Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 60, No. 18, 2012
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.06.049

EDITORIAL COMMENT

Markers of Collagen Synthesis, Atrial Fibrosis, and the Mechanisms Underlying Atrial Fibrillation*

Jonathan M. Kalman, MBBS, PhD,†‡
Saurabh Kumar, BSc(Med)/MBBS,†‡
Prashanthan Sanders, MBBS, PhD§

Melbourne and Adelaide, Australia

Post-operative atrial fibrillation (POAF) affects 10% to 60% of patients following cardiac surgery, creating increased thrombo-embolism risk and hemodynamic compromise and resulting in prolonged length of stay and increased mortality (1). The impact of POAF extends beyond that of the immediate hospitalization with up to 25% developing ongoing late AF (1). POAF has a substantial impact on healthcare resources with estimates of over $2 billion/year in treatment-related costs in the United States alone, a figure likely to increase given the surgical population is aging with an increasing number of comorbidities that predispose to AF (1).

See page 1799

Thus, it is timely that Swartz et al. (2), in this issue of the *Journal*, report their findings from a prospective study that implicates pre-existing selective left atrial (LA) fibrosis in the pathogenesis of POAF and that recognizes the potential for serum markers of collagen synthesis (C-terminal peptide from pro-collagen-I [PICP] and N-terminal peptide from pro-collagen III [PIIINP]) to identify fibrosis risk. Importantly, there was a modest linear correlation between serum PICP and percentage of LA fibrosis. This study adds to prior work from this group, demonstrating a relationship between atrial fibrosis and development of post-surgical AF, and it potentially has wider implications for patients at risk of AF outside of this surgical context (3). Critically, the study identified a simple peripheral marker of atrial fibrosis and hence of AF risk.

Fibrosis is a fundamental component of atrial structural remodeling that contributes to AF persistence and may be viewed as a final common endpoint of a range of different cardiac insults. Development of regional fibrosis results in electrical uncoupling of adjacent muscle bundles leading to discontinuities in transverse conduction, localized regions of conduction slowing and block, and increased heterogeneity; the net result being promotion of both focal and macro-reentry (4). The spatial distribution and degree of fibrosis have been shown to influence AF activation frequency and wave-front dynamics and the development of LA sources may be predicated on the presence of LA fibrosis (3,5). Time-dependent increases in fibrosis and atrial substrate complexity possibly play a critical role in AF progression from paroxysmal through persistent and permanent forms of the arrhythmia (6).

The correlates of atrial fibrosis in clinical mapping studies also include regional low voltage and electrical silence, conduction slowing with circuitous propagation, and recent evidence of rotor formation (7–10). It is well recognized that atrial fibrosis can occur as a result of AF as part of an arrhythmia-related remodeling process. In addition, conditions associated with atrial stretch and activation of the renin-angiotensin system including hypertension (11), heart failure (12), and valvular heart disease (13) all produce a similar fibrosis-based substrate even before the development of an atrial arrhythmia. Interestingly, a recent study in patients with apparently lone AF, showed early evidence of a similar substrate even though studied at least 2 weeks from an AF episode (14). Furthermore, emerging data suggests that in this population the substrate may progress despite arrhythmia cure (15), raising the possibility that it represents an underlying primary myopathy (16).

The present study strengthens the notion that despite the supervening role of transient factors in the development of POAF, vulnerability to the arrhythmia even in this setting is critically determined by the presence of existing LA fibrosis. This may also explain the ongoing long-term risk of AF in these patients late after cardiac surgery. Beyond the biopsy evidence of LA fibrosis, the study also demonstrated increased LA levels of collagen I and III in patients who developed POAF and elevation in LA pro-fibrotic markers transforming growth factor beta and angiotensin II, providing a molecular link to the increased fibrosis.

Noninvasive assessment of collagen turnover and fibrosis has been used to investigate the natural history and treatment of hypertensive heart disease, diastolic dysfunction, and paroxysmal and persistent AF (17,18). Markers of both synthesis and degradation are increased in different AF populations, although results have not always been consistent

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the †Department of Cardiology, The Royal Melbourne Hospital, Melbourne, Australia; ‡Department of Medicine, University of Melbourne, Melbourne, Australia; and the §Centre for Heart Rhythm Disorders, University of Adelaide and the Royal Adelaide Hospital, Adelaide, Australia. Dr. Kalman has reported that he has no relationships relevant to the contents of this paper to disclose. Dr. Sanders has received lecture fees and research funding from St. Jude Medical, Biosense-Webster, Bard Electrophysiology, and Medtronic; serves on the advisory board of St. Jude Medical, Biosense-Webster, Bard Electrophysiology, Medtronic, and Sanofi-Aventis; and is supported by the National Heart Foundation of Australia. Dr. Kumar is a recipient of the postgraduate research scholarship funded by the National Health and Medical Research Council and the National Heart Foundation of Australia.

JACC Vol. 60, No. 18, 2012
October 30, 2012:1807–8

(17,18). Markers of collagen turnover have also been associated with AF recurrence after catheter ablation and the likelihood of maintaining sinus rhythm after electrical cardioversion of persistent AF (19).

