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New Imaging Technologies To Characterize Arrhythmic Substrate

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Abstract

The cornerstone of the new imaging technologies to treat complex arrhythmias is the electroanatomic (EAM) mapping. It is based on tissue characterization and in particular on determination of low potential region and dense scar definition. Recently, the identification of fractionated isolated late potentials increased the specificity of the information derived from EAM. In addition, non-invasive tools and their integration with EAM, such as cardiac magnetic resonance imaging and computed tomography scanning, have been shown to be helpful to characterize the arrhythmic substrate and to guide the mapping and the ablation. Finally, intracardiac echocardiography, known to be useful for several practical uses in the setting of electrophysiological procedures, it has been also demonstrated to provide important informations about the anatomical substrate and may have potential to identify areas of scarred myocardium.

Introduction

In the last years our understanding of the arrhythmic substrate in various cardiomyopathies, resulting in substrate-based approaches for targeted complex arrhythmias ablation was improved. Further, the growth in better technologies and techniques for complex procedures such as atrial fibrillation (AF), left atrial flutter and ventricular tachycardia (VT) ablation have overcome the limitations and greatly improved the success rates of radiofrequency catheter ablation (RFCA). This review summarizes the relationship between the arrhythmic substrate feature sand and novel approaches in the new technologies for RFCA of complex arrhythmias.

Anatomopathological Features Underlying Arrhythmia Induction

VT in the context of ischemic cardiomyopathy are caused by reentry involving a ventricular scar. During the infarct healing process, necrotic myocardium is replaced with fibrous tissue. Dense fibrotic scar creates areas of anatomical conduction block, and fibrosis between surviving myocytes decreases cellular coupling and distorts the path of propagation causing areas of slow conduction and block, which promotes reentry. Endocardial recordings from sites of VT origin during sinus rhythm consistently demonstrate low-amplitude, prolonged, multicomponent potentials. The duration of the local electrogram represents the abnormally slow, fractionated conduction. Differently, arrhythmogenic right ventricular cardiomyopathy/ dysplasia (ARVC/D) involves primarily the right ventricle (RV). In this condition, portions of the RV are replaced by fibro-fatty tissue. Focal inflammation and necrosis can be seen at histologic study. The interventricular septum and left ventricle may also show involvement. VT are common in ARVC/D because of the extensive myocardial fibrosis that provides the substrate for reentry. Also in non-ischemic dilated cardiomyopathy the myocardial fibrosis is an important factor in the substrate leading to VT. However, in patients with non-ischemic cardiomyopathy the cause of fibrosis is not well defined. The reentry circuits are typically associated with regions of lowvoltage electrograms, consistent with scar.[1,2]

Arrhythmogenic Substrate And Scar Identification By Electroanatomic Mapping

Electroanatomic mapping (EAM) systems have been introduced into clinical electrophysiology in 1997.[3-5] Sinus-rhythm EAM was found to identify infarct areas in animal models.[6,7] In human studies, however, high-density EAM scar definition using multiple electrogram (EGM) parameters has been matched against a gold-standard technique based on tissue characterization and validation studies have confirmed that low voltage corresponds to the presence of scar defined by delayed enhanced MRI (DE-MRI).[8] This comparison was first evaluated in the study of Codreanu and co-workers, which confirmed that bipolar EGM characteristics could reliably differentiate scar from healthy tissue.[9] The most important EGM characteristic initially analyzed was bipolar peak-to-peak voltage. This was shown to be a powerful discriminant of scarred areas from background normal myocardium when, after analysis of post-

