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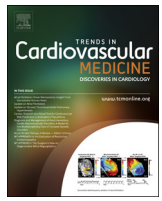

Atrial fibrillation driver mechanisms: Insight from the isolated human heart

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ABSTRACT

Although there have been great technological advances in the treatment of atrial fibrillation (AF), current therapies remain limited due to a narrow understanding of AF mechanisms in the human heart. This review will highlight our recent studies on explanted human hearts where we developed and employed a novel functional-structural mapping approach by integrating high-resolution simultaneous endo-epicardial and panoramic optical mapping with 3D gadolinium-enhanced MRI to define the spatiotemporal characteristics of AF drivers and their structural substrates. The results allow us to postulate that the primary mechanism of AF maintenance in human hearts is a limited number of localized intramural microanatomic reentrant AF drivers anchored to heart-specific 3D fibrotically insulated myobundle tracks, which may remain hidden to clinical single-surface electrode mapping. We suggest that *ex vivo* human heart studies, by using an integrated 3D functional and structural mapping approach, will help to reveal defining features of AF drivers as well as validate and improve clinical approaches to detect and target these AF drivers in patients with cardiac diseases.

Key words: Atrial fibrillation, Reentrant driver, Intramural microanatomic reentry, Fibrosis, Optical mapping, Catheter ablation.

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and a significant cause of hospitalization and morbidity, affecting more than 2.7 million Americans today and projected to increase to 16 million by 2050 [1]. Though there have been significant technological advances in this field, both pharmacological and ablation treatment options for AF remain limited. Several new ablation approaches focused on patient-specific AF mechanisms have been developed with varying outcomes [2]. One of the major limitations of AF ablation is a limited understanding of the mechanisms underlying the disease, as recently reviewed by Wright and Narayan [2] in this journal. Proposed mechanisms that sustain or drive AF include multiple replicating wavelets, focal activity, unstable drifting rotors, and localized stable reentry [3,4]. Importantly, these conflicting hypotheses may stem from the atrial surface mapped, with endocardial (FIRM) mapping detecting mainly reentrant/rotor AF drivers [5] and multiple wavelets and breakthrough observed by epicardial mapping [6].

Recent results from our *ex vivo* human experiments [7–9] lead us to postulate that the primary mechanism of AF maintenance in human hearts is a limited number of localized intramural reentrant AF drivers anchored to heart-specific 3D fibrotically insulated microanatomic tracks, which may remain hidden to clinical single-surface electrode mapping. Single-sided clinical mapping studies may lack the resolution necessary to resolve specific electro-anatomical substrates driving the “chaotic” activity throughout the

