IJC Heart & Vasculature 34 (2021) 100816

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Editorial

Right atrial blood supply and complexity of induced atrial fibrillation: What's left?

Atrial fibrillation is a complex arrhythmia with multiple underlying causes, including abnormal automaticity originating in the pulmonary vein region of the left atrium [1], heterogeneous conduction and repolarization, and increased but regionally variable interstitial fibrosis occurring as a response to regional changes in wall stress. These factors promote ectopic atrial activation and increase the propensity for re-entrant arrhythmias. While the mechanisms of AF can be studied in patients with AF, variations in the etiology of AF can complicate the interpretation of the analyses.

In 1994, Konings and colleagues in Professor Allessie's group made a major contribution to the classification of AF, identifying three distinct patterns of electrical activity in the right atrium (RA) using high density epicardial mapping of AF evoked with pacing in patients undergoing cardiac surgery [2]. Complexity of RA conduction during AF was variable, ranging from a single broad wavefront of uniform conduction velocity (type I) to the presence of three or more wavelets associated with multiple areas of slow conduction and arcs of conduction block (type III). This unipolar electrogram based system has been widely adopted and has provided durable and important insights into the role of heterogeneous conduction in AF, including identification of the role of longitudinal dissociation in persistent AF [3] and the role of conduction heterogeneity in obesity related AF vulnerability [4].

In the past decade, there has been an increasing recognition of the changes in atrial structure and function that underlie risk of AF; these changes have been described as atrial cardiomyopathy [5]. Consistent with this concept, it has been reported that changes in epicardial conduction precede the development of AF [6]. In this issue, Dudink and colleagues in Maastricht report on a 62 patient study in which they used epicardial RA mapping to determine the relation between the atrial blood supply and the complexity of acute AF [10]. In a healthy heart, the high rate activity of AF greatly increases metabolic demand (~3 fold) and oxygen consumption [7]. Many cardiac surgery patients undergo coronary artery bypass graft surgery to alleviate the impaired coronary artery blood flow that is due to the presence of atherosclerotic lesions. In their study, Dudink and colleagues used high-density (256 electrode) epicardial mapping to assess the relation of RA blood suppy (assessed by coronary angiography) on the complexity of AF [10]. The authors sought to test the hypothesis that right coronary artery occlusion (which provides blood flow to the RA) would contribute to the development of a substrate for AF that would increase complexity of pacing-induced AF.

The authors found that, while there was a trend toward a reduction in AF wave size with increased extent of coronary artery disease (based on the number of vessels with significant coronary occlusion), the measured AF complexity parameters had no significant relation to the blood supply scores. Univariate analysis showed that age, increased severity of coronary artery disease (CAD; 3-vessel vs. zero vessel disease), LDL and total cholesterol levels, and right atrial volume were all associated with an increase in maximal atrial activation time difference ($P < 0.10$). However, in a multivariate analysis only increased age and 3-vessel disease were independently associated with the maximal activation time difference. What does this mean? As noted by the authors, CAD and AF are both diseases that progress slowly, over decades. Occlusion of the right coronary artery (RCA) may be compensated by the develop of collaterals that can sustain blood flow normally provided by the RCA.

While the relation of right atrial coronary supply and right atrial AF complexity is not statistically strong, this does not mean that impaired blood supply has no impact on RA structure and/or function. Ischemia and increased wall stress promote increased expression of atrial endothelin-1 (ET-1), a paracrine peptide that is produced by atrial myocytes and endothelial cells. ET-1 protein and mRNA levels are increased in AF, and in the setting of heart failure [8]. ET-1 promotes activation and proliferation of atrial fibroblasts and deposition of extracellular collagen (interstitial fibrosis) that can slow conduction, especially in the transverse direction. It is of interest that, although not significant ($p = 0.12$) due to the small size of the study, there is a trend toward slowing of conduction velocity with increasing numbers of occluded coronary arteries.

In this study, the authors have addressed only the relation of right atrial blood flow and electrophysiology. While both atria can impact the persistence of AF, triggering of AF is frequently a left-sided phenomena, beginning with ectopy originating in the region around the pulmonary veins. Thus, it will be of interest in future studies to evaluate changes in LA blood flow, LA conduction parameters and AF complexity. The pulmonary veins add a level of structural complexity to the LA anatomy that increases opportunities for focal and reentrant activity. AF promotes functional mitral regurgitation [9] that, due to increased LV systolic pressure, has a greater impact on LA than RA pressure and distention.