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infarct patients and normal controls, the presently used cut-off values of >1.5 mV for normal myocardium and <0.5 mV for dense scar were derived. Amplitudes between 0.5 mV and 1.5 mV were found to be present at the edges of dense infarct scars and corresponded to the scar border zone. EAM can be performed if a particular cardiac chamber can be reached and mapped with a mapping catheter.[10] In addition to bipolar EGM amplitude, bipolar EGM duration and fractionation were also found in similar early studies to be increased in the presence of scarring because of electrical uncoupling of adjacent myocytes by islands or shards of replacement or interstitial fibrosis,[11] which is necessary conditions for the development of reentrant arrhythmias. Adequate catheter contact with the myocardial wall, however, is a requirement for an adequate voltage map (figure 1). Bipolar recording more accurately reflects local changes in electrical activity and is less influenced by far-field electrical activity, possibly explaining its ability to provide information about intramural scar location but still unable to predict transmural depth. More recently, and particularly in the setting of non-ischemic cardiomyopathy where epicardial and intramural substrate predominates, the utility of unipolar EGM amplitude for the delineation of deeper layers of more diffuse fibrosis has been demonstrated, both in the right and left ventricles.[12] Hutchinson et al. assessed the role of unipolar recording during voltage maps created during VT ablation.[13] In 11 patients with epicardial low voltage regions noted during epicardial mapping, 9/11 patients had corresponding low voltage (≤ 8.27 mV) unipolar recording from the endocardial surface. This data suggested that unipolar recording might have a greater field of view, which could predict an epicardial substrate during endocardial mapping. This same methodology was used to assess the RV epicardium in patients with ARVC/D with an endocardial unipolar voltage of <5.5 mV indicative of an epicardial low voltage region.[14] The presence of a critical extent of unipolar-defined substrate (>32% of total LV endocardial surface) has now been shown to predict non-reversibility of non-ischemic cardiomyopathy, consistent with detection of a critical diffuse burden of irreversible microfibrosis that may not be identified with bipolar recording or standard MRI techniques.

Late Potential Activity, Voltage Map Channels And Scar dechannelling Technique

Late potentials (LPs) are high frequency, low amplitude, microvolt-size signals at the end of the QRS complex related to fragmented and delayed electrical activity in the ventricles. LPs were detected in patients with ventricular arrhythmias, ventricular aneurysms and ARVC/D. LPs are associated with reentry mechanism responsible for the induction of sustained VT and it has been reported a higher frequency of sudden cardiac death. LPs can be identified non-invasively using a quick and inexpensive diagnostic tool, the signal averaged electrocardiogram (SAECG).[15-17] However, conventional SAECG criteria for the presence of LPs in patients with a prolonged QRS duration are inaccurate. As reported by Gatzoulis et al. modification of these criteria is necessary to obtain useful information in these patients.[18]

Invasively, LPs activity is a discrete bipolar electrical signal recorded after the prevalent EGM occurring after the end of the surface QRS complex. LPs are marker of slow conduction and can be used to identify the critical isthmus of the reentry circuit of VT[19] (Figure 2). Pacemapping from LPs sites allows an 11/12 or 12/12 concordance with VT morphology more frequently than in other low amplitude EGM sites and entrainment maneuvers show a mean stimulus-QRS interval longer than in other sites inside the scar area.[20,21] Several studies have been shown that LPs can be used as targets of catheter ablation for unmappable VT.[22-25] According to the study of Vergara et al., complete abolition of LPs predicts arrhythmic recurrences. Indeed, they found arrhythmic recurrences only in 9.5% of patients in which LPs were eliminated at the end of the procedure. Complete abolition of LPs over the scar area represents an effective strategy of substrate modification for the ablation of scar-related VT.[26]

Recently, Efremidis and coworkers reported a case of effective radiofrequency ablation of VT in a patient with Naxos disease in which at the site of earliest endocardial activation was found a LPs area. The entire area of LPs were targeted and ablated resulting in non-inducibility of VT.[27]

Moreover, it has been demonstrated that, adjusting the voltage cutoffs that define the scar, it is possible to identify conducting channels in the setting of ischemic cardiomyopathy.[28,29] As previously described by Arenal et al. and Bogun et al. these "corridors" of slow conduction within the scar often contain LPs.[21,22] However, if large scars are present, the use of these channels alone in identifying the critical isthmus has low specificity, and therefore their ability to accurately guide ablation is poor. Mountantonakis and coworkers demonstrated that the presence of LPs within a channel increases the likelihood that the channel will be important for maintaining VT.[30] In patients with ARVC/D, Berruezo et al. showed that a combined endo-epicardial approach including complete elimination of all conducting channels, so-called scar dechannelling technique, achieves a high acute success rate with low incidence of recurrence during a one year follow-up.[31]

