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EDITORIAL COMMENT

Atrial Metabolic Stress

Linking Metabolic Alterations and Atrial Fibrillation?*

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Atrial fibrillation (AF) is the most maintained arrhythmia, with a continuously increasing prevalence in view of an aging population, an increase in cardiovascular disease, and the obesity pandemic.[1] The prevalence of AF is expected to rise from 5.2 million in 2010 to 12 million in 2030, which constitutes a major public health concern. AF is accompanied by a 1.5- to 2-fold increased mortality risk, and it is associated with multiple adverse outcomes, such as a 2.4-fold risk for stroke, a 1.5-fold risk for dementia, a 1.6-fold risk for chronic kidney disease, a 1.3-fold risk for peripheral artery disease, a 1.5-fold risk for myocardial infarction, a 2-fold risk for sudden cardiac death, and a 5-fold risk for heart failure.[1] Comprehensive care for patients with AF implies the appropriate treatment of comorbidities and risk factors along with behavioral changes to lower the likelihood of developing AF and reducing its burden. Once AF manifests, 3 pillars of treatment goals must be addressed: stroke risk assessment and treatment, if appropriate; optimizing all modifiable risk factors; and symptom management using rate- and rhythm-control strategies that consider AF burden in the context of an individual patient's needs.[1] Notably, the results of the recently conducted EAST-AFNT (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) outline improved cardiovascular outcomes with early rhythm-control treatment compared with a rate-control strategy in patients with early AF and cardiovascular conditions.[2] There also appears to be a paradigm shift from rate to rhythm control of AF with improved outcomes in patients with congestive heart failure.[3]

AF commonly leads to left atrial (LA) enlargement associated with a drop in LA function reflecting maladaptive structural and functional "remodeling," which again favors the development of electric remodeling and a conductive environment to foster AF; related LA remodeling is commonly defined as a change in LA volume of >15% compared with baseline, as determined by echocardiography or cardiac magnetic resonance (CMR).[4] In addition, alterations in LA function, which may precede changes in LA volume, can be determined using LA strain imaging. The combined assessment of functional and structural LA remodeling, however, appears to be effective in monitoring LA diseased states. Furthermore, delayed gadolinium enhancement CMR or computed tomography-aided electric mapping may visualize and quantify LA fibrosis, allowing prediction of the potential success of medical or electric cardioversion or ablation procedures to regain sinus rhythm. An imbalance in LA metabolism and remodeling as an underlying cause for persistent AF, however, remains to be further elucidated.

In this issue of *JACC: Basic to Translational Science*, Marchandise et al[5] provide novel insight by demonstrating that patients with persistent AF presented abnormal increases in ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake of the LA and LA appendage (LAA) compared with control subjects, while after return to sinus rhythm, abnormal atrial ^{18}F-FDG uptake widely resolved. Such observations outline an excess in LA glucose metabolism and metabolic wasting underlying persistent AF. As AF is associated with irregular high-frequency excitation and contraction, the abnormal increase in LA glucose metabolism unravels AF-related atrial metabolic stress associated with the development of LA remodeling that again likely

