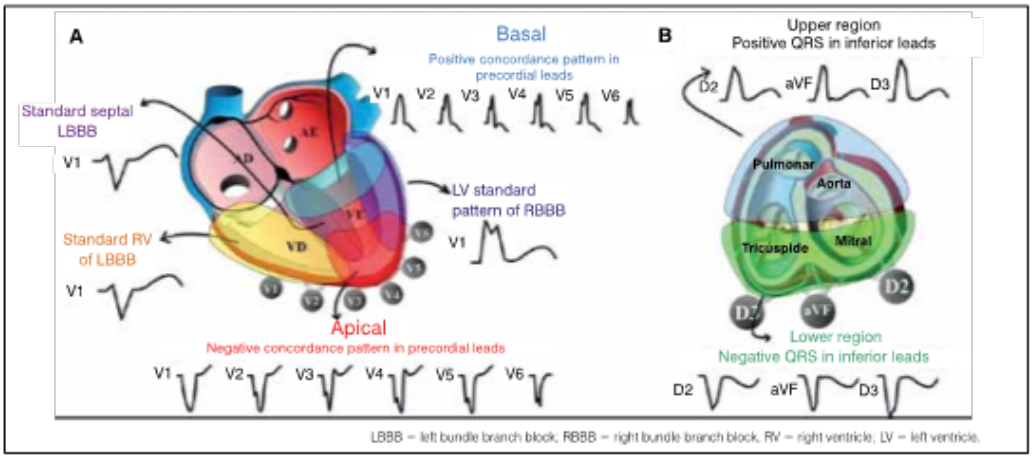

Figure 5 – (A) Sagittal and (B) transverse section of the heart. (A) Complete left bundle-branch block (LBBB) ventricular tachycardia suggests a RV (right ventricular) origin, comprising Right ventricular outflow tract tachycardia (RVOT) .The V3 and V4 leads can characterize the basal and apical left ventricular (LV) regions and, by the vectorial result in the electrocardigram, differentiate the basal (predominant R waves) from the apical (prdominant S waves) origins.

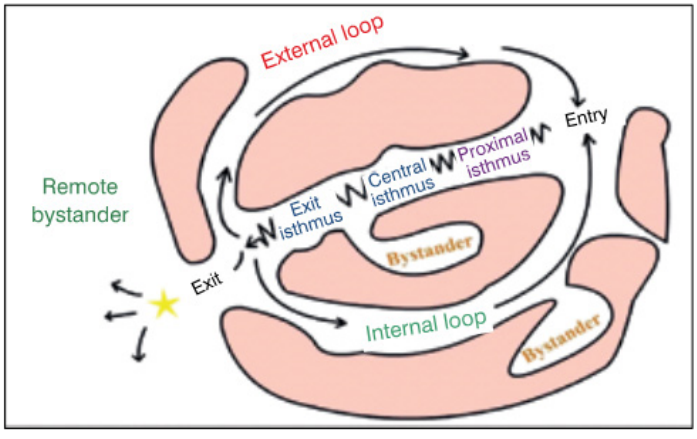

Figure 6 – Reentry models in a scheme represented by pink areas of non-conducting fibrosis, surrounded by viable muscle that allows the passage of the stimulus in the form of "8". "Bystander" areas do not actively participate in the circuit but can communicate with the external stimulus loop that will enter a central channel called "isthmus", a channel of viable tissue, surrounded by barriers of unexcitable tissue, wich aids in the stability and perpetuation of arrhythmia. This mechanism forms the basis for "reentry", a continuous and circular process of wavefront propagation, wich returns and reactivates its place of origin.

