Acute Myocardial Infarction, Ischemic Stroke, Sympathetic Stress, and Inflammation

Birds of a Feather

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Stroke, the leading cause of neurological death, is the leading cause of disability in the US. Ischemic stroke represents about 85% of all strokes and is a heterogeneous condition. Generally speaking, ischemic strokes can be classified into different categories according to their presumed mechanism as follows: infarct with large artery thrombosis; embolism attributed to cardiac sources or cardioembolic; lacunar infarction; or cryptogenic infarction or infarct of undetermined cause. Cardioembolic strokes are a major mechanism of ischemic strokes with nonvalvular atrial fibrillation alone accounting for about 25% of all ischemic events. Other cardiac conditions that have been associated with cardioembolic strokes include acute myocardial infarction (AMI), ventricular aneurysm, rheumatic valvular disease, mechanical prosthetic valve, and left atrial or ventricular thrombi to name the most common.

The association between ischemic stroke and AMI has been recognized for several decades. The risk of ischemic stroke in patients presenting with AMI has declined from 2.4% to 3.5% in earlier reports to about 0.6% to 1.8% in more recent studies incorporating thrombolytic or anticoagulant therapy in the acute phase. Despite such infrequent occurrence of ischemic strokes after AMI, the outcome of patients is poor with high mortality (17%) and disability (80%).

It is commonly accepted that the relationship between ischemic strokes in the setting of AMI is most likely multifactorial. Factors frequently cited in the literature include older age, history of prior stroke, diabetes, or hypertension, and the presence of large akinetic segments of myocardium with or without left ventricular thrombus. These studies have evaluated the risk of ischemic strokes between 30 days to 5 years after AMI. In this issue of Stroke, van de Graff et al present an interesting study investigating the relationship between time to revascularization for AMI and risk of in-hospital ischemic stroke. The authors analyzed data from the National Registry of Myocardial Infarction 3 and 4 databases that included 45,997 patients who received thrombolytic therapy and 47,876 patients who were treated with primary percutaneous transluminal coronary angioplasty for AMI. The authors found that the risk of in-hospital ischemic stroke after AMI was independently associated with timing to revascularization and that this association was not related to improved cardiac function. This is a significant finding for various reasons. First, it underscores the importance of early revascularization for patients presenting with AMI, not only to improve cardiac outcome but also to reduce neurological complications. Second, similar to what has been reported for acute ischemic stroke, earlier treatment for AMI improves outcome. Third, cardiac dysfunction may not be as important a factor as previously reported in the short-term risk of ischemic stroke in patients with AMI.

If cardiac dysfunction is not an important factor, then what are the possible explanations for this apparent time-dependent decreased risk of ischemic stroke reported by van de Graff et al? As the authors stated in their article, it has been elucidated that inflammatory response plays an important role in the genesis and progression of atherosclerotic lesions. Inflammation of vulnerable atherosclerotic plaques may contribute to the development of acute coronary syndromes and such plaque instability may extend to other vascular beds such as the carotid arteries. High levels of serum C-reactive protein are frequently observed in unstable angina and AMI. Such elevation of C-reactive protein is mostly regulated by proinflammatory cytokines and is largely unaltered by the administration of anti-inflammatory medications. van de Graff et al postulate that such inflammatory response induces a thrombogenic state that may be responsible for the increased risk of early ischemic strokes in patients with AMI. Thus, the earlier coronary revascularization may result in a lesser inflammatory response and an associated lower risk of ischemic stroke. One factor that is not addressed in this article is the role of sympathetic stress in AMI. Sympathetic activity may promote coagulation (via upregulation of platelet activation and factor VIII and downregulation of the fibrinolytic system) and inflammation (via upregulation of T helper cytokines). Evidence suggests that sympathetic activity along with inflammation can induce, and be further stimulated by, thrombotic events such as AMI and ischemic strokes. We find further support in the fact that higher heart rate, presumably a surrogate marker for sympathetic activity, is an independent predictor of ischemic stroke in patients with AMI. van de Graff et al reported that there was no difference in the use of β-blocking medications among the various groups stratified by time from presentation to initiation of therapy. However, the authors did not comment on the
dosages given and the minimum heart rate and blood pressure achieved, which may reflect limitations in the data collection process for the databases used. One can only speculate that those patients treated earlier may have received β-blocking drugs sooner accompanied by lower sympathetic activity leading to a lower risk of in-hospital ischemic stroke compared with those patients treated at later time epochs. Further prospective studies are needed to elucidate this very important question. Regardless of the mechanisms involved, this study suggests one thing: that the earlier the treatment of AMI the lower the risk of cerebrovascular complications.

Disclosures
None.

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Key Words: acute myocardial infarction ■ acute stroke ■ inflammation ■ sympathetic stress ■ thrombolysis
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Stroke. 2006;37:2449-2450; originally published online September 7, 2006;
doi: 10.1161/01.STR.0000242802.13557.2d

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