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Editorial Comment

# Wrinkles in the Atrium

## Age, Atrial Fibrillation, or Something Else*

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Without question, the most striking risk association for developing atrial fibrillation (AF) is advancing age (1). Structural and electrophysiological changes occur in nearly all tissue with aging. The cellular electrophysiological changes seen with AF are understood to be of complex etiology and accepted to be either or both cause and effect with regard to AF. However, it has generally been accepted both intuitively and based on prior evidence that fibrosis in the atrium, as in the skin, is a consequence of normal aging—wrinkles in the atrium (2–4).

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In this issue of the *Journal,* Platonov et al. (5) report their findings from a well-conducted study that questions the accepted age and atrial fibrosis relationship. The authors conducted meticulous histological examinations at important sites in both atria in patients with paroxysmal AF, permanent AF, and AF-free controls. The study was blinded, systematic, and utilized objective computer-assisted evaluation of fatty infiltration, inflammatory cell count, and fibrosis. They found a twofold to threefold increase in these changes in patients with AF compared to controls, and the same findings were more prevalent and extensive with permanent compared to paroxysmal AF patients. A principal finding from this study was that no correlation existed between age and fibrosis at any atrial location.

Before we decide whether the findings of Platonov et al. (5) question or refute the conventional wisdom with regard to age and atrial fibrosis, we must critically examine their findings in the context of the incredibly complex and nuanced details that underpin any examination of structural correlates with abnormal electrophysiology.

### Where Are the Structural Changes?

As important as quantifying the extent of histopathological changes with AF is the exact site of occurrence. The investigators sampled sites with unique fiber orientation, and thus conduction properties (crista terminalis and Bachmann's bundle), and the posterior left atrium, including closer to the pulmonary veins (PV) (6). The nature of this meticulous study is highly labor intensive, essentially precluding widespread or even more hypothesis-driven, targeted tissue sampling.

**Left atrium versus right atrium.** Interestingly, there was no difference in this study between the extent of fibrofatty changes in the right atrium (RA) and the left atrium (LA). If we consider the 3 main explanations for fibrosis in the atrium—namely, resulting from AF, part of the aging process, and causing AF—and the fact that AF determination on the basis of invasive studies is likely not a RA phenomenon, and this study shows the lack of association with age, then AF giving rise to fibrosis remains a causative role. As discussed in the following text, a common link between these various phenomena may be diastolic abnormality of the left ventricle, and we would expect greater changes in the LA. However, once AF develops, perhaps it becomes the overriding determinant of further or progressive fibrotic changes.

**LA versus PVs.** Any study looking to evaluate the determinants or associations with AF may assume that AF is a single disease process. The ground-breaking changes initiated more than a decade ago on the basis of invasive electrophysiology trigger elimination for paroxysmal AF (7,8). It is clear that AF is at least 2 disease entities: a trigger-driven paroxysmal form, and a "substrate"-based persistent form. In this context, one needs comparative, quantitative, and temporal data between the PVs (trigger site), PV ostia (yet an explained site of conduction delay in patients with AF), and the atrial tissue (9,10).

**LA near the inferior PV.** In the study by Platonov et al. (5), the only site-specific, time-dependent change was in the LA at the level of the inferior PV (fibrosis, $p = 0.051$) and combined count of fibrofatty change ($p = 0.002$) (5). Why should a particular location show more fibrosis or fatty change than others? In addition to possible regional pro-

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pensities for fibrotic reaction, the kinesiological characteristics of cardiac motion may play a role. Atrial fibrillation is more common in taller persons (11) and in athletes, including long-distance runners (12). The fulcrum for cardiac translatory movement is the site of attachment of the pericardium around the atrial–PV junction and may explain relatively accelerated evidence of tissue damage at some sites more than others.

**Nerve tissue.** The so-called substrate for AF includes the atrial tissue and the autonomic tone influencing it (13,14). The histological basis for the dysautonomia associated with AF is unknown. Further, the recent demonstration of interstitial Cajal-like cells in and around the atrial-PV junctions requires histopathological characterization and association with regionality in the structural changes seen in patients with AF (15,16).

## What Are the Structural Changes?

The investigators systematically examined for several histological abnormalities including fibrosis, fatty infiltration, capillary density, cardiomyocyte size, and inflammatory cell count. Importantly, fibrofatty change extent, which was as much as 3-fold higher in patients with AF, correlated with lymphomononuclear infiltration. Of all the possible structural changes, the 1 that appears most likely to be an initiator of the disease process leading to AF would be the inflammatory changes. It would be intriguing to know whether the ratio of inflammatory to fibrotic change might help distinguish whether such a disjoint of present can mark effects related to AF, per se, and the aging process alone (17).