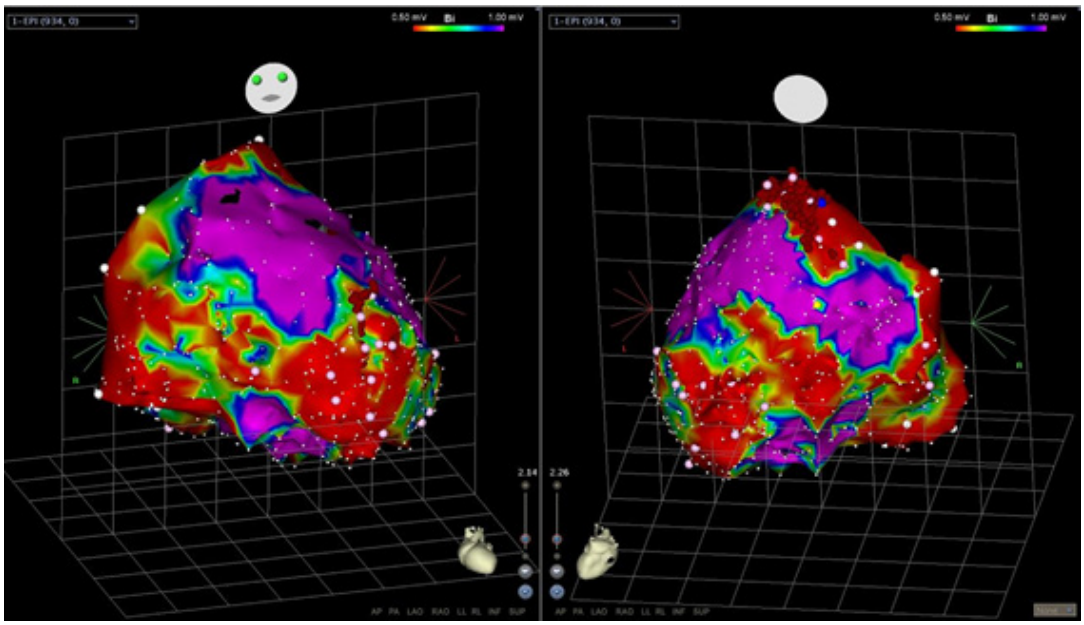

Figure 7 – Electroanatomic mapping of the heart in anterior and posterior views showing regions of low voltage (red), which, combined with conventional electrophysiological techniques, define the location for ablation (red points) in the left ventricular epicardium.

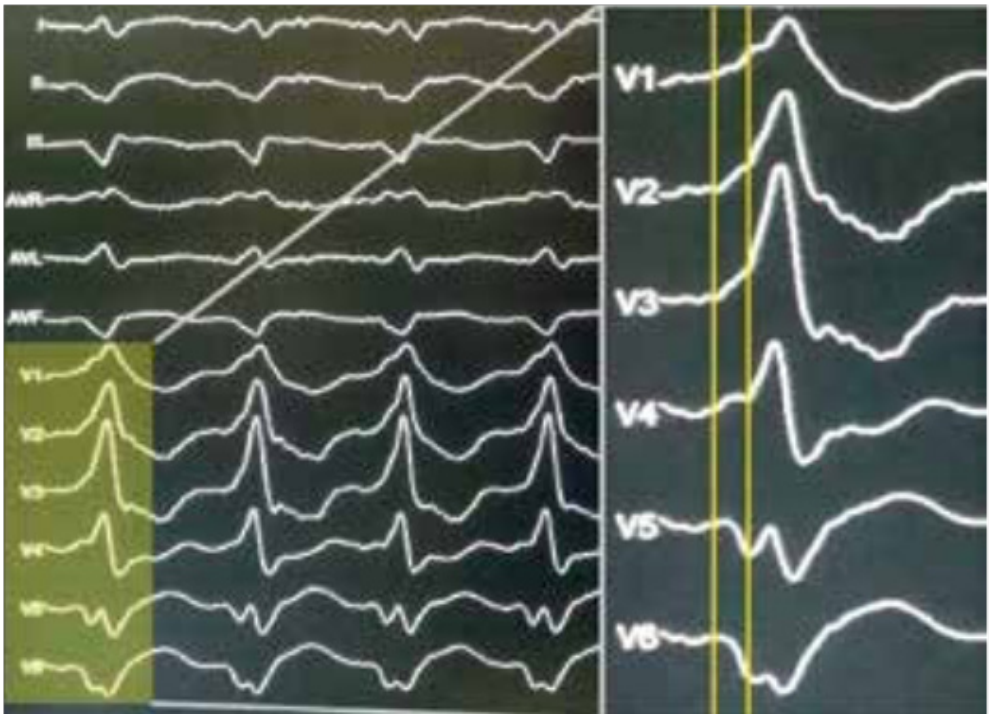

Figure 8 – Electrocardiogram of a patient with sustained ventricular tachycardia with an epicardial focus, showing the pseudo-delta waves (between yellow lines in precordial leads V1 to V6) originated by the slow conduction of epicardial activation

Ventricular Arrhythmias and The His Purkinje (HP) System

The HP system consists of specialized fibers insulated from the ventricular myocardium until their peripheral arborization into muscle. In the right ventricle, they present with a single branch and in the left ventricle with two interconnected fascicles, coordinating the electrical conduction from the AVN (atrioventricular node). The HP system has cellular, ionic, and electrophysiological structures that differ from the rest of the conduction system and may lead to ectopic beats or VTs that can be treated by conventional ablation techniques.

Arrhythmias arising from the HP system may explain sudden death and electrical storms in the normal heart. Ectopic activity triggered by the HP system may be found in patients with idiopathic ventricular fibrillation (VF). This information has given rise to the demand for techniques and strategies aiming the elimination of these foci. Opportunistic ablations[12] were indicated in cases where ectopic beats facilitate the mapping and ablation of VF, thereby controlling this delicate and catastrophic clinical situation (Figure 9).

