The Pathophysiological Mechanism Is an Independent Predictor of Long-Term Outcome in Stroke Patients with Large Vessel Atherosclerosis

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Background: Etiopathological mechanisms underlying ischemic stroke play a crucial role in long-term prognosis. We aimed to investigate the association between the mechanism of stroke due to large vessel disease, and long-term outcome. *Methods:* All consecutive patients registered in the Athens Stroke Registry with atherosclerotic stroke between 1993 and 2010 were included in the analysis. The patients were subdivided into 3 groups according to the presumed underlying mechanism: low-flow infarcts, artery-to-artery embolism, and intrinsic atherosclerosis. They were followed up for up to 10 years or until death. The end points of the study were 10-year all-cause mortality, stroke recurrence, and composite cardiovascular events. *Results:* Five hundred two patients were classified as follows: 156 (31%) as low-flow (watershed) strokes, 256 (51%) as artery-to-artery embolic strokes, and 90 (18%) as intrinsic atherosclerotic strokes. The cumulative probability of 10-year mortality rate was similar between groups of patients with different stroke mechanisms: 49.9% (95% confidence interval [CI], 38.5-61.3) for patients with low-flow mechanism, 47.6% (95% CI, 39.4-55.8) for patients with artery-to-artery embolism, and 48.5% (95% CI, 34.0-63.0) for patients with intrinsic atherosclerosis. Patients in the intrinsic atherosclerosis group had significantly higher risks of recurrence (adjusted hazard ratio [HR] = 2.1; 95% CI, 1.19-3.73) compared with those in the artery-to-artery embolism group. Moreover, patients in the intrinsic atherosclerosis and low-flow groups had significantly higher risks of composite cardiovascular events compared with those in the artery-to-artery embolism group (adjusted HR = 1.94; 95% CI, 1.26-3.00; and adjusted HR = 1.64; 95% CI, 1.13-2.38, respectively). *Conclusion:* Low-flow and intrinsic atherosclerosis strokes are associated with a high risk for future cardiovascular events and stroke recurrence. However, long-term mortality is similar across different subgroups.
Key Words: Stroke—Cerebral infarction—Atherosclerosis—Stroke mechanism—Prognosis—Embolism—Borderzone infarct.

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Introduction

After an initial transient ischemic attack (TIA) or ischemic stroke, patients with large artery atherosclerosis are at high risk for either a first-ever or a recurrent stroke.[1] Moreover because of the diffuse, systemic nature of atherosclerosis, patients with a history of stroke or TIA are also at risk for ischemic events involving coronary arteries, a phenomenon termed "cross-risk."[2]

The etiopathological mechanism underlying ischemic stroke plays a crucial role in long-term prognosis and risk of recurrence. In large vessel disease in particular, three different major mechanisms have been described: low-flow (borderzone/watershed infarcts), artery-to-artery embolism, and intrinsic atherosclerosis.[3,4] However, to our knowledge, scarce data exist concerning the association between the mechanisms and long-term outcome. Moreover, the prognosis of low-flow stroke has not been studied in full extent until recently.

The aim of the present study was to investigate the association between the stroke mechanism and long-term outcome in terms of mortality, stroke recurrence, and composite cardiovascular events in patients with ischemic stroke due to large vessel disease, with emphasis on low-flow stroke.

Methods

We used data from the Athens Stroke Registry, which is an ongoing prospective registry of all consecutive patients with acute first-ever stroke who were admitted to the Alexandra University Hospital (Athens, Greece) within 24 hours of stroke onset.[5] All patients with ischemic stroke who registered between January 1, 1993, and December 31, 2010, were included in the analysis. The Institutional Review Board of Alexandra Hospital, Athens, approved the use of this registry for scientific purposes.

Detailed data were prospectively registered for each patient, including demographics, medical history, vascular risk factors, prior treatment, stroke severity on admission (by means of the National Institutes of Health Stroke Scale [NIHSS] score), laboratory results, imaging data, and treatment. The initial evaluation consisted of a noncontrast CT scan of the brain, standard blood tests, a chest X-ray, and 12-lead electrocardiogram in all patients. Systolic blood pressure and diastolic blood pressure on admission were the mean of 3 consecutive measurements. All patients were admitted from the emergency room and hospitalized in a 5-bed acute-stroke unit. If patients were not eligible for thrombolysis (ie, onset time >3 hours) or they did not meet the inclusion criteria for recombinant tissue plasminogen activator (rTPA), they were given 325 mg of aspirin. Low molecular weight heparins were given to bedridden patients (for deep vein thrombosis prophylaxis). Automatic noninvasive blood pressure readings and cardiac monitoring were performed in all patients admitted to the acute-stroke unit. Doppler ultrasonography of the cervical arteries was used in all patients during hospitalization. Cerebral angiography was necessary in the majority of cases to further understand the stroke mechanism. If the ultrasonography showed an occlusion responsible for an ipsilateral stroke, no cerebral angiography was necessary for further investigation. A second CT scan or magnetic resonance imaging (MRI) of the brain was performed from days 4 to 14. Additional cardiac tests were performed to rule out cardioembolic or other stroke mechanisms. Strokes cases were classified according to the definitions used by the Athens Stroke Registry and the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[5,6] Stroke patients with large vessel atherothrombotic stroke were subdivided into 3 groups based on the pathogenic mechanism.

After analyzing neuroimaging (topographic patterns on computed tomography or MRI[7]) and angiographic clinical data,[3,8] we subdivided stroke mechanisms into 3 different categories according to the presumed underlying mechanism: artery-to-artery embolism, low-flow infarct, and intrinsic atherosclerosis. The topography of the infarct lesions was determined according to the published arterial supply templates.[9] All possible embolic occlusions from the heart were excluded.

Artery-to-Artery Embolism

MRI or CT scan demonstrated infarcts distal to the stenosed vessel in the territory of the relevant artery. Proximal artery was occluded or had more than 70% stenosis. Clinically these were characterized by symptoms maximum at onset in the majority of cases.

Low-flow (Borderzone) Infarcts

A low-flow mechanism was implied when infarcts were located in borderzone areas (cortical borderzone infarcts and/or internal borderzone infarcts), distal to the severely stenosed or occluded vessel. Clinically these borderzone infarcts were associated with a stepwise onset, preceding syncopal symptoms and/or episodes of hypotension.[10]

Intrinsic Atherosclerosis

The infarcts were characterized clinically by a nonlacunar syndrome and on neuroimaging by a larger lesion on Diffusion Weighted Imaging or CT scan (>2 cm). Angiographic evidence of an occlusive lesion or significant stenosis (>50%) in the relevant artery was necessary. No significant stenosis (>50%) of the related extracranial arteries was documented. Infarcts were localized to an area adjacent to the stenosed vessel or were extensive, involving the entire or most of the relevant arterial territory.[11] In patients with more than one vessel with significant stenosis or occlusion (relevant to the stroke), a