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EDITORIAL COMMENT

Utilizing Biomarkers to Refine Risk Prediction in Atrial Fibrillation

A Step Toward Precision Medicine*

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Atrial fibrillation (AF) has emerged as a new cardiovascular epidemic over the last few decades. It is the most common arrhythmia in clinical practice and portends a significant stress on our nation's medical system. During the last 20 years, hospital admissions for AF have increased almost 60% in the setting of a rising prevalence of chronic heart disease and an aging population (1). Development of refined prediction tools and strategies to guide therapy has become an investigational priority.

Atrial fibrosis is a hallmark of AF. Fibrotic changes within the atrium, assessed by histological evaluation, are associated with increased transformation from paroxysmal to permanent and reduced success of medical antiarrhythmic therapy (2). Assessment of atrial tissue fibrosis could be a promising new tool to risk-stratify a population at risk for AF or patients with a known history of AF.

SEE PAGE 1398

In this issue of the *Journal*, Ravassa et al. (3) successfully identify that a particular combination of circulating biomarkers reflecting excessive atrial myocardial interstitial fibrosis (MIF) is associated with a greater prevalence of AF and with incidence and recurrence of AF after catheter ablation.

The authors begin by defining a complex biochemical profile of increased MIF based on 2 separate serum markers that is worth explaining in some detail. The first, a ratio of serum carboxy-terminal telopeptide of collagen type I to serum matrix metalloproteinase-1 (serum CITP:MMP-1 ratio), has been previously shown to be inversely related to myocardial collagen crosslinking (4). In the present study, patients with a low CITP:MMP-1 ratio were deemed to have significantly increased fibrosis by the basis of elevated collagen crosslinking—and were defined as "CCL+." Second, the authors evaluated serum levels of carboxy-terminal propeptide of procollagen type I (PICP)—which has previously been shown to directly correlate with myocardial collagen deposition (5). Those patients with serum PICP above a set cutoff were deemed to have increased fibrosis by the basis of significantly elevated collagen deposition—and were defined "CD+." Following these criteria, study subjects were classified into 3 groups reflecting combinations of these biomarkers: CCL+CD+, CCL+CD− or CCL−CD+, and CCL−CD−.

The present study was 2-part. First, the authors demonstrated through retrospective analysis that patients with heart failure with the CCL+CD+ profile were 3 times more likely to have AF compared with those with the CCL−CD− profile. These patients without a previous history of AF but with the CCL+CD+ profile were significantly more likely to develop new-onset AF compared with CCL−CD− patients when followed over an average of 5 years.

In the second part of their study, the authors turn to a separate study population—that of patients undergoing AF ablation. They found that the CCL+CD+ profile was significantly associated with AF recurrence after ablation independent of clinical variables such as age and history of heart failure. On electroanatomical mapping, these CCL+CD+ patients exhibited voltage profiles associated with the presence of fibrotic scar more so than AF patients without that combination.

Accumulation of fibrotic tissue is a major component of cardiac remodeling. Myocardial fibrosis

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reduces left ventricular compliance, increases atrial filling pressures, and subsequently promotes the development of atrial fibrosis. The presence of atrial fibrosis can provoke regional conduction abnormalities, increasing the risk for development of AF (2).

Ravassa et al. (3) observed that the incidence of AF in CCL+CD+ heart failure patients was particularly high, suggesting that patients with heart failure complicated by AF may have increased myocardial fibrosis. There is limited existing data on the assessment of fibrosis in heart failure patients via circulating biomarkers. Neither atrial nor ventricular fibrosis is specific to AF, and no marker specific to atrial fibrosis has yet been identified. Previously, others have failed to show that markers of collagen turnover in the serum reflect the extent of atrial fibrosis (6). In the present study, the risk of AF development was directly related to CCL and CD status on a dose-response-like curve: the least risk was associated with CCL−CD− status, moderate risk related to CCL−CD+ or CCL+CD− status, followed by the highest risk in CCL+CD+ patients.

Perhaps the most compelling finding in the present study is the connection between CCL+CD+ profile and AF recurrence after ablation. Catheter ablation for AF is associated with a relatively high recurrence rate, ranging as high as 50% to 70% at 5-year follow-up (7,8). One of the major causes of variability of recurrence after ablation may be a heterogeneous patient population with varying severities of atrial fibrosis (9). Detection of left atrial fibrosis by electroanatomical voltage mapping and by degree of atrial fibrosis via delayed-enhanced magnetic resonance imaging have both been shown to be predictive of successful outcome after AF ablation (10,11). Thus, although it follows that detection of left atrial fibrosis in patients with AF via circulating biomarker would be effective for predicting success of ablation, a reliable marker for this has not yet previously been identified. Therefore, the use of CCL+CD+ status for predicting maintenance of sinus rhythm appears promising.

In conclusion, the investigators have demonstrated that a combination of biomarkers related to fibrosis is associated with the prevalence, incidence, and recurrence of AF. Although the data from Ravassa et al. (3) are encouraging, it is important to remember that it is a single-center study. In addition, in their heart failure study, heart failure patients with either ischemic or structural disease were excluded. Hence, although their results are convincing, this portion of their study may not reflect the breadth of patients seen in typical clinical practice. There is no doubt that we need to move forward with a larger study to determine ease of testing and generalizability to a larger cohort/population. Their work is a step toward tailoring medical treatment to more granular characteristics of individual patients, a step toward precision medicine.

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REFERENCES

1. Friberg J, Buch P, Scharling H, Gadsbphioll N, Jensen GB. Rising rates of hospital admissions for atrial fibrillation. Epidemiology 2003;14:666–72.

2. Dzeshka MS, Lip GY, Snezhitskiy V, Shantsila E. Cardiac fibrosis in patients with atrial fibrillation: mechanisms and clinical implications. J Am Coll Cardiol 2015;66:943–59.

3. Ravassa S, Ballesteros G, López B, et al. Combination of Circulating type I collagen-related biomarkers is associated with atrial fibrillation. J Am Coll Cardiol 2019;73:1398–410.

4. Lopez B, Ravassa S, Gonzalez A, et al. Myocardial collagen cross-linking is associated with heart failure hospitalization in patients with hypertensive heart failure. J Am Coll Cardiol 2016;67:251–60.

5. Lopez B, Querejeta R, Gonzalez A, Larman M, Diez J. Collagen cross-linking but not collagen amount associates with elevated filling pressures in hypertensive patients with stage C heart failure: potential role of lysyl oxidase. Hypertension 2012;60:677–83.

6. Neuberger HR, Cacciatore A, Reil JC, et al. Procollagen propeptides: serum markers for atrial fibrosis? Clin Res Cardiol 2012;101:655–61.

7. Ouyang F, Tilz R, Chun J, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation 2010;122:2368–77.

8. Weerasooriya R, Khairy P, Litalien J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol 2011;57:160–6.

9. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc 2013;2:e004549.

10. Akoum N, Daccarett M, McGann C, et al. Atrial fibrosis helps select the appropriate patient and strategy in catheter ablation of atrial fibrillation: a DE-MRI guided approach. J Cardiovasc Electrophysiol 2011;22:16–22.

11. Verma A, Wazni OM, Marrouche NF, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol 2005;45:285–92.

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