Situations similar to an HP system ectopia were also recognized in cases of VF associated with the presence of moderator band of the right ventricle, long QT syndrome, and early repolarization syndrome.

Focal VTs

The mechanism of focal idiopathic monomorphic VTs may be secondary to automaticity, micro-reentry, or related to the activity of cyclic AMP.[4] Thus, stimulation of beta-adrenergic receptors by catecholamines results in the release of calcium from the sarcoplasmic reticulum and, subsequently, increase of intracellular calcium, delayed afterdepolarizations and triggering of the VTs. These VTs are more often located in the right ventricular outflow tract (RVOT) and the left ventricular outflow tract (LVOT).

RVOT VTs are the most common VTs and are more frequently located in the septum (mainly in the cusps, followed by the aortic mitral continuity) than in the free wall of the right ventricle.

RVOT is positioned to the left and anterior to the LVOT; the pulmonary valve is positioned superior to the aortic valve. A careful placement of electrodes on the anterior region of the thorax allows the electrocardiographic recording of precordial derivations and a differential diagnosis between RVOT VT and LVOT VT (Figure 10). The typical morphology of the QRS complex is a complete left bundle-branch block, with lower axis deviation. R wave transition in precordial derivations suggests left ventricular outflow when it occurs in V2, and occasionally in V3. Anatomical details are important for the success of the procedure, which has been around 90% in published series.[13]

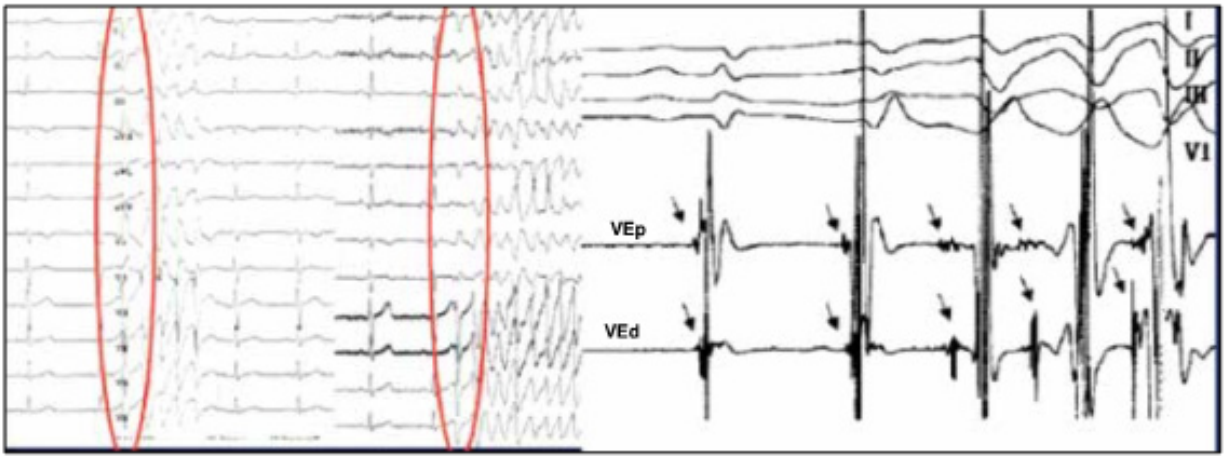

Figure 9 – EPatient with idiopathic ventricular fibrillation related to the His-Purkinje system. Left: Electrocardiogram showing that the morphology of the ventricular extrasystole that triggers polymorphic ventricular tachycardia (VT) is compatible to its origin in the His-Purkinje system of the posterior-inferior left ventricle. Right: Intracardiac signals, surface ECG leads I, II, III and VI, ablation proximal (LVp) and distal (LVd) indicating the potential and the probable region of slow conduction that gives rise to polymorphic VT.

