Atrial fibrillation (AF) is associated with increased morbidity, mortality, and ischemic stroke, and these ischemic strokes are almost always severe. Thrombus formation in the left atrium with ensuing embolism in the cerebral circulation is deemed to be the cause.

According to the Virchow’s triad, hypercoagulability, endothelial dysfunction, and venous stasis should be prerequisite for thrombus formation in the left atrium. Several markers of clotting and platelet activation have been detected in AF patients, including high-plasma levels of the prothrombin fragment F1+2, a marker of thrombin generation, and P-selectin, a marker of clotting activation. The existence of a prothrombotic state may predispose to vascular disease. In a prospective study performed in 231 AF patients, we showed that plasma levels of CD40L, a marker of platelet activation, was associated with and predicted vascular outcomes, such as ischemic stroke and myocardial infarction (MI), during a follow-up period of 2 years. Endothelial dysfunction has been documented by measuring von Willebrand factor, which has been found to be elevated in AF patients and associated with poor vascular outcomes. The rate of endothelial damage seems temporarily related to AF duration because the highest levels have been observed in patients with permanent compared with those with paroxysmal or persistent AF. Venous stasis is the third component; it is supposed to be related not only to arrhythmia but also to AF-induced atrium remodeling, which could further lower contractility via several mechanisms, including low Ca2+ mobilization and impaired myosin phosphorylation. Furthermore, AF-related remodeling of left atrium may have a negative impact on the cardiac circulation as it is associated with downregulation of atrial NO, a molecule with vasodilator and antiaggregating properties. It is still unclear, however, whether remodeling-related venous stasis per se is actually implicated in favoring thrombus formation in AF. In this issue of Circulation: Arrhythmia and Electrophysiology, Nishida et al addressed this important point by analyzing whether AF-related remodeling enhances the risk of thrombus formation using radiofrequency ablation (RFA) to develop thrombosis in the atria. A control group and 3 canine atria remodeling models were investigated. The atria remodeling models included (1) atrial tachycardia induced by atrial tachypacing, (2) congestive heart failure because of ventricular tachypacing, and (3) chronic AF induced by atrial tachypacing. After remodeling, 4 RFA lesions were induced in each atrium; then, 7 days after RFA, cardiac excision and thrombus quantification were determined. Over 70% of lesions disclosed thrombus formation with no significant difference in the prevalence or number of thrombi among groups. Also, there was no difference in total thrombus volume/dog and thrombus volume normalized to number of lesions/dog or lesion area among the 3 groups. Indices of electric and structural remodeling were not associated with post-RFA thrombosis. Analysis of clotting activation, as assessed by plasma thrombin–antithrombin complexes, and inflammation, as assessed by C-reactive protein, did not show difference among groups. The conclusion of this elegant study is that thrombus formation is not affected by a range of types of atrial remodeling, challenging the hypothesis that AF remodeling per se may favor thrombosis in situ. As mentioned by the authors, the study has some limitations in terms of the duration of post-RFA observation (7 days) and chronic AF duration (5 weeks) before RFA. Thus, the possibility that longer periods of AF remodeling might enhance atrial thrombogenesis cannot be excluded.

Another important issue that should be taken into account is that this experimental model does not perfectly mimic AF in humans. Patients with AF often have different risk factors of atherothrombosis, including hypertension, which may be detected in ≈70% to 80% of the population, diabetes mellitus, and dyslipidemia. Thus, risk factors for systemic atherosclerosis are associated with AF. Atherosclerosis is associated with stroke. Thus, patients with complex atherosclerotic plaques in the thoracic aorta detected by transesophageal echocardiography had 4-fold increased rate of stroke compared with plaque-free patients. Peripheral artery disease is an established marker of systemic atherosclerosis, which identifies patients at higher risk of MI and stroke. The prevalence of peripheral artery disease in AF is greatly variable ranging from 4% to 16%; this is likely dependent on incomplete objective diagnosis of peripheral artery disease because ankle/arm pressure ratio, which is an objective measure of peripheral artery disease, was not analyzed. Recognition of the association between systemic signs of atherosclerosis and AF is important to explain the complex clinical picture complicating the course of AF patients. Thus, atherosclerosis of coronary tree with ensuing development of acute coronary syndromes such as MI is a typical feature.
of AF clinical history. In recent clinical trials with the new oral anticoagulants, the rate of annual MI was 1.1%, which was less than the rate of stroke. In an analysis of trials in which the rate of MI was recorded, the occurrence of MI was, however, relatively close to stroke; particularly in AF patients ≥70 years of age, the event rate was sometimes even higher.

