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Original research

The logical operator map identifies novel candidate markers for critical sites in patients with atrial fibrillation

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The identification of suitable markers for critical patterns during atrial fibrillation (AF) may be crucial to guide an effective ablation treatment. Single parameter maps, based on dominant frequency and complex fractionated electrograms, have been proposed as a tool for electrogram-guided ablation, however the specificity of these markers is debated. Experimental studies suggest that AF critical patterns may be identified on the basis of specific rate and organization features, where rapid organized and rapid fragmented activities characterize respectively localized sources and critical substrates. In this paper we introduce the logical operator map, a novel mapping tool for a point-by-point identification and localization of AF critical sites. Based on advanced signal and image processing techniques, the approach combines in a single map electrogram-derived rate and organization features with tomographic anatomical detail. The construction of the anatomically-detailed logical operator map is based on the time-domain estimation of atrial rate and organization in terms of cycle length and wave-similarity, the logical combination of these indexes to obtain suitable markers of critical sites, and the multimodal integration of electrophysiological and anatomical information by segmentation and registration techniques. Logical operator maps were constructed in 14 patients with persistent AF, showing the capability of the combined rate and organization markers to identify with high selectivity the subset of electrograms associated with localized sources and critical substrates. The precise anatomical localization of these critical sites revealed the confinement of rapid organized sources in the left atrium with organization and rate gradients towards the surrounding tissue, and the presence of rapid fragmented electrograms in proximity of the sources. By merging in a single map the most relevant electrophysiological and anatomical features of the AF process, the logical operator map may have significant clinical impact as a direct, comprehensive tool to understand arrhythmia mechanisms in the single patient and guide more conservative, step-wise ablation.

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1. Introduction

Despite the last twenty years have witnessed a significant progress in our understanding of atrial fibrillation (AF) and remarkable technological advances in mapping systems and intervention technologies, several crucial questions on AF mechanisms remain open and the optimal ablation treatment to be defined (Roten et al., 2012). Given the ineffectiveness of the sole pulmonary vein (PV) isolation, especially in persistent forms of AF, recent investigations have been focused on identifying additional targets to guide substrate modification (Ganesan et al., 2013b). However, while in experimental and cardiac surgery settings the identification of critical arrhythmic sites can beneficiate from the use of high-density mapping systems, which consent the accurate reconstruction of propagating wavelets, clinical mapping systems usually present a limited number of simultaneously recorded electrograms and low spatial resolution (Eckstein et al., 2009). In this context the contribution of advanced methods of signal processing and analysis may be crucial to infer pattern properties from the quantification of single/few electrogram features (Ravelli and Masè, 2014). As well the use of imaging integration techniques may favour the precise localization of critical sites in the complex, patient-specific, atrial anatomy (Tops et al., 2008).

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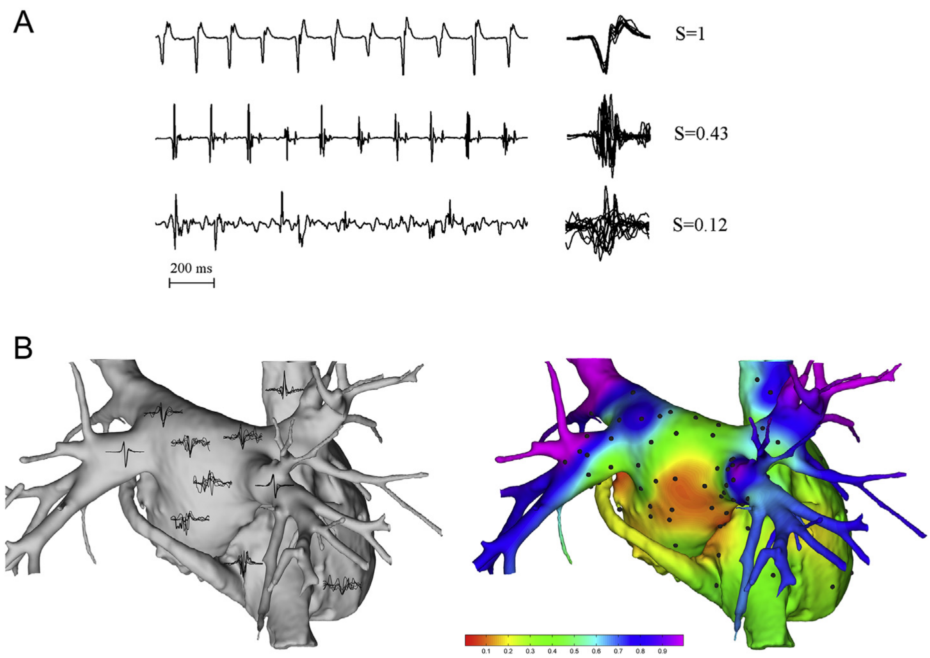