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predicts AF persistence. The study included 36 patients without diabetes with nonvalvular persistent AF undergoing first AF ablation and 5 healthy, age-matched control subjects without AF who underwent ^{18}F-FDG positron emission tomography (PET) after overnight fasting and the administration of a nicotinic acid derivative. Standardized uptake values (SUVs) of ^{18}F-FDG in the whole LA, LAA, and left ventricle were compared with LA ejection fraction and strains using speckle-tracking echocardiography. In 26 patients with initial AF, the same protocol was repeated after return to permanent sinus rhythm at 3-month follow-up. Patients with persistent AF demonstrated significantly higher abnormal SUVs and thus abnormal glucose uptake in the LA and LAA compared with control subjects, respectively. After successful and permanent restoration of sinus rhythm with catheter ablation, LA SUV decreased to 1.9 $\pm$ 0.3 from the initial value of 2.5 $\pm$ 0.7, with a similar decrease in the LAA to 1.9 $\pm$ 0.6 from the initial value of 3.2 $\pm$ 1.1, whereas the SUV in the left ventricle remained virtually the same (11.1 $\pm$ 5.6 vs 12.2 $\pm$ 4.7). Notably, the decreases in LA and LAA glucose metabolism after the restoration of sinus rhythm ensued at 3-month follow-up despite a marked increase in global peak LA longitudinal strain, LA ejection fraction, and active atrial contraction. Such observations demonstrate that persistent AF is indeed associated with unbalanced atrial glucose uptake. As the abnormal increase in atrial glucose metabolism in persistent AF widely normalized after the restoration of sinus rhythm, the increase in glucose metabolism or atrial inflammation may indeed reflect a critical contributor to the manifestation of AF in this specific cardiovascular risk and nondiabetic population. Importantly, there were only a few patients with minor congestive heart failure ($n = 3$), so the effects of increases in left ventricular preload leading to relative congestion in the LA may be seen as a minimal confounding factor for increases in LA glucose metabolism. The small number of control subjects ($n = 5$) vs patients with persistent AF ($n = 26$) is an issue for some criticism, as it may have contributed to observed differences in body weight, with a median body mass index of 29 kg/m^2 in patients with AF vs 25 kg/m^2 in control subjects, which may have contributed, at least in part, to reported LA SUV increases in patients with AF. Notably, active smokers should have been excluded from the present study, as smoking may be associated with systemic inflammation that may also lead to minor increases in abnormal LA ^{18}F-FDG uptake. Cardiovascular risk conditions with increases in arterial blood pressure and/or diabetes may lead to diastolic left ventricular dysfunction favoring the development of AF. In the present study, however, all patients had arterial blood pressures within the normal range, and none had diabetes mellitus. As regards concurrent medical treatment, 8% of patients were treated with beta-blockers, 25% with amiodarone, and 17% with Class 1 antiarrhythmic drugs. All patients except for 1 received direct oral anticoagulation, and 28% patients received statins. Notably, no patients were on angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors, which may have favorably interfered with LA structural remodeling in patients with persistent AF. The study population with persistent AF was quite heterogenous. Fifteen percent of patients had histories of congestive heart failure, and 14% had transient ischemic attacks, strokes, or thromboembolic events. Nineteen percent had coronary artery disease, and 4 patients had endured myocardial infarction. Despite the heterogeneity of cardiovascular disease in this population, the substantial decrease in SUV in the LA and LAA after the restoration of sinus rhythm via ablation provides direct evidence of a cause-and-effect relationship between abnormal increases in LA glucose metabolism and underlying persistent AF. There is some uncertainty regarding whether AF-related increases in glucose metabolism are in part a reflection of atrial inflammation or just atrial metabolic stress that warrants further clinical evaluations.

An interesting and emerging concept may be seen in the identification of LA cardiopathy (LAC), consisting of substantial structural and electric remodeling that frequently precedes the clinical presentation of AF and that itself reflects a risk factor for stroke and dementia even in the absence of AF.[4] It is likely that such patients with substantial LAC, but still without AF, may benefit from direct oral anticoagulant agents for improved clinical outcomes, but this is subject to ongoing clinical investigations. Of further interest may be the application of ^{18}F-FDG PET for the identification of abnormal increases in LA glucose metabolism and/or atrial inflammation in patients with LAC that could reflect a functional substrate to trigger the new onset of persistent AF. Notably, the application of integrated CMR and ^{18}F-FDG PET may emerge as a unique tool with high diagnostic accuracy for the comprehensive identification and characterization of functional, metabolic, and structural LA remodeling in LAC, which may carry important diagnostic and prognostic information, deserving further investigations.

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Overall, Marchandise et al[5] extend our view of LAC to LA metabolic imbalance in persistent AF that widely resolves after the restoration of sinus rhythm and in the presence of reversed LA functional remodeling after 3-month follow-up. The investigators should be complimented, as the present study[5] adds a new concept of metabolic wasting in persistent AF that could reflect a mechanistic link between cardiovascular risk constellations and the initiation or persistence of AF in LAC, which is likely to open new avenues of research and clinical investigations in the challenging field of AF and a variety of treatment options.

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