In the present study by Swartz et al. (2), elevated markers of collagen synthesis (PICP and PIIINP) were associated with POAF. Importantly, they make the unique observation of a linear correlation between PICP and LA fibrosis, raising the possibility that simple assay of this peptide may be used to identify patients with pre-existing substrate and at heightened risk of POAF. However, important questions remain unanswered. Of note is that AF patients in this study were older, had larger left atria, greater left ventricular mass, higher prevalence of diastolic dysfunction, and more mitral valve disease. Would these markers still be valid if both groups of patients were equal in the prevalence of these baseline factors? These risk factors have been associated with increased atrial fibrosis and increased levels of these markers per se. Ultimately, the validity of these markers will require evaluation in large multicenter studies before we have a more complete picture of their incremental value and positive predictive accuracy for development of post-surgical AF. A simple serum marker with the ability to identify atrial substrate might also facilitate evaluation of various cardioprotective and cardioreparative therapeutic interventions. Looking more broadly, will these markers be useful for identification of subclinical atrial substrate in other groups at risk of AF or in diverse AF populations? Correlation of serum markers with magnetic resonance imaging–based detection of atrial fibrosis might assist in providing an answer to the latter question.

This study provides important new information on the link between serum markers of collagen synthesis and atrial fibrosis and the risk of developing AF. In doing so, it opens new avenues of research into this common and yet incompletely understood arrhythmia.

Reprint requests and correspondence: Prof. Jonathan M. Kalman, Department of Cardiology, Royal Melbourne Hospital, Melbourne, Victoria 3050, Australia. E-mail: jon.kalman@mh.org.au.

REFERENCES

1. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51:793–801.
2. Swartz MF, Fink GW, Sarwar MF, et al. Elevated pre-operative serum peptides for collagen I and III synthesis result in post-surgical atrial fibrillation. J Am Coll Cardiol 2012;60:1799–806.
3. Swartz MF, Fink GW, Lutz CJ, et al. Left versus right atrial difference in dominant frequency, K(+) channel transcripts, and fibrosis in patients developing atrial fibrillation after cardiac surgery. Heart Rhythm 2009;6:1415–22.
4. Spach MS, Boineau JP. Microfibrosis produces electrical load variations due to loss of side-to-side cell connections: a major mechanism of structural heart disease arrhythmias. Pacing Clin Electrophysiol 1997;20:397–413.
5. Tanaka K, Zlochiver S, Vikstrom KL, et al. Spatial distribution of fibrosis governs fibrillation wave dynamics in the posterior left atrium during heart failure. Circ Res 2007;101:839–47.
6. Verheule S, Tuyls E, van Hunnik A, Kuiper M, Schotten U, Allessie M. Fibrillatory conduction in the atrial free walls of goats in persistent and permanent atrial fibrillation. Circ Arrhythm Electrophysiol 2010;3:590–9.
7. Teh AW, Kistler PM, Lee G, et al. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. J Cardiovasc Electrophysiol 2012;23:232–8.
8. Roberts-Thomson KC, Stevenson IH, Kistler PM, et al. Anatomically determined functional conduction delay in the posterior left atrium: relationship to structural heart disease. J Am Coll Cardiol 2008;51:856–62.
9. Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. J Cardiovasc Electrophysiol 2012;23:447–54.
10. Lee G, Teh AW, Kumar S, et al. Characterisation of activation patterns in human persistent atrial fibrillation: multiple wavelets or focal drivers (abstr)? Heart Rhythm 2012;9:S33.
11. Kistler PM, Sanders P, Dodic M, et al. Atrial electrical and structural abnormalities in an ovine model of chronic blood pressure elevation after prenatal corticosteroid exposure: implications for development of atrial fibrillation. Eur Heart J 2006;27:3045–56.
12. Sanders P, Morton JB, Davidson NC, et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. Circulation 2003;108:1461–8.
13. John B, Stiles MK, Kuklik P, et al. Reverse remodeling of the atria after treatment of chronic stretch in humans: implications for the atrial fibrillation substrate. J Am Coll Cardiol 2010;55:1217–26.
14. Stiles MK, John B, Wong CX, et al. Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: characterizing the "second factor." J Am Coll Cardiol 2009;53:1182–91.
15. Teh AW, Kistler PM, Lee G, et al. Long-term effects of catheter ablation for lone atrial fibrillation: progressive atrial electroanatomic substrate remodeling despite successful ablation. Heart Rhythm 2012;9:473–80.
16. Kottkamp H. Fibrotic atrial cardiomyopathy: a specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications. J Cardiovasc Electrophysiol 2012;23:797–9.
17. Kallergis EM, Manios EG, Kanoupakis EM, et al. Extracellular matrix alterations in patients with paroxysmal and persistent atrial fibrillation: biochemical assessment of collagen type-I turnover. J Am Coll Cardiol 2008;52:211–5.
18. Tziakas DN, Chalikias GK, Papanas N, Stakos DA, Chatzikyriakou SV, Maltezos E. Circulating levels of collagen type I degradation marker depend on the type of atrial fibrillation. Europace 2007;9:589–96.
19. Okumura Y, Watanabe I, Nakai T, et al. Impact of biomarkers of inflammation and extracellular matrix turnover on the outcome of atrial fibrillation ablation: importance of matrix metalloproteinase-2 as a predictor of atrial fibrillation recurrence. J Cardiovasc Electrophysiol 2011;22:987–93.

Key Words: atrial fibrillation ■ cardiac surgery ■ fibrosis.