Fig. 1. Morphological assessment of signal organization by wave similarity analysis. Electrograms with different degrees of morphological complexity are shown in panel A, while panel B displays CT-integrated wave-similarity maps in a patient with atrial fibrillation. The values of the similarity index are color coded with green indicating high-similarity and red low-similarity values. Modified with permission from (Ravelli et al., 2012).

1.1. "Rate" versus "morphology" approach for the identification of critical sites

Experimental studies based on high-density mapping systems have provided major contributions to the understanding of AF mechanisms and indicated potential hallmarks of critical target sites, which have inspired the development of specific ablation strategies. Two main mechanisms have been alternatively, if not concurrently, proposed as perpetuators of AF: rapid activations by a driver source and disordered propagation of multiple wavefronts (Jalife et al., 2002; Schotten et al., 2011). According to the source model, mainly supported by optical mapping experiments in the isolated sheep heart, AF is sustained by rapid organized sources, based either on focal and/or reentrant activity and spatially localized, which display frequency and organization gradients towards the surrounding tissue (Haissaguerre et al., 1998; Jalife et al., 2002). The presence of frequency gradients informed the development of spectral mapping and dominant frequency (DF) analysis of single electrograms to systematically identify areas with high DF, potentially associated with localized sources. However, the role of high DF sites in driving human AF has still to be definitively proven, and data on DF-guided ablation outcomes remain limited (Sanders et al., 2005; Atienza et al., 2009; Brooks et al., 2009). Alternatively to DF analysis, a recent study has drawn attention on the spectral organization properties of potential localized sources, showing that sites with organized activation displayed higher stability over time and their ablation led to increased organization in remote areas (Jarman et al., 2014).

Differently from the source model, the multiple wavelet model assumes AF as a turbulent, self-sustaining process, where atrial activation is related to the complex propagation of a limited number of wandering wavelets. Multiple wavelet propagation is characterized by complex processes such as wavefront break, collision or fusion (Allessie et al., 1985), which can be further complicated by the tridimensional structure of the atria and by an elevated epi-endocardial dissociation during AF (Schuessler et al., 1993; de Groot et al., 2010; Allessie et al., 2010; Eckstein et al., 2011, 2013). Konings et al. (1997) showed that in presence of these complex dynamics electrograms displayed distinctive morphological features and a high degree of fragmentation. The observation that electrogram morphological complexity marks critical AF substrates inspired Nademanee's morphologic ablation approach, based on targeting complex fractionated atrial electrograms (CFAE, Nademanee et al., 2004).

Despite initial promising results, the efficacy of CFAE ablation remains debated (Orlov, 2011). The high success rate reported by Nademanee and coworkers has not been replicated in other centres, and adjuvant CFAE ablation in persistent AF patients seems to produce clinical results only comparable with other contemporary ablation approaches (Brooks et al., 2010). Moreover, since CFAE sites have been related to several underlying mechanisms, not all critical for sustaining AF (Narayan et al., 2011; Jadidi et al., 2012), concerns have been raised regarding the risk of excessive ablation and increased procedural risk. Variability in CFAE ablation outcome may be explained by the low specificity of CFAE definition, which is further compounded by the variability of CFAE measurements (Lau et al., 2012). To overcome these limitations and potentially distinguish bystander from critical CFAE, new nonlinear indexes, such as Shannon Entropy (Ng et al., 2010; Ganesan et al., 2013a) and wave similarity (Faes et al., 2002; Ravelli et al., 2012; Lin et al., 2013) have been proposed, which provide a specific quantification of the morphological features of the atrial signal (see Fig. 1). As well, recent investigations in heart failure rabbits have suggested that CFAE areas with high activation frequency may have intrinsic arrhythmogenic properties, significantly different from other atrial areas (Chang et al., 2013), and thus may play an active role in the arrhythmic process.

1.2. Combined rate and organization approach to critical site detection: the logical operator map

Experimental studies have clearly pointed out that distinctive rate and organization features characterize critical sources and substrates in AF, where, in particular, rapid and organized

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