The efforts of the authors of this study to carefully evaluate the mechanisms of AF induction in patients with no history of AF are commendable. Parallel studies in animal models, while feasible

https://doi.org/10.1016/j.ijcha.2021.100816

and perhaps less "noisy," cannot easily address the impact of age or the many other clinical variables that accompany patients undergoing surgery. These studies can both promote the development of novel hypotheses, and evaluate the validity of hypotheses generated in preclinical studies. Regardless of the study outcomes, the translational relevance is high.

References

[1] M. Haissaguerre, P. Jais, D.C. Shah, A. Takahashi, M. Hocini, G. Quiniou, S. Garrigue, A. Le Mouroux, P. Le Metayer, J. Clementy, Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins, New Engl. J. Med. 339 (1998) 659–666.

[2] K.T. Konings, C.J. Kirchhof, J.R. Smeets, H.J. Wellens, O.C. Penn, M.A. Allessie, High-density mapping of electrically induced atrial fibrillation in humans, Circulation 89 (1994) 1665–1680.

[3] M.A. Allessie, N.M. de Groot, R.P. Houben, U. Schotten, E. Boersma, J.L. Smeets, H.J. Crijns, Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation, Circulat. Arrhythmia Electrophysiol. 3 (2010) 606–615.

[4] C. Schram-Serban, A. Heida, M.C. Roos-Serote, P. Knops, C. Kik, B. Brundel, A. Bogers, N.M.S. de Groot, Heterogeneity in conduction underlies obesity-related atrial fibrillation vulnerability, Circulat. Arrhythmia Electrophysiol. 13 (2020) e008161.

[5] A. Goette, J.M. Kalman, L. Aguinaga, J. Akar, J.A. Cabrera, S.A. Chen, S.S. Chugh, D. Corradi, A. D'Avila, D. Dobrev, G. Fenelon, M. Gonzalez, S.N. Hatem, R. Helm, G. Hindricks, S.Y. Ho, B. Hoit, J. Jalife, Y.H. Kim, G.Y. Lip, C.S. Ma, G.M. Marcus, K. Murray, A. Nogami, P. Sanders, W. Uribe, D.R. Van Wagoner, S. Nattel, EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication, Heart Rhythm. 14 (2017) e3–e40.

[6] P. Kanagaratnam, P. Kojodjojo, N.S. Peters, Electrophysiological abnormalities occur prior to the development of clinical episodes of atrial fibrillation: observations from human epicardial mapping, Pacing Clin. Electrophysiol. 31 (2008) 443–453.

[7] C.W. White, R.E. Kerber, H.R. Weiss, M.L. Marcus, The effects of atrial fibrillation on atrial pressure-volume and flow relationships, Circ. Res. 51 (1982) 205–215.

[8] F. Mayyas, M. Niebauer, A. Zurick, J. Barnard, A.M. Gillinov, M.K. Chung, D.R. Van Wagoner, Association of left atrial endothelin-1 with atrial rhythm, size, and fibrosis in patients with structural heart disease, Circulat. Arrhythmia Electrophysiol. 3 (2010) 369–379.

[9] M.M. Benjamin, R.L. Smith, P.A. Grayburn, Ischemic and Functional Mitral Regurgitation in Heart Failure: Natural History and Treatment, Curr. Cardiol. Rep. 16 (2014) 1–11.

[10] E.A.M.P. Dudink, E. Bidar, J. Jacobs, A. van Hunnik, S. Zeemering, B. Weijs, J.G.L. M. Luerman, The relation between the atrial blood supply and the complexity of acute atrial fibrillation, IJC Heart & Vasculature (2021), https://doi.org/10.1016/j.ijcha.2021.100794, In this issue.

David R. Van Wagoner
Department of Cardiovascular & Metabolic Sciences, Cleveland Clinic, 9500 Euclid Avenue, M/S ND-50, Cleveland, OH 44195, USA
E-mail address: vanwagd@ccf.org
Received 30 May 2021
Accepted 31 May 2021