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When is Structure, Function? Revisiting an old concept in atrial fibrillation

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Introduction

The mechanistic role of cardiac structure is central to the conceptualization and therapy of arrhythmias, yet it is poorly understood in all but the simplest cases. A century after Mines first conceptualized reentry based on structural pathways^{1,2}, it is common to dichotomize reentry into ‘anatomical’ and ‘functional’. However, in many ways this is an uneasy distinction.

While the cavotricuspid isthmus is the anatomical basis for typical atrial flutter, it is the anisotropic properties of musculature in this region³ that may facilitate reentry⁴. Similarly, while a ventricular infarct is ‘structural’, it promotes reentry ‘functionally’ by gap junctional remodeling, conduction slowing⁵ and repolarization dispersion in the penumbra⁶ or in trans-infarct channels⁷.

The mechanistic contribution of structure is particularly hazy when considering the role of fibrosis in atrial fibrillation (AF). It is abundantly clear that when it comes to AF, not all fibrosis is created equal⁸ – some patients have minimal atrial fibrosis with advanced AF⁹, while others without AF can have extensive fibrosis¹⁰. Fibrosis can serve a myriad of roles in AF (figure) – slowing conduction velocity (CV) that can anchor reentry in human AF and support the rotor hypothesis¹¹, breaking up spiral waves from repolarization restitution^{12,13} to produce fibrillatory conduction or self-regenerating disorder (multi-wave reentry), facilitating source sink mismatch encouraging ectopic triggers¹⁴, or even altering cellular electrophysiology¹⁵ and thus potentially modulating electrical remodeling.

The translational work by Angel et al.¹⁶ in the *Journal* this month sheds light on this clinically important relationship between fibrosis and AF.

Fibrotic Remodeling Slows Atrial Conduction Non-Uniformly at Predictable Sites

Angel et al.¹⁶ studied whether tachypacing-induced fibrosis slows CV after a potential ectopic trigger of AF, and how this may interact with fiber architecture. Conduction was

studied in high-density electrode plaques near the LA appendage in tachypaced and control goats. In addition to electrical remodeling with shortened atrial effective refractory period¹⁷, the authors found that tachypaced AF goat atria showed greater “obstructive fibrosis”, defined as longer than a myocyte (100 μm) than controls (17.5 ± 8.0 fibers/ mm^2 vs. 8.6 ± 3.0 fibers/ mm^2). This structural remodeling caused functional CV slowing (35%) transverse to but not along fiber orientation. The authors concluded that these changes may increase the likelihood of reentry and AF from a short-coupled trigger. The authors should be congratulated for these elegant experiments linking CV slowing after a potential AF trigger (function) with atrial fibrosis and fiber architecture (structure).

How critical is fibrosis to anisotropic atrial conduction?

One unanswered question from the study is the extent to which observed anisotropic CV slowing at fibrotic regions actually initiates or maintains AF, since AF episodes or transitions were not studied. Their concept is certainly supported by recent studies in which triggers initiated human AF by dramatically slowing CV and initiating reentry at sites that were anatomically conserved for diverse trigger locations¹⁸. On the other hand, clinical electrogram amplitude was not reduced at AF-initiating sites^{19,20}, making it unclear if they represent regional scar or fibrosis. Rapid rates themselves can cause inflammation, hypoxia and down-regulation of numerous molecular pathways, all of which may be pro-fibrotic^{21,22}. On the other hand, fibrosis is not universally observed in the tachypaced goat model²³, suggesting that other mechanisms may contribute to AF.

Anisotropic conduction could result directly from electrical remodeling that alters cellular gap junctional distribution and conductance^{24,25} even in the absence of fibrosis. In addition, the quantification of anisotropy in the current study is limited in that authors assumed that fiber directions were orthogonal, dichotomized at a 45 degree threshold, and not represented as continuous vectors, for instance as reported in recent optical mapping studies of human AF^{11,26}. Assessment of anisotropic conduction would also have been more robust if performed from two sites rather than a single site, since propagation direction may influence CV²⁷.

Translating these findings to human AF

There will be differences between goat and human AF, both in atrial substrate from lack of co-morbid hypertension and aging, trigger types (50Hz pacing in the goat versus spontaneous ectopy) and trigger location (RA in this study vs. mostly LA in humans). Nevertheless, the mechanistic role of fibrosis in AF shown by this study is plausible based on translational studies across animal species now extending to humans. Fibrosis may contribute to the stabilization of rotors in the local source model for human AF, or to the disorganized activation present in all AF models. While the localized source hypothesis remains debated in human AF, evidence continues to mount. Some recent studies questioning AF rotors are difficult to interpret, such as showing long atrial cycle lengths of 250–500 ms (slow atrial rates, dominant frequency 2–4Hz) in patients ostensibly with AF²⁸ or mapping in small plaques that cannot exclude sources in much larger unmapped regions of atria²⁹. Notably, recent optical mapping of AF in human right¹¹ and left²⁶ atria reveal

stable rotors anchored to microfibrosis. These data agree with clinical studies of targeted ablation^{30,31}, and the finding that rotor ablation in optical studies terminated human AF¹¹ further supports the findings of Angel et al.¹⁶ in contributing to AF maintenance or termination³².

In conclusion, Angel et al. provide novel data to support the concept that structural remodeling and fibrosis may cause anisotropic conduction slowing that may facilitate AF. More generally, these data reemphasize the exquisite intertwining of structure and function in fibrillation. To define future diagnostic and therapeutic targets, studies are required to address why some forms of fibrosis facilitate clinical AF while others may not, and if clinical AF may occur without fibrosis.

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FIGURE. Two mechanisms linking fibrosis to atrial fibrillation

A) Anchoring of modeled spiral wave (white arrows) in canine posterior left atrium, which was spatiotemporally stable when fibrosis (red dots) occurred in specific distributions. The left inferior pulmonary vein (LIPV) is labeled for orientation, and the endocardial border is shown as dashed red³³. B) Stable observed micro-reentrant circuit (yellow trapezium) driving AF in human right atrium, localized to areas of fibrosis (pink) as well as late gadolinium enhancement (white) in optical studies of human AF.¹¹ C) Modeling of rapid activation breaking down into fibrillatory waves due to structural heterogeneity in rat left ventricle. Inset zooms in to reveal wave breakdown from fibrosis (grey) as dispersed activation times in color map¹³. D) Disorganized activity due to fibrosis (white) on late gadolinium MR image of human right atrium, here representing fibrillatory conduction from breakdown of a micro-reentrant driver (black arrow)¹¹.