Endothelial Function and Cerebrovascular Disease: Implications for Diagnosis and Treatment

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Opinion statement

Cerebrovascular disease remains one of the most common causes of morbidity and mortality in the United States. There is strong evidence to implicate endothelial dysfunction in the initiation and progression of atherosclerosis and its complications. It is now well known that endothelial dysfunction represents a systemic syndrome involving multiple vascular beds, including the cerebral vasculature. Currently, no gold standard treatment for endothelial dysfunction exists. Nonetheless, several treatment strategies have been found to be helpful in improving endothelial function. A few of these strategies have been implicated in stroke risk reduction as well, adding another line of evidence to the relationship between endothelial function and cerebrovascular disease.

Introduction

It is now well recognized that the endothelium is an active biologic organ strategically located between the vascular wall and the circulation and is indispensable for a healthy vascular homeostasis (Table 1). Endothelial dysfunction is functionally characterized by an impairment of endothelium-dependent vasodilation, which is mainly caused by a reduced bioavailability of endothelium-derived nitric oxide (NO). In addition, endothelial dysfunction is associated with an imbalance in favor of increased inflammation, oxidative stress, thrombosis, and proliferation of the vasculature contributing to the initiation and development of atherosclerosis [1].

Endothelial dysfunction represents a systemic disorder involving multiple vascular beds [2]. Accordingly, measurement of endothelial function in a particular vascular bed (eg, the coronary arteries or the brachial artery) mirrors the functional state of the entire endothelium, including that lining the cerebral vasculature. Endothelial function testing relies on assessing endothelium-dependent vasodilation. Such tests range from the invasive coronary angiographic measurements coupled with Doppler flow assessment of coronary blood flow in response to intracoronary injection of endothelium-dependent vasodilators (eg, acetylcholine), to less invasive methods employing intra-arterial infusion of endothelium-dependent vasodilators coupled with measurements of forearm arterial response