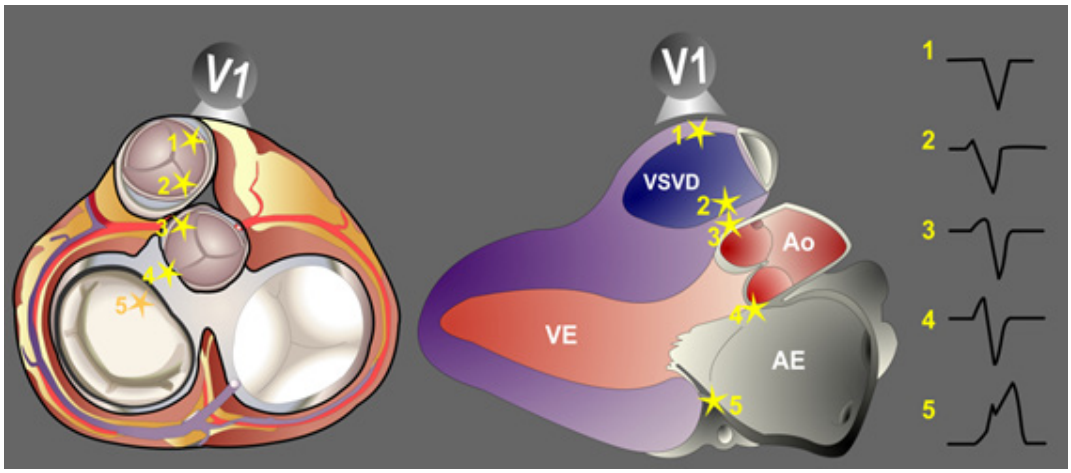

Figure 10 – Transversal and sagittal sections of the heart showing relations between the right ventricular outflow tract, aorta, left atrium, and left ventricle and the morphology of the QRS complex in lead V1, in five possibilities of the origin of ventricular tachycardia. Note the increase in R-wave amplitude when the origin of the ventricular tachycardia and ventricular extrasystoles are more posterior. Modified from Asirvatham.[14]

Imaging During VT Ablation

Imaging modalities for the investigation of patients with VT have expanded. Transthoracic Doppler echocardiography, a simple and routinely performed method, can analyze the thickening of the wall and infer the presence of scarring, although it has limitations in image definition in 10-15% of the cases.[15]

Most VT ablation techniques are related to electroanatomical systems (Carto, Biosense Webster Inc.; NAVX, St Jude Medical; Rhythmia Mapping, Boston Scientific Inc.). Although the big technological leap has allowed the examination of a virtual organ using a catheter, details of scars and myocardial thickness may be incorrectly estimated. The use of cardiac magnetic resonance (CMR) imaging allows endocardial, epicardial, or even intramural delineation of the scar, with a better planning for ablation strategy. Similarly, integration of CMR imaging with electroanatomical mapping (EAM) allows the identification of heterogeneous regions where transmural and scar borders frequently correspond to the isthmus of the reentrant circuits, which are potential targets of ablation.[16-18]

These advances in echocardiography, cardiac computed tomography with multiple detectors, CMR imaging, and EAM can provide integrated hybrid images, far beyond the simple measurement of ejection fraction, with further details of innervation, cardiac metabolism, scar architecture, and electrical activation. Also, these imaging methods have enabled the development of models for proof-of-concept studies to predict not only the arrhythmogenic substrate and characteristics of its circuits, but also future arrhythmic events.[19,20]

Translational Aspects of AF Ablation

It is estimated that 1-2% of the population has AF and, in selected cases, mainly after failure of pharmacological treatment, ablation may be indicated.[21] The perception of AF symptoms is very variable; AF is more frequently asymptomatic in men, in patients with older age, and in those with persistent AF. After ablation, many patients with AF become asymptomatic, hindering the effectiveness of the procedure.

AF Substrate

In addition to cardiomyocytes, vascular cells, nerve cells, and fibrous tissue are present in the atria and in the myocardial sleeves of pulmonary veins with the presence of P-cells, Purkinje cells and transitional cells, normally found in the atrioventricular and sinoatrial node, and in the bundle of His. One hypothesis is that spontaneous depolarization in P-cells may lead to electrical impulses that are propagated to the left atrium through Purkinje cells. Sudden change of fibers direction in pulmonary veins may induce decremental conduction. Therefore, combination of enhanced automaticity, triggered activity and microreentry are related to the mechanisms of pulmonary veins arrhythmogenesis.[22]

A few days after AF, atrial electrical remodeling, action potential shortening, and heterogeneity in refractoriness and conduction velocity occur, which favor the reentry mechanism. After months, interstitial fibrosis occurs, with induction of persistent AF, alteration of expression of ion channels, and suppression of activity of calcium and sodium currents (ICaL and INa and increment of IK1).