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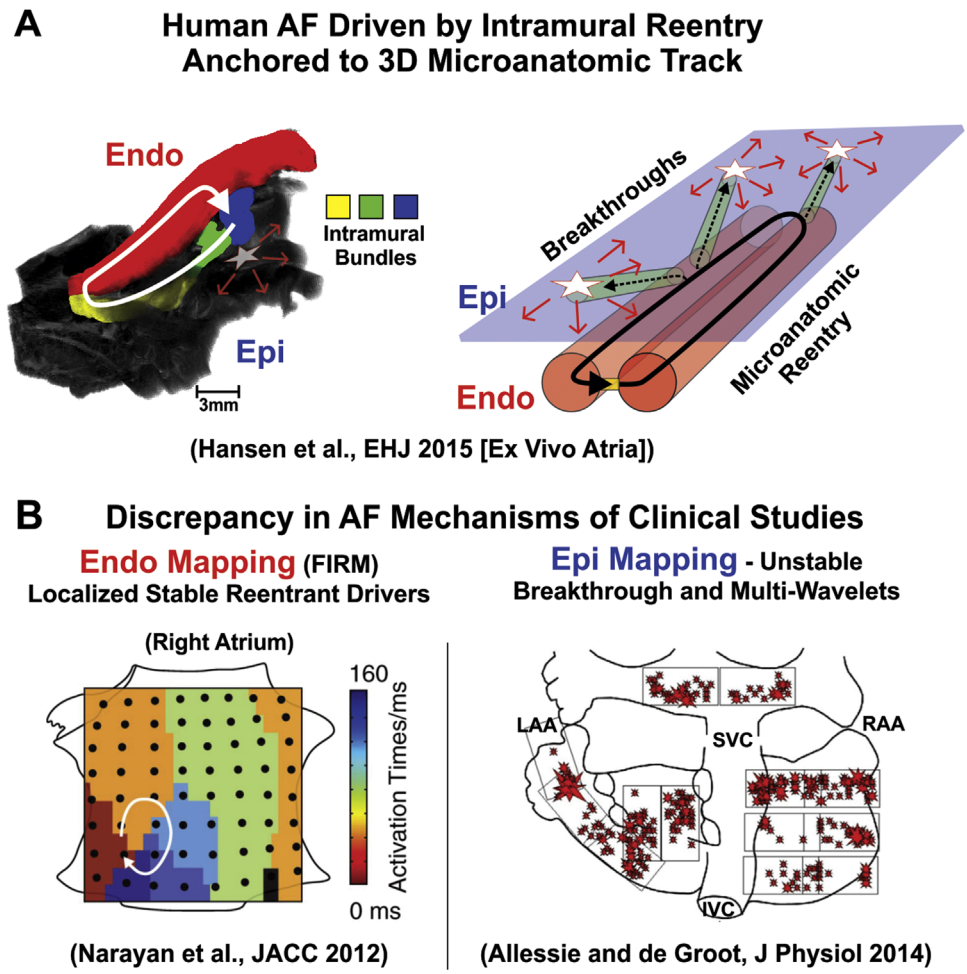

Fig. 1 – AF driver mechanism: intramural microanatomic reentry explains mixed results from clinical studies. (A) Human AF driven by intramural reentry projected differently on epicardial and endocardial surfaces. (B) Clinical studies showing the uncertainty of AF driver mechanisms: endocardial mapping shows localized stable reentrant drivers; epicardial mapping shows unstable breakthrough. AF, atrial fibrillation; Endo, endocardium; Epi, epicardium; FIRM, focal impulse and rotor modulation; IVC/SVC, inferior and superior vena cava; RAA/LAA, right and left atrial appendages. (Adapted with permission from Hansen et al. [7], Narayan et al. [5], and Allessie and de Groot [4].)

complex intramural 3D atrial structures during AF [10]. Thus, the optimal strategy for AF treatment for each patient remains unclear [10].

Importantly, high-resolution optical mapping, which may provide deeper insight on heart-specific AF mechanisms, is not currently possible to utilize clinically but is possible *ex vivo* using coronary-perfused human hearts. This review provides insights on AF mechanisms gained from experimental mapping studies of human hearts *ex vivo*, focused on defining patient-specific AF driver mechanisms and how translating these findings may improve clinical strategies to identify and target these AF drivers in patients.

Controversy of AF mechanisms

AF driver mechanisms in human hearts are widely debated [3,4]. Despite over a century of research, the mechanisms of initiation and maintenance of AF remain elusive [1,11], and the same proposed mechanisms have been debated for over 100 years. Although the idea of local sustaining sources, such as reentrant drivers, rotors, and/or discrete focal discharges, has been hypothesized, a lack of definitive evidence has concealed a conclusive answer in the human heart [6,10].

Almost 100 years ago, Lewis et al. [12] proposed that AF could be driven by a single reentry circuit with fibrillatory conduction propagating from it, later supported by electrode [13] and optical [14] mapping in animal models of acetylcholine-induced AF. Recently, several clinical groups [5,15] have identified different types of localized reentrant drivers in AF patients (Fig. 1) by using 64-channel endocardial basket (focal impulse rotor mapping—FIRM) catheters and non-invasive body surface epicardial mapping (ECVUE) [16] in both paroxysmal and persistent AF. Importantly, both approaches [5,16] revealed localized reentrant AF drivers present in a patient-specific manner across both left and right atria. Furthermore, these studies demonstrated that targeted ablation could successfully treat AF, which supports a localized driving mechanism for AF maintenance, rather than multiple random wavelets that could not be targeted. However, other groups using epicardial local high-density electrode mapping [6,17] and biatrial epicardial mapping [18]