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Journal of Cardiology & Current Research

Editorial

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The association of complex fractionated atrial electrograms, high dominant frequency sites and atrial fibrillation

Keywords: complex fractionated atrial electrograms, high dominant frequency; Abnormal endocardial atrial electrogramsm conventional, endocardial atrial, catheter mapping

Abbreviations: AF, atrial fibrillation; HDF, high dominant frequency; CRAE, Complex fractionated atrial electrograms; 3D EAM, 3 dimensional electroanatomical mapping

Volume 13 Issue 1 - 2020

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Received: December 30, 2020 | **Published:** January 13, 2020

Editorial

The specialized architecture and microanatomy allows the small sinoatrial node to pace the large atria efficiently by maintaining a balanced and controlled relationship. The sinoatrial node automaticity and conduction depends on certain important factors, namely, the unique heterogeneous distribution of intracellular ion channels, Ca^{2+} handling proteins, and autonomic receptors within the sinus node.[1,2] The normal sinus rhythm may be interrupted when there is an association of diffuse atrial remodeling characterized by structural change, with accompanying conduction abnormalities, and increased dispersion of atrial refractoriness. When there are less depolarized myocardial cells and more interstitial fibrosis as the atrial substrate leading to decreasing local voltage, then conduction block and low electrogram amplitude may occur. These atrial changes may lead to reentrant rhythms and especially atrial fibrillation (AF) which can be targeted by catheter ablation.[3–5]

Complex fractionated atrial electrograms (CFAE) and high dominant frequency (HDF) sites recorded by 3 dimensional electroanatomical mapping (3D EAM) theoretically represent abnormal substrates. However, sinus rhythm voltage recorded at the CFAE sites has been shown to be normal.[6–8] It has also been shown that most CFAE and HDF sites identified during AF do not correspond with HDF sites or low voltage areas identified during sinus rhythm.[9–12] However, for terminating persistent AF, extensive ablation, including ablation at sites of CFAE and HDF and/or multiple linear ablations may also be necessary.[3–6]

It has been shown that abnormal human atrial myocardium has certain electrophysiological changes, namely, elevated resting membrane potential, depressed maximal amplitude of the action potential, and decreased upstroke velocity.[13–15] These electrical abnormalities are histologically correlated to degenerative changes of the atrial muscle structure.[15] Investigations based on the recording of abnormally prolonged and fractionated atrial local electrograms during sinus rhythm by catheter endocardial mapping have provided important knowledge about the electrophysiological properties of the pathological atrium.[16–18] Human atrial tissues, where fractionated electrograms are recorded, consist of muscle fibers that are widely separated and their orientation distorted by connective tissue. These histological changes of the atrial tissue derive in decreased intercellular connections, which might increase resistance to current flow, and thereby slow conduction. Therefore, abnormally prolonged and fractionated atrial electrograms recorded during sinus rhythm result in an irregular atrial conduction.[19–21] This irregularity is characterized by a non-homogeneous local electrical activity, related to an anisotropic, non-uniform and delayed conduction through a pathological atrial myocardium. In such altered atrial substrate arrhythmias may develop due to reentry.[19] The 3D electroanatomic mapping revealed anatomic and structural atrial abnormalities that were associated with a change in the nature of sinus pacemaker activity. In addition, there were loss of the normal multi-centric pattern of onset of sinus impulse, shift of the pacemaker complex to low crista terminalis sites, and the presence of abnormal and circuitous conduction around lines of conduction block.[22]

Detailed and quantitative pathological studies performed in patients with AF have demonstrated extensive atrial myocardial fibrosis in the vicinity of the sinus node and internodal tracts.[23] Therefore, an abnormally prolonged and fractionated atrial endocardial electrogram could translate a localized and non-homogeneous electrical activity related to a delayed, non- uniform and anisotropic conduction through a pathological atrial myocardium.[19–21] In additional histological studies, it was observed that the tissues where the abnormally prolonged and fractionated electrograms originate present fibro-degenerative processes.[24] When the atrial walls are markedly altered by fibrosis, the depolarization wave must frequently change direction with respect to the longitudinal orientation of the myocardial fiber. This would cause unidirectional block, slow conduction, and dispersion of the refractory periods in certain places, generating the fundamental elements of the re-entry mechanism.[16–21]

Centurión OA et al.[25] designed a study to evaluate the relationship between certain electrophysiological parameters obtained by programmed atrial stimulation that would indicate increased atrial vulnerability in patients with susceptibility to develop AF. Among the electrophysiological indicators of increased atrial vulnerability were studied the fragmented atrial activity, atrial conduction delay,

repetitive atrial firing and sustained atrial fibrillation, all induced by programmed atrial stimulation with single extra-stimulus. We aimed to clarify the importance and significance of the recording of abnormal atrial electrograms (AAE) during sinus rhythm in patients with sinus node dysfunction susceptible to developing atrial fibrillation. We showed that patients who had AAE had a significantly increased atrial vulnerability, compared to those with normal electrograms. Abnormal atrial electrograms showed a very good specificity and positive predictive value when evaluating the induction of sustained AF. The specificity demonstrated was 94% with a positive predictive value of 93%.[25] In this latter study[25] we have found a significantly longer conduction time of sinus impulses in our patients who possess AAE within the right atrium, as compared to those patients with who do not have AAE. No significant difference was observed in the functional or effective refractory periods of the atrium among patients with or without AAE. In this regard.