Ablation Using MRI Technology

Preprocedural cardiac MRI is valuable due to its ability to provide high-resolution anatomic mapping and tissue characterization in the absence of ionizing radiation. DE-MRI can be used to localize the arrhythmia substrate within the chamber of interest prior to the procedure. There is growing evidence that DE-MRI may be useful in patients with AF in terms of treatment decisions and assessment of ablation efficacy.

Over the past twenty years, technologies for the treatment of both supraventricular and ventricular arrhythmias has significantly advanced and ablation is now the first-line therapy for many arrhythmias.[32-34] As mentioned above current catheter-based techniques employ EAM provides real-time guidance for the operator during the procedure.[35] Image fusion techniques that merge chamber morphology data from preprocedural MRI or CT with intraprocedural anatomical and electrical data are now widely used for accurate depiction of critical anatomic details that aid in the selection of ablation sites. Given its strengths in non-invasive identification of myocardial fibrosis, an anatomical substrate for arrhythmia, contrast-enhanced cardiac MRI has an emerging role in anatomic mapping of scar and ablation planning.[36]

Magnetic Resonance Imaging and Atrial Fibrillation

Magnetic Resonance Imaging (MRI) basally was used for EAM mainly for fusion of volumetric MRI data obtained during the procedure. The MRI anatomic map precisely defines the anatomy of the chamber of interest, which is particularly important in AF ablation. MRI is useful in the pulmonary vein's (PV) anatomy evaluation. The left atrium (LA) and PVs are accurately visualized.[14]

MRI has also been used to define the location of the esophagus relative to the LA that may reduce the risk of esophageal injury.[37]

In the last years new techniques for evaluation of DE within the LA have recently been developed.[38,39]

Left atrial imaging is technically challenging, as the thin walls of the LA demand very high spatial and contrast resolution that push the boundaries of current MRI technology. Detecting fibrosis in the LA wall using MRI was first applied by Marrouche group at the CARMA Center, and enabled them to visualise the location, extent, and amount of atrial fibrotic changes. In this study the LA was scanned using late gadolinium enhancement to evaluate the extent of enhancement in the LA before AF ablation, and correlated with low voltage area in EAM (CARTO; Biosense Webster, Diamond Bar, California, USA) during AF ablation.[40]

Although several studies have been conducted to determine predictors of AF recurrences following catheter ablations, identifying the ideal candidate for catheter ablation of AF remains a significant challenge. Akoum et al. reported important data that can be utilised for personalising the strategy of AF ablation.[41] Based on the amount of pre-ablation DE in the LA wall patients are divided into four stages of left atrial structural remodelling. Utah stage I is defined as ≤5% enhancement (minimal), Utah stage II as >5% and ≤20% enhancement (mild), Utah stage III as >20% and ≤35% enhancement (moderate), and Utah stage IV as >35% enhancement (extensive). Patients with minimal left atrial fibrosis (Utah stage I) had excellent results after AF ablation, whereas poor results were obtained in patients with extensive left atrial structural remodelling (Utah stage IV).