## Why Do These Changes Occur?

Platonov et al. (5) have tackled in a delightfully straightforward and meticulous manner an exceedingly complex set of conundra to try and clarify. Which came first. . .LA size increase or fibrosis, age or AF, AF or fibrosis, inflammation or AF, and so forth? It becomes important to consider whether a common link between these parameters is present.

**LV diastolic dysfunction.** One candidate for a common link/cause with regard to fibrosis, LA size, and AF is LV diastolic dysfunction (DD). Much like AF, LVDD is exceedingly common among the elderly (18), and is even debated in terms of a normal feature of aging versus pathology. Diastolic dysfunction leads to an increase in atrial pressures and size, and presumably will promote fibrosis and possibly the persistent forms of AF. There may be, in addition, site-specific dilation of compliant structures such as the PVs and left atrial appendage, and likely affects the LA more than RA initially. So, is DD the age-associated disease that underpins AF? The importance of this entity has been recognized (19). Unfortunately, however, little is known about whether DD is a disease or itself an explained constellation of abnormalities having an unidentified link that distinguishes normal senescence with pathology.

## Electrophysiology and Structural Abnormalities

Any attempt at a straightforward correlation between structural abnormalities, electrocardiographic data, and arrhythmogenesis, even when outstandingly conducted as the present study is, is necessarily simplistic and possibly naïve. Platonov et al. (5) picked sites like Bachmann's bundle, important for interatrial conduction. From a prior study, for example, signal average P-wave analysis from the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) study data would appear to support a role for conduction defects in developing AF. A specific P-wave morphology suggested interatrial block in patients in whom AF developed, whereas terminal P-wave abnormalities represented delayed conduction into the PVs and did not differ between patients with paroxysmal AF remaining in sinus rhythm and those with new onset AF. Although the logic is elegant, when we consider the complexity of electropathology including simultaneous foci and re-entry, concealed re-entry during sinus rhythm, micro–re-entry concealed or manifest, Wedensky facilitation, Prinzmetal phenomena, and perhaps above all, the importance of relative changes in refractoriness compared to conduction abnormality, it is exceedingly difficult to draw such simple conclusions (20–22). Diseased tissue in the region of the PV may not show conduction delay if there is retrograde penetration from a firing focus in the vein and similar retrograde penetration and Wedensky facilitation from a focus firing in the vein, and the same phenomenon (actual pathology in the vein) would give rise to abnormalities in the middle of the P-wave from retrograde concealed block affecting antegrade penetration. Although dysautonomia can explain both changes in refractoriness and conduction, structural changes and refractoriness have a less clearly defined relationship—even more so than atrial flutter—and no discussion of AF arrhythmogenesis can be complete without considering the structural basis, if any, for abnormal refractoriness.

## Context and Future Studies

Platonov et al. (5) are to be congratulated on making a genuine contribution to our understanding of AF, age, and structural changes. Their study was small, and the historical collection of clinical data, including frequency of AF, treatment, and whether patients without clinical AF actually did not have AF, are unavoidable limitations that must, however, temper our acceptance of the notion that age, per se, is not the cause of atrial fibrosis.

**Bigger. . . better?** Although we would love to see larger studies with greater tissue site sampling, the present study is an excellent example of how a relatively small study, when well conceived and carefully executed while being cognizant of the need for less ambitious objectives for the study, can make an original and potentially ground-breaking contribution to the understanding of AF pathogenesis.

Another similar, carefully performed, small study with detailed electrophysiology determinations and tissue sam-

pling could be another breakthrough, possibly as a study with electrophysiology and histopathology providing a basis for the changes seen with delayed-enhancement magnetic resonance imaging (3,23,24). Once the electropathological nature of magnetic resonance imaging changes is established, larger, longitudinal studies with a greater mix of patient and AF profiles would be exceedingly revealing.

**AF, age, and fibrosis.** Whether these entities represent cause, effect, or epiphenomenon is unlikely to be known in the near future. The present study by Platonov et al. (5) represents an important stepping stone to clarify these issues while questioning conventional wisdom regarding age and fibrosis. The wrinkles in the atrium may not just simply go with our gray hairs!

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**Key Words:** age ■ atrial fibrillation ■ fibrosis ■ radiofrequency ablation.