Leier CV[13] reported a significant prolongation of the mean right intra-atrial conduction time at 50ms, and the mean interatrial conduction time at 92ms in 21 patients with atrial flutter. In our study[25] the mean intra-atrial (54 ms) and the mean interatrial conduction time (100ms) of sinus impulses were significantly longer in the AAE (+) Group. This prolongation in conduction time of sinus impulses through a diseased atrial muscle may be related to a lengthening of the pathway to be traversed, and/or slowing of conduction velocity. In addition, AAE also proved to be a useful marker in separating patients with more extensive atrial electrical disease who are more likely to have inducible atrial fibrillation from others. AAE may indicate an inhomogeneous local electrical activity related to a delayed and non-uniform anisotropic conduction through a diseased atrial muscle.[19–21] When atrial walls are markedly altered and distorted by fibrosis, the propagating depolarization is required to change direction frequently with respect to fiber orientation, creating sites for potential block leading to AF. The potential clinical significance is that detection of AAE during sinus rhythm in patients with sinus node dysfunction may help to identify those with greater atrial conduction defects and higher incidence of induced and spontaneous episodes of AF.[25]

3D electroanatomic bipolar voltage mapping is a diagnostic auxiliary method that has been utilized in clinical electrophysiological studies for substrate description in atrial arrhythmias. Recent advances in 3D EAM systems have facilitated catheter manipulation within the atrium at reduced fluoroscopy exposure time. Using this 3D EAM system low bipolar endocardial voltage can be identified and localized for guiding catheter ablation. The electrical information obtained can be used in different ways to record different information. For example, certain map points recorded can be utilized for the color-coded display of the electrical activation sequence known as activation mapping. In addition, the display of post-pacing intervals known as entrainment mapping can be recorded, as well as, the display of unipolar/bipolar electrograms as part of fractionation or voltage mapping.[26] These mapping systems are based on non-fluoroscopic visualization of mapping catheters and a 3D reconstruction created by the manipulation of a mapping catheter.

Complex fractionated atrial electrograms (CFAEs) are regarded as surrogates of non- homogeneous and anisotropic conduction of myocyte bundles through a diseased fibrotic atrial myocardium. CFAEs are defined as atrial electrograms with low voltage (≤0.15mV) signals with ≥2 deflections/perturbations of the baseline. It has continuous deflection of a prolonged activation complex; and/or a very short cycle length (≤120 milliseconds), with or without multiple atrial potentials.[27,28] The mechanisms of CFAEs generation have been related to factors which maintain and perpetuate AF. However, the mechanism of development of CFAEs has also been considered to be passive consequences of near-by rapid AF drivers.[28] CFAE may designate atrial sites with delayed conduction or block, wave-front collision or anchor points for reentry. AF ablation studies reported improved outcomes using the technique of CFAE ablation in addition to PVI ablation.[29] However, an important limitation is that CFAE are largely identified by subjective visual inspection. Hence, it relies on operator judgement. The STAR AF trial[30] demonstrated that PVI plus CFAE ablation had the highest freedom from AF vs. PVI or CFAE ablation alone in high-burden paroxysmal/persistent AF. However, STAR-II AF showed contrasting results in only persistent AF patients.[31] This latter trial contradicted the results of the STAR AF,finding no difference in freedom for AF at 1 year in the three groups studied, namely, between PVI alone, PVI plus ablation lines, or PVI plus CFAE ablation strategies, a finding with 3D EAM studies subsequently reproduced by other investigators.[32] Therefore, there are conflicting and controversial data on the importance of CFAE ablation for a better clinical outcome.

Although these EAM systems have been very valuable and reliable for the navigation of AF ablation, they have some limitations prone to make mistakes. For example, the integrated automated mapping algorithms are susceptible to annotation and interpolation errors. This requires a manual point-by-point verification of annotated points which is a time-consuming process. The need to overcome these disadvantages and to improve illustration of the underlying AF mechanisms has led to the development of advanced mapping systems for substrate ablation which have a higher resolution focusing on improving signal quality acquisition. It also improves processing time with lower noise, precision of annotation, and development of automated algorithms that visualize electrophysiological information. Advanced mapping systems emerged from the need to better understand and ablate complex tissue substrates, and representative maps with CFAE and HDF locations. These new systems tried to overcome the spatiotemporal and processing limitations of contemporary EAM systems. In addition, it focused on higher quality signals improving acquisition and illustration of electrophysiological data. The improved electrical signals produced by advanced narrow-spaced catheters, and the automated high-density mapping may also enhanced techniques for scar-based ablation strategies. Future mapping systems would allow detailed visualization of the atrial anatomy and pathophysiology in a MRI-like fashion in order to individualize and monitor lesion formation in a real-time fluoroscopy-free environment. Novel imaging modalities may improve our understanding of what is really necessary or distrustful for improving clinical outcome in AF ablation.

Acknowledgments

None

Conflicts of interest

Author declares that there are no conflicts of interest.

Funding

None.

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Citation: Centurión OA, Alderete JF, Candia JC. The association of complex fractionated atrial electrograms, high dominant frequency sites and atrial fibrillation. *J Cardiol Curr Res.* 2020;13(1):7–9. DOI: 10.15406/jccr.2020.13.00463