DE-MRI has been used also to identify ablation lesions in the left atrial wall and surrounding the PVs, as well as gaps in circumferential PV isolation that are associated with increased risk of recurrence.[38,42]

For the first time the group of Marrouche also demonstrated that the large areas marked as ablated in the EAM did not result in long-term scar and could well be the reason for high recurrence rates of arrhythmias like AF.[43]

Scar Mapping Using Delayed Enhancement MRI

DE-MRI is considered the gold standard for imaging of scar tissue. In patients with structural heart disease, ventricular arrhythmias originate from scar tissue. Furthermore, in the presence of ventricular arrhythmias, cardiac MRI helps to rule in or rule out the presence of structural heart disease. We will focus on the use of DE-MRI to identify scar tissue in various cardiomyopathies, and the potential value for mapping and ablation of ventricular arrhythmias. Furthermore, we will discuss the value of MRI for ruling out structural heart disease. Cardiac MRI typically utilizes a T1-weighted fast gradient echo images acquired during a held breath. Maximal resolution is typically on the order of 1–2 mm for each dimension in the x, y and z planes. One potential pit-fall encountered with the use of registered 3D images is loss of accurate positional data if the patient moves during the study, requiring repeat acquisition of reference points. The utility of DE imaging using cardiac MRI for the identification of ventricular myocardial scar has been well established.[44] In myocardial fibrosis, the extracellular matrix is expanded due to replacement of normal myocytes with collagen. Gadolinium contrast agent washes in and out of normal myocardium relatively rapidly; however, it is retained within the fibrotic myocardium both due to the increased extracellular fluid volume and decreased capillary density.[45] The difference between gadolinium retention in normal tissues versus fibrotic myocardium is maximal at approximately 10–20 min after contrast administration, which is the optimal time for obtaining DE images.[46] These sequences are further optimized for maximal contrast between normal tissue and scar by applying a 180° inversion recovery pulse before image acquisition. The 180° pulse has the effect of flipping the magnetic moment of the spinning protons 180° from their equilibrium position. In the setting of acute myocardial infarction (MI), myocardial necrosis results in disruption of myocyte membranes, allowing increased space for the distribution of gadolinium. In the setting of chronic MI, collagenous scar tissue has replaced the necrotic tissue and the increase in interstitial MRI allows for exact anatomic reconstruction of cardiac anatomy, and can be used in conjunction with DE to localize scar tissue. In the setting of chronic MI, collagenous scar tissue has replaced the necrotic tissue and the increase in interstitial tissue increases the volume of distribution for gadolinium, resulting in hyperenhancement. Initial studies used a signal intensity of 2–3 standard deviations above normal appearing myocardium in order to define the presence of DE.[47]

MRI And Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Cardiac MRI plays a key role in the diagnosis of ARVC/D. High resolution cine imaging is widely considered the gold standard for the quantitative assessment of RV volume and systolic function. The high spatial and temporal resolution enables a detailed assessment of the RV for regional wall motion abnormalities. The modified Task Force Criteria include an assessment of a combination of RV function and wall motion abnormalities. RV volumes have been adjusted for body surface area and sex. Previous criteria that included wall thinning, and fatty infiltrations, as well as wall motion abnormalities such as hypokinesis, have been abandoned for akinetic and dyskinetic wall motions in order to achieve higher specificity.[48] Fibro-fatty tissue has been described in ARVC/D, and DE-MRI has also been found to indicate scar tissue in this particular cardiomyopathy (Figure 3). Inducibility of VT does correlate with the presence of DE. Correlations of abnormalities within the MRI and electrophysiologic findings such as low voltage areas have been done in a qualitative manner in small series of patients.[49]

MRI And Other Forms Of Non-Ischemic Cardiomyopathy

DE-MRI has been used to differentiate various forms of cardiomyopathy. Mid-wall DE has become the imaging hallmark of idiopathic dilated cardiomyopathy. Patchy multifocal DE with a basal and septal involvement preferentially affecting the mid- and epicardial myocardium is typically seen in cardiac sarcoidosis The presence of scar by DE-MRI has been correlated with the spontaneous occurrence of VT as well as the inducibility of VT and outcome in patients with non-ischemic cardiomyopathy.[50,51] In the setting of non-ischemic cardiomyopathy, it is important perform adequate scar imaging with cardiac MRI to assess the etiology of the cardiomyopathy prior to implantation of a cardioverter defibrillator. Identification of scar tissue in patients with idiopathic dilated cardiomyopathy or cardiac sarcoidosis has been useful in assisting with mapping and ablation of ventricular arrhythmias. As described by Bogun it has valuable role to identify the location of the scar if corresponds to the location of the arrhythmogenic substrate.[52] If the scar was located endocardially, all arrhythmias were mapped to