For decades, the conceptual mechanistic hypotheses of AF were (a) multiple reentrant waves, (b) automatic foci, and (c) single reentry with fibrillatory conduction. Recently, a series of sophisticated studies (in vitro and in vivo) involving computer simulations, surface mapping, and spherical catheters (basket) has indicated other possible mechanisms, such as automatic activities generating multiple wavefronts, with the presence of rotors or spiral waves, resulting in peripheral fragmentation of the electric activity fronts. Thus, current knowledge indicates that ectopic activities and reentrant phenomena, anchored in complex anatomical structures or atrial fibrotic regions, can generate and maintain AF. Over time, AF, initially related to triggers, becomes more dependent on substrate changes and structural remodeling related to its natural history.[22]

Isoproterenol, a beta-adrenergic agonist, increased the activity in pulmonary veins after infusion of the vessels, increasing production of EAD (early afterdepolarizations) from cardiomyocytes.[22] In contrast, infusion of phenylephrine, known to cause reflex vagal activation, reduced focal activity in the pulmonary veins . The extensive innervation of pulmonary veins by sympathetic and parasympathetic nerves and resulting autonomic tone may play a role in the generation of ectopic activity arising in the pulmonary veins.

The autonomic nervous system, comprised of extrinsic sympathetic and parasympathetic (brain neurons and medulla) and intrinsic (epicardial ganglion plexuses, predominantly parasympathetic) components. The density of nerve bundles is higher in the epicardial region of the antrum, 5 mm from the cavoatrial junction and pulmonary veins. This proximity between nerve structures and myocytes greatly favors local ectopic activity, sympathetic or parasympathetic stimulation with proarrhythmic action in the atrium, and, consequently, shortening of the refractory period and increased repolarization heterogeneity. Although parasympathetic activity is more related to the genesis of AF in patients without heart disease, and sympathetic activity in patients with heart disease, sympathovagal discharge is strongly pro-arrhythmogenic and pro-fibrillatory, often triggering paroxysms of atrial tachycardia and AF. Results of autonomic modulation as an adjunct therapeutic strategy in AF ablation are controversial; there have been favorable[23,24] and unfavorable results,[25,26] in addition to experimental evidence of increased induction of AF with partial vagal denervation. The possible dysfunction of the autonomic nervous system in AF seems to be complex, with individual variations and responses. Due to their localization, ganglionated plexi ablation often occurs during wide circumferential pulmonary vein ablation.

Translational Anatomical Basis For AF Ablation

One of the seminal observations of Haissaguerre et al.,[27] was the behavior of cardiomyocytes, which, when embedded in the pulmonary veins, favor the emergence of automatic foci and micro-reentry activities. Older anatomical studies[28] have shown that the muscle transition between the atria and the veins is geometrically favorable for electrical disturbances and is an important target for AF catheter ablation and mapping (Figure 11). Thus, the elimination of triggers and the arrhythmogenic substrate must be part of the therapeutic strategy for AF, by using catheter ablation that basically involves the confection of circumferential lesions around the right pulmonary veins and arteries, addressing the venoatrial junctions, which are critical locations for the genesis and maintenance of AF by its automatic capacity, micro-reentrant sites, and rich in ganglionic plexus.

Proof-of-concept studies have been consolidated in recent decades, and the role of pulmonary veins in the genesis of AF has been confirmed clinically and experimentally. The selective monitoring of veins (Figure 12) determining the culprit vein, venous tachycardia triggering AF, and the ability of the antral ablation, supported by sophisticated imaging systems, enabled the development of techniques that allow the elimination of clinically important AF in approximately 70–80% of patients.[29]

Non-pulmonary Vein Triggers

Supraventricular tachycardias (nodal reentrant tachycardias or AVRT) may be present in 4% of cases. High doses of isoproterenol (20–30 mcg/min) may reveal other triggering points to be addressed during AF ablation in up to 11% of cases. These are clustered in places which contain cardiomyocytes that can exhibit arrhythmogenic

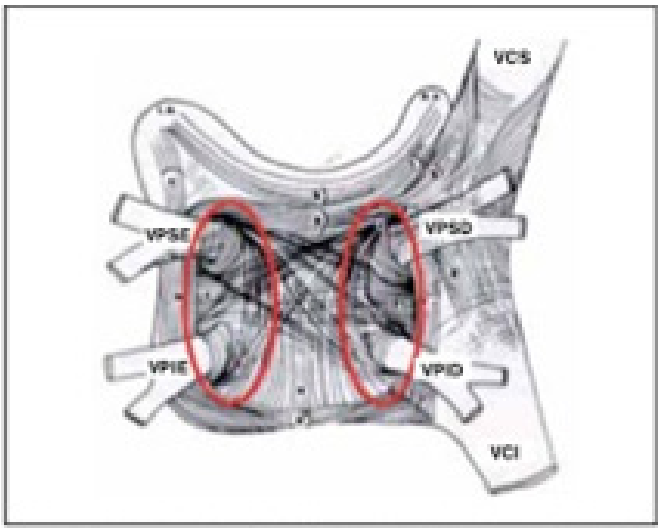

Figure 11 – Posterior view of the left atrium (red circle) showing that the complex mesh of muscle fibers is more entrapped in the pulmonary vein ostium, allowing anisotropic conduction and arrhythmogenic phenomena. Modified from Nathan et al.,[28]

