Atherosclerosis of the Thoracic Aorta
Further Characterization for Higher Risk of Vascular Events*
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Data from pathology (1), transesophageal echocardiography (TEE) (2), and, more recently, scanning and magnetic resonance imaging (3) studies have shown that atherosclerotic disease of the aortic arch is an independent risk factor for ischemic stroke, associated with a high risk of recurrent vascular events. These findings have been summarized in the literature (4,5) and confirmed in a meta-analysis (6), and establish a link between the presence of atherosclerotic disease in the aortic arch and risk of ischemic stroke and vascular events.

Prognostic implications. Atherosclerotic disease of the aortic arch with large plaques (≥4 mm in thickness) is present in one-third of patients with cryptogenic stroke, and accounts for one-third of the population with total ischemic stroke age 60 years or older who have at least 1 vascular risk factor (7). In addition to aortic plaque thickness, data from clinical and case-control studies suggest that morphologic parameters such as ulcerations, calcifications (8), superimposed thrombus, and/or hypoechoic plaques may better characterize plaques associated with an increased risk of complications (9).

In this issue of the Journal, Di Tullio et al. (10) report the results of the APRIS (Aortic Plaque and Risk of Ischemic Stroke) study, in which 255 patients with a first acute ischemic stroke and 209 stroke-free control subjects underwent TEE. The association between arch plaques and hypercoagulability—and its effect on stroke risk—was assessed in a case-control design. All subjects were followed prospectively for 55.1 ± 37.2 months to assess rates of ischemic stroke and death. The authors report that patients presenting with recent acute brain infarcts who had large (≥4 mm) or complex (ulcerated and/or mobile) aortic arch plaques were at increased risk of ischemic stroke. The risk was increased 2.4-fold in those with large plaques after adjustment for demographics and other stroke risk factors, and by 3.3-fold when the plaques were both large and complex, as reported previously (4).

In a previously published study (8), we found that, among morphologic parameters such as plaque thickness, surface irregularities, calcifications, and hypoechoic plaques, plaque thickness ≥4 mm was associated with the highest event rate. When we combined plaque thickness with hypoechoic plaques or surface irregularities, no additive prognostic value was obtained. However, a very significant prognostic additive value was observed when large plaques with no calcifications were compared with large plaques without calcifications. The role of other factors, particularly inflammation and coagulation parameters, was not investigated (9), but in a later study involving elderly patients with ischemic stroke, we found no association between lupus anticoagulant concentration and prognosis (11).

Severe atherosclerosis of the aortic arch (defined as plaques ≥5 mm and plaques with mobile components regardless of thickness) has been associated with higher levels of C-reactive protein, fibrinogen, plasmin/antiplasmin complexes, and D-dimers, but no follow-up data are available to determine their prognostic value (12).

In the study by Di Tullio et al. (10), compared with control subjects, stroke patients had elevated concentrations of the coagulation factor fibrinogen (p < 0.001) and prothrombin fragment F 1.2 (p = 0.04), an indicator of thrombin generation involved in both the intrinsic and extrinsic coagulation mechanisms. The patients did not, however, have elevated levels of lupus anticoagulant (p = 0.50). During follow-up, which was available in 86% of stroke patients and in all control subjects, the incidence rates of stroke or death were significantly higher in those with stroke (133 events per 1,000 person-years) versus control subjects (17 events per 1,000 person-years). For the first time, aortic plaques were found to be associated with increased event rates in subjects with prothrombin fragment F 1.2 above versus below the median value (230 events per 1,000 person-years vs. 85 events per 1,000 person-years, respectively, p = 0.05). In stroke patients with large plaques, event-free survival was marginally lower among those with prothrombin fragment F 1.2 levels above the median (p = 0.046). However, owing to the relatively small number of events (12 deaths and 9 strokes) during follow-up, the authors did not find any significant increase in the probability of death (p = 0.094) or stroke recurrence (p = 0.186) (data not shown), suggesting that the concept of coagulation activation as an important prognostic factor, in addition to the role of plaque thickness and complexity, requires further evaluation.

There are several limitations to this study: cases and control subjects were not ideally balanced, with significant differences between groups in terms of age, prevalence of hypertension and diabetes, history of atrial fibrillation, and...
carotid stenosis. In addition, carotid duplex Doppler examination was not performed in every subject, and coagulation variables were not available or interpretable in all individuals. However, when the authors excluded patients and control subjects (n = 40) with a history of atrial fibrillation, prothrombin fragment F 1.2 remained significantly associated with large plaques in stroke patients versus those with no plaques (p = 0.02) (data not shown).

**Markers for atherosclerosis.** Thoracic aorta atherosclerosis is also a powerful marker for generalized atherosclerosis (coronary, carotid, and peripheral arterial disease, including aneurysms) (4). Among vascular risk factors, smoking and hypercholesterolemia are associated with severe aortic arch plaques. Plasma fibrinogen (13) and homocysteine (14) concentrations have been related to the severity and extent of aortic atherosclerotic lesions. Homocysteine may induce endothelial dysfunction, and, thus, atheroma progression, resulting in thrombus accretion on the atheromatous plaque, or it may be a risk marker of atherosclerosis rather than being a risk factor or a causal pathway for vascular events.

Plasma fibrin D-dimers are generated, and, therefore, increased in concentration, when the endogenous fibrinolytic system degrades fibrin. They consist of 2 identical subunits derived from 2 fibrin molecules. Levels of coagulation markers, including D-dimers, prothrombin fragments 1-2, and thrombin-antithrombin complexes, are increased in patients with atrial fibrillation, indicating abnormal thrombogenesis. In the study by Habara et al. (15), D-dimer levels were correlated with left atrial appendage thrombus, and could, therefore, be determined for risk stratification for thromboembolism in patients with stroke and complex aortic plaques.

An association has also been reported between progression of aortic arch atherosclerosis and vascular events (stroke, transient ischemic attack, myocardial infarction, and death), with a significant separation of survival curves between the progression and nonprogression groups as assessed with a 12-month TEE on follow-up (16).

**Role of new markers in risk stratification.** Future studies will be required to clarify whether the combination of clinical, echocardiographic, and biological risk factors (including D-dimers, von Willebrand factor, high sensitivity C-reactive protein, interleukin-6, and so on) will help to stratify more accurately the risk of thromboembolism in patients with stroke and complex aortic plaques.

Identification of atherothrombosis in the aortic arch could be important in the treatment of patients with ischemic stroke. Several therapeutic options, including anticoagulants, antiplatelets, cholesterol-lowering drugs, and surgery, have been discussed. Two retrospective observational nonrandomized studies reported a potential benefit of warfarin versus antiplatelet drugs in patients with mobile components in their aortic plaques (4). However, data from 2 randomized multicenter studies—FAPS (French Aortic Plaques in Stroke) (16) and WARSS (Warfarin-Aspirin Recurrent Stroke Study)—which included patients with a recent ischemic stroke, showed no evidence to demonstrate the superiority of warfarin over aspirin in this population (9). The ARCH (Aortic arch Related Cerebral Hazard) trial, which is evaluating warfarin versus clopidogrel plus aspirin in stroke patients with aortic plaques ≥4 mm, will help to answer this important question. In the meantime, oral anticoagulation therapy should be restricted to patients with TEE-detected superimposed thrombi. Antiplatelet therapy (aspirin or clopidogrel) is the usual treatment option in secondary prevention after stroke (17,18). Indications for surgical aortic endarterectomy should be restricted to highly selected patients with a low operative risk who have had multiple and documented embolic events despite receiving optimal medical treatment.

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