the endocardium. In the case of an epicardial scar, the origin of the arrhythmias was originating from the epicardium, which significantly ease mapping and ablation planning and orient the operator to the priority of epicardial approach from the beginning. In the case of intramural scars, only arrhythmias in which the scar extended to the endocardium or epicardium could be mapped and ablated from the endocardium or epicardium, respectively.

Intracardiac Echocardiography

During the past 20 years, electrophysiological procedures have been performed almost exclusively under fluoroscopic guidance. However, due to the need to reduce fluoroscopic exposure and the increased complexity of procedures, accurate imaging of intracardiac anatomic structures and interventional catheter devices has been required.[53,54]

Intracardiac echocardiography (ICE) has proved to be helpful for several practical uses in the setting of electrophysiological procedures, including: (1) identification and evaluation of the endocardial structures before and after procedure; (2) safe guidance of transseptal puncture, particularly in the setting of complex or unusual anatomy; (3) real-time determination of catheter placement relative to cardiac structures; (4) evaluation of catheter contact with cardiac tissues; (5) visualization of evolving lesions during radiofrequency (RF) energy delivery; (6) monitoring of complications.[55-59]

To date two different types of ICE imaging systems are available: the mechanical ultrasound catheter radial imaging system, a single, rotating, crystal ultrasound transducer mounted on a non-steerable 9Fr catheter (Ultra ICE, EP Technologies, Boston Scientific Corp, San Jose, CA) and the electronic phased-array catheter sector imaging system, a forward-facing 64-element phased-array transducer scanning in the longitudinal plane mounted on the distal end of an 8 or 10 Fr 4-way steerable tip catheter (AcuNav, Acuson Corporation, Siemens Medical Solutions, Malvern, PA). A newer 64-element phased-array and bidirectional curve ultrasound catheter (St. Jude Medical, St. Paul, MN) is the ViewFlex Plus which runs on the ViewMate ultrasound system (EPMedSystems, Inc., Berlin, NJ).

Moreover, the feasibility of the integration of EAM and intracardiac echocardiography has been demonstrated. The introduction of the CARTOSOUND Image Integration Module (Biosense Webster, Diamond Bar, CA) has expanded ICE applications. Indeed, the CARTOSOUND incorporates the electroanatomical map to an ICE 3D volume reconstruction of the cardiac chambers using real-time ICE imaging.[60-63]

Despite a wide use of ICE imaging during RFCA for AF,[64,65] ICE has not been routinely used during RFCA for VT.[53] Several studies have described that the use of ICE in VT ablation present the following advantages: to accurately guide and locate catheter placement on specific anatomic targets and confirm catheter contact with the endocardium; to guide transseptal access; to facilitate mapping and ablation of left ventricular outflow tract VT (visualization of coronary artery ostia and aortic cusp); to guide the subxiphoid pericardial puncture and visualize the puncture-related complications; and to monitor tissue injury and complications during the procedure (i.e. cardiac perforation and tamponade, valvular injury and thromboembolic events[66-68] ICE imaging created volumes have been shown to accurately assist in VT ablation.[63] In addition, recent studies focused on the ability of ICE to identify the arrhythmogenic substrate during VT ablation: scars, aneurysms, akinesia or dyskinesia (Figure 4). Adequate visualization of the akinetic and/or dyskinetic regions using ICE is feasible, enabling guidance of catheter positioning and identifying potential target areas for RFCA.