The coexistence of atherosclerosis with AF has an important impact for favoring not only atherothrombotic-related clinical events but also the occurrence of AF itself. Prospective studies demonstrated that patients with or at risk of atherosclerosis are more prone to experiencing AF. The Rotterdam study performed a population-based cohort study in 4407 people ≥55 years who were not affected by AF or coronary heart disease. The study encompassed an ultrasonography analysis of the associations between intima-media thickness, a surrogate marker of atherosclerosis, and plaques of the extracranial carotid arteries and the risk of AF during a median follow-up of 7.5 years. During the observational period, 269 (6.1%) new cases of AF were identified. Patients with a higher burden of atherosclerosis were at higher risk of experiencing AF during the follow-up. In particular, the highest quartile of intima-media thickness (1.2–3 mm) and the severity of carotid plaques were significantly associated with a higher risk of AF. Of note, this association was stronger in women than in men. Another study examined the relationship between AF and metabolic syndrome, which includes patients with a constellation of atherosclerotic risk factors, and is a strong predictor of poor vascular outcomes. In a prospective, community-based, observational cohort study with annual health check-up, 28449 subjects without AF were included. The prevalence of metabolic syndrome ranged from 13% to 16% according to the classification used; during a mean follow-up of 4.5 years, 265 (0.9%) new cases of AF were identified. The age-adjusted rates of AF were higher in subjects with metabolic syndrome compared with those without, indicating an association between this atherosclerotic risk factor with new-onset AF. These 2 large prospective studies suggest, therefore, that patients with subclinical atherosclerosis and no overt manifestation of cardiovascular disease are more prone to developing AF and that atherosclerosis may favor the occurrence of AF. Thus, atherosclerosis could gradually reduce blood supply to myocardial tissue and cause atrial damage, which eventually leads to premature myocyte apoptosis, fibrotic replacement, and electric changes associated with reentry processes. Inflammation and oxidative stress have been deemed as factors predisposing to vascular and cellular damage triggering AF. Experimental models of atrial electrophysiological stimulation were associated with enhanced oxidative stress, and antioxidant treatment was able to decrease the vulnerability to AF. In mice deficient of myeloperoxidase, an enzyme that produces reactive oxidant species, experimental provocation of atrial fibrosis was blunted compared with wild type; of interest, upon right atrial electrophysiological stimulation, myeloperoxidase-deficient mice were protected from AF, suggesting that myeloperoxidase activity is crucial for structural remodeling and atrial vulnerability to AF. Studies in humans corroborated these findings, showing that, in addition to myeloperoxidase, other enzymatic pathways generating reactive oxidant species are upregulated and potentially implicated in atrial remodeling. Thus, atrial myocytes from AF patients produce reactive oxidant species via upregulation of NADPH oxidase, the most important cellular producer of reactive oxidant species, and antioxidant treatment reduced the occurrence of AF in patients undergoing cardiac surgery. Furthermore, NOX2, the catalytic subunit of NADPH oxidase, is upregulated in patients with paroxysmal/persistent AF, suggesting a causative role for this NADPH oxidase isoform in triggering AF. Finally, in patients with paroxysmal/persistent AF undergoing electric cardioversion, serum levels of vitamin E and oxidative stress were associated with a higher recurrence rate. The relationship among inflammation, oxidative stress, and AF was also confirmed by the fact that high values of C-reactive protein were detected in AF patients and predictive of vascular outcomes.

The clinical picture of AF patients seems to be similar to patients with typical atherosclerotic risk factors and, hence, at risk of vascular disease in cerebral and coronary vascular trees. This is supported by the coexistence of hypertension, diabetes mellitus, and dyslipidemia in the majority of AF patients and by the association with biomarkers of inflammation, oxidative stress, and prothrombotic state. The coexistence of inflammation, oxidative stress, and prothrombotic state may have an important impact on the clinical history of AF acting at different levels. Thus, they could combine to promote atherothrombotic disease with MI and atherosclerotic ischemic stroke as typical clinical sequelae. However, experimental data suggest that these factors also promote atrial remodeling, endothelial damage, and eventually thrombosis-related venous stasis, which could be favored by the coexistence of a systemic prothrombotic state (Figure). For this reason, ischemic stroke of AF patients would be better defined as a consequence of atherothromboembolism occurring in subjects who may be genetically predisposed to atrial remodeling and AF. The study by Nishida et al would support this point of view as they did not find any change of clotting activation after induction of atrial remodeling or AF, indicating that venous stasis per se without concomitant atherosclerotic risk factors may not be complicated by hypercoagulability and eventually thrombosis. Of course, this hypothesis should be tested in experimental
model such as that by Nishida et al.,

1 taking into account the clinical setting of AF. For instance, retesting the experimental model in animals prone to atherosclerosis could better reflect human AF and be useful for the analysis of the mechanisms that, along with venous stasis, promote left atrial thrombosis.

In conclusion, experimental and clinical data suggest that in AF atherothrombosis and thromboembolism coexist and that atherothromboembolism better defines the pathophysiology and clinical complications of this disease. Inflammation, oxidative stress, and a prothrombotic state, along with functional and structural changes of atria, combine to create an unique and clinical complications of this disease. Inflammation, oxidative stress, and a prothrombotic state, along with functional and structural changes of atria, combine to create an unique and clinical complications of this disease. Inflammation, oxidative stress, and a prothrombotic state, along with functional and structural changes of atria, combine to create an unique and clinical complications of this disease. Inflammation, oxidative stress, and a prothrombotic state, along with functional and structural changes of atria, combine to create an unique and clinical complications of this disease.

Disclosures

None.

References


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