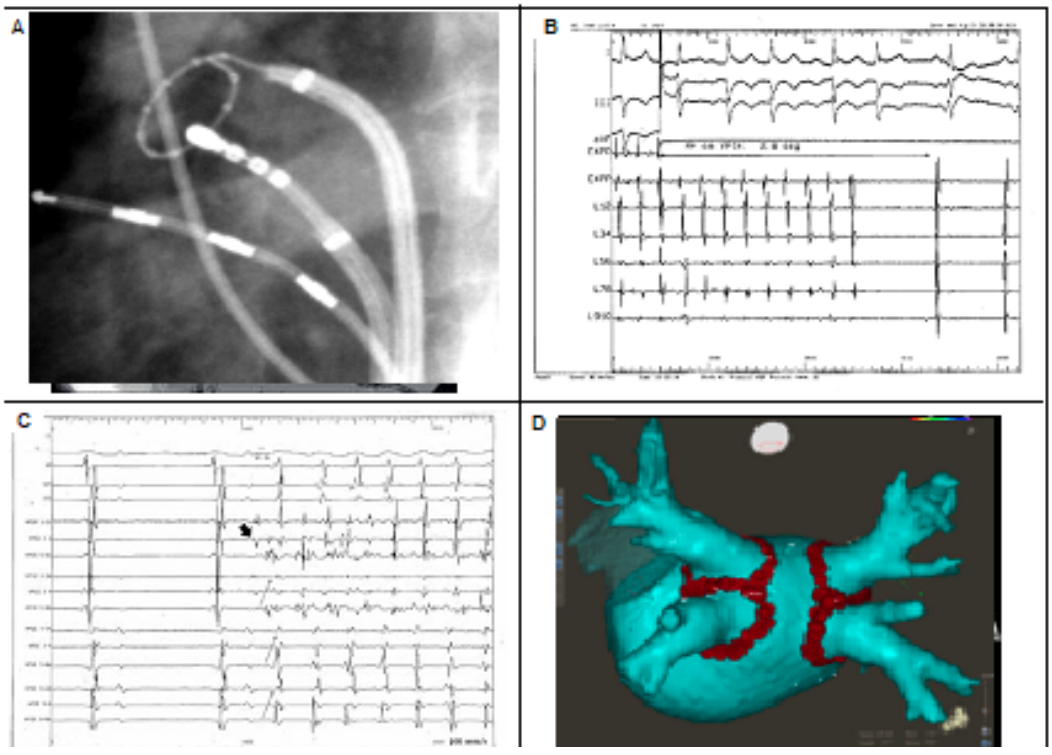

Figure 12 – Images of pulmonary vein ablation for treatment of atrial fibrillation (AF). (A) Posteroanterior radiograph showing the insertion of microcatheters into pulmonary veins to detect the culprit vein. (B) Induction of AF. (C) Resolution of tachycardia and AF control after application of radiofrequency in the left superior pulmonary vein (LPSV) in another patient. (D) Electroanatomic voltage map of the left atrium in anteroposterior view, projected on a 3D model, showing the area of antral ablation and isolation of the pulmonary veins (red dots).

activity: the inferior mitral annulus (MA), the posterior left atrium, the interatrial septum (fossa ovalis limbus), the crista terminalis (CT) and Eustachian ridge, the coronary sinus (CS), the superior vena cava (SVC), the LAA, and the ligament of Marshall (LOM). All these sites have been shown to contain cardiomyocytes that can exhibit arrhythmogenic activity (Figure 13). Enhanced automaticity, triggered activity and localized micro-reentrant circuits are the mechanisms involved in these sites.

Embryonic sinus venous tissue present in the SVC is capable of spontaneous firing. Histological studies have demonstrated the presence of pacemaker cells within the Eustachian ridge, which can be a source of abnormal automaticity. The left atrium wall should be considered as an extension of pulmonary veins with arrhythmogenic potential. The 3 to 5 cm muscular portion of the proximal CS may serve either as a trigger for AF or as a part of a reentrant circuit and, at the level of the valve of Vieussens, triggers from the LOM may be identified. Triggers from inferior vena cava are rare.

Complex Fractionated Electrograms, Fibrosis, Rotors, and Left Atrial Appendage

The success rate of ablation of paroxysmal AF (up to 80%) is not achieved in patients with persistent AF (>1 week) or long-standing (>1 year) persistent atrial fibrillation, probably because of other mechanisms involved.