Substrate mapping of VT involves characterization of areas likely to support reentry based on anatomy and electrophysiological characteristics. Substrate mapping typically begins with identification of the region of ventricular scar, based on electrogram characteristics.[33]

Since voltage is used to define scar, consistent catheter contact is necessary. If catheter contact is not sufficient (i.e. ridges, geometric distortions), the EAM could suggest an erroneous scar. For this reason, substrate mapping relies heavily on the correct interpretation of electrograms. Whilst using traditional EAM only those regions in which there is a good contact are correctly mapped, ICE imaging has potential advantages: ICE can reliably identify scar both by wall thickness and motion a process that does not require wall contact. Moreover, ICE allows to visualize all segments of the left ventricle from multiple planes in real-time.

The first experience that demonstrated the feasibility of ICE guidance for identifying the VT anatomical substrate was published by Bunch and co-workers.[69] According to the authors ICE imaging was more accurate in prediction of scar borders than transthoracic echocardiography, particularly in the basal segments of the heart.

Bala et al. showed the usefulness of ICE in a series of patients with non-ischemic cardiomyopathy and recurrent VT.[70] In these patients ICE imaging identified abnormal increased echogenicity in the lateral wall of the left ventricle. This substrate was characterized by detailed endocardial and epicardial mapping, analysis of electrograms in low-voltage areas and correlation with MRI and CT angiography. They found predominantly normal LV endocardial voltage and abnormal epicardial substrate identified by ICE imaging (Figure 5). In all patients detailed epicardial mapping revealed that areas of low amplitude, wide, split and late electrograms were related with areas of increased echogenicity. In a subset of patients, MRI confirmed abnormal substrate in the lateral wall, correlating to the ICE-defined abnormality. These areas can be successfully targeted for RFCA to provide effective VT control.

In concordance with these observations in patients with non-ischemic VT, the anatomical VT substrate in the study of Hussein et al. was found to have increased echogenicity.[71]

Noteworthy, this study was extended to a population with both ischemic and non-ischemic VT patients. ICE was confirmed to have the potential to assess anatomical substrate characterization for VT ablations. In addition, using a software - Image J, Java-based standard image processing software, National Institutes of Health, Bethesda, MD - that allows measurement of signal intensity units in every pixel, a quantitative assessment of signal intensity and heterogeneity was performed in order to better characterize the VT scar and border zone on ICE images.[72-75] Scar zones, identified on endocardial voltage maps, were found to have increased tissue echogenicity compared to myocardial areas without scar in ischemic and non-ischemic patients. Border zones were found to have more heterogeneous signal intensities than normal myocardium.

Computed Tomography

It is well known that epicardial catheter ablation for ventricular arrhythmias is an important therapeutic option not only after endocardial ablation failure but also as first approach especially in patients with non-ischemic cardiomyopathy. However, epicardial mapping and ablation in epicardial space may have limitations, in particular EAM and RFCA may be limited by the presence of coronary

arteries and epicardial fat. CT is a reliable imaging technique that allows visualization of the coronary arteries and epicardial fat.[76,77] The group of Zeppenfeld recently evaluated the feasibility and accuracy of accurate real-time integration of CT-derived coronary artery anatomy and fat distribution during the ablation procedure.[78] After registration of a single coronary injection, the distance between target sites of ablation and coronary arteries can be accurately evaluated by integrated CT, with a mean surface error of only 2.8 mm. Moreover, in contrast to previous observations, the authors demonstrated that unipolar voltage is not influenced by epicardial fat, probably because the larger field of view.[13,79] Therefore, unipolar voltage mapping may be useful for identification of subepicardial or intramural scar even when thick fat is present. In conclusion, in this study a thick epicardial fat layer (>7 mm) and the presence of coronary arteries are important reasons for epicardial ablation failure.

Conclusion:

The new imaging technologies are promising tools to better characterize the arrhythmic substrate. The high density mapping with the assessment of late, fragmented potentials and channels help to localize the critical isthmus in the complex arrhythmias. In addition, the real-time image integration of preacquired MRI and CT information is feasible and accurate to assess epicardial fat and coronary artery, important issues during epicardial ablation. Finally, ICE integration with EAM and catheter tip-tissue contact analysis provides optimization of the lesions during complex procedures.

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