The need for new percutaneous strategies for the treatment of more chronic cases led to the reproduction of the maze (labyrinthine) surgery , by creating linear lesions in the left atrial roof and in the mitral isthmus and ablation of complex fractionated electrograms. Also, ablation of rotors detected by phase map analysis for the has been suggested for the approach of AF as described in the CONFIRM (Conventional Ablation for Atrial Fibrillation with or without Focal Impulse and Rotor Modulation) study .[30]

Despite the physiopathological basis for persistent AF ablation, the first encouraging results[31,32] were not reproducible and not superior to the conventional, pulmonary vein isolation alone. Clinical and laboratory

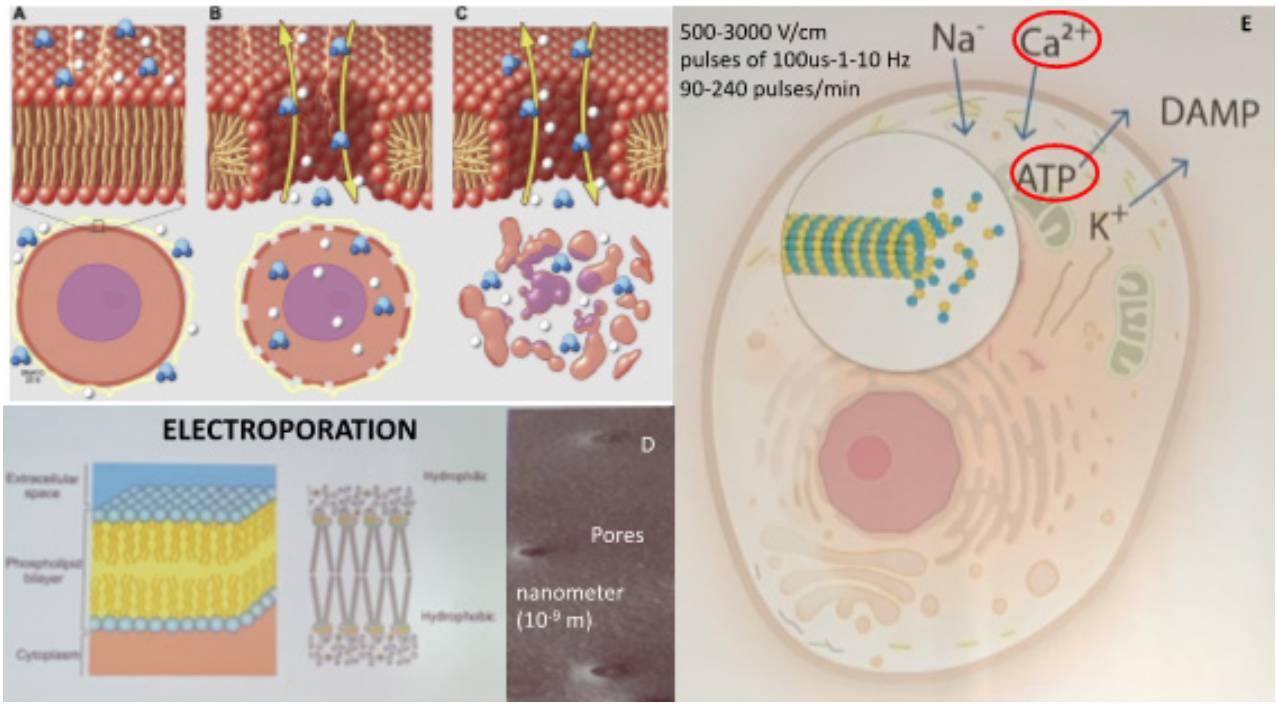

Figure 13 – Electroporation - modified from Maor.43 Formation of pores driven by local electric field gradient (from A to C), followed by water penetration in the bilayer interface, creating pores (D). Leakage of ions and osmotic balance, loss of cell homeostasis entrance of calcium and release of damage-associated molecular patterns (DAMP) with alteration of function and structure of membrane proteins (E)

observations now suggest that atrial signals that show complex activity (0.06–0.25 mV or <120 ms cycle), although represent passive electrical signals resulting from wave front collision, do not necessarily mean local intrinsic activity. No significant benefit was gained by the addition of ablation of these complex fractionated electrograms to the standard procedure, as described in the STAR AF II (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II)[33] and CHASE-AF (Randomized Catheter Ablation of Persist End Atrial Fibrillation Study) trial.[34]

The clinical impact of the approach of fibrosis as a substrate is not yet defined. The use of delayed-enhancement CMR to classify structural changes of the atrium by degrees of fibrosis (stages I–IV of Utah) is difficult to reproduce, and the electrophysiological approach of fibrosis (<0.5 mV [dense fibrosis] or 0.5–1.5 mV [moderate fibrosis]) has not shown consistent clinical results. Finally, ablation guided by the identification of atrial areas with rotational and fibrillatory activity and triggers of AF (rotors with >50 sustained rotations) in the CONFIRM[30] study, or by electrocardiographic imaging[34] and dominant frequency analysis,[35] were not reproducible and were not superior to isolation of the pulmonary veins.[36,37]

Perioperative Imaging in AF Ablation

The most used stroke risk score is CHA2DS- 2-VASc (C = heart failure, H = arterial hypertension, A = age >65 years, A2 = age >75 years, S = previous vascular accident, V = vascular disease, S = women). Thrombogenesis in non-valvular AF, mediated mainly by the left atrial appendage, presents a risk of <0.3% when CHA2DS2-VASc is 0 and> 5% when CHA2DS2-VASc is ≥2. Patients with a score of ≥2 receive oral anticoagulation that usually is not uninterrupted during ablation. In these patients, preoperative transesophageal echocardiography is always performed to rule out the presence of thrombus. In addition to the ability to detect thrombi, computed tomographic angiography and intracardiac ultrasound provide important images that may be useful during the procedure, either for image coupling or for intracardiac echocardiography monitoring of atrial structures and catheters, providing higher safety to the procedure.

Although patients with CHA2DS2-VASc ≥2 still require anticoagulation after AF ablation, some studies have suggested that suspension of oral anticoagulation may be considered after successful AF ablation, when the meticulous monitoring demonstrates the absence of these arrhythmias.[39] Studies in progress such as the EAST (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial, ClinicalTrials.gov identifier NCT01288352), the CABANA (Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial, NCT00911508), and the OCEAN (Optimal Anticoagulation for Higher Risk Patients Post-catheter Ablation for Atrial Fibrillation, NCT02168829) may provide more consistent data for this approach.

The presence of silent cerebral microembolism in patients with AF ablation can be detected very accurately by diffusion magnetic resonance imaging (with or without fluid-attenuated inversion recovery) 30 min after ablation and, depending on the ablation systems used, can be detected in up to 50% of the cases. These worrying findings that require more meticulous and prolonged monitoring may also be present in other invasive procedures such as coronary angiography, stenting of carotid arteries, and insertion of valve prostheses. Fortunately, most studies have shown a regression without glial sequelae, with complete normalization of imaging examinations at 3 months,[40] with no solid data of declining of neurocognitive functions[41] in the populations studied.

New frontiers of AF ablation – the pulsed-field ablation

Two other important modalities of ablation use radiofrequency and cryothermal energy; these are thermal energy sources and both rely on time-dependent conductive heating/cooling, ablating all tissue types indiscriminately, with similar clinical results.[38] The dependence on contact and also the heat-sink effect caused by blood flow impairs lesion formation that can explain the high recurrence of arrhythmia. The desirable improvement of safety and efficacy of catheter ablation resulted in the investigation of alternative uses of energy.

Pulsed electric fields (PEF) has gained attention since 2005.[42] It refers to application of intermittent, high-intensity electric fields for micro or nanoseconds, resulting in increased cellular permeability, with penetration of water into the lipid bilayer/water interface. This results in electroporation, creating pores around 10 nm in size form (Figure 14), and generation of selective lesions without tissue heating and preservation of critical surrounding structures.

Differently from radiofrequency and cryothermal energy, PEF are not dependent on contact, have no risk of thrombus formation, and have high tissue specificity. To date, there has been no evidence of phrenic nerve or esophageal injury, or pulmonary venous stenosis. Data from the AF Symposium 2020 reported 113 paroxysmal atrial fibrillation patients treated in three centers and by five operators, with no complications. In 52 remap procedures, durable pulmonary vein isolation was present in all patients.

PEF-based pulmonary vein and left atrial ablation are feasible and safe procedures, with excellent acute efficacy. Although several aspects of the techniques, such as the durability, level of pulmonary vein isolation, and effect on clinical recurrence of atrial fibrillation remain to be confirmed, PEF ablation is a paradigm-shifting energy source that has the potential to transform the field of AF ablation.

Conclusion

The translational research of cardiac arrhythmias has ensured the development of techniques of percutaneous ablation with superior results, including resolution of some supraventricular tachyarrhythmias, such as VTs without structural heart disease and some cases of paroxysmal AF. Some frontiers of knowledge, such VT with structural cardiopathy and long-standing persistent AF, are important medical challenges that require extensive clinical and experimental research.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Author Contributions

Conception and design of the research: De Paola AAV. Acquisition of data: De Paola AAV. Analysis and interpretation of the data: De Paola AAV. Writing of the manuscript: De Paola AAV. Critical revision of the manuscript for intellectual content: De Paola AAV.

Potential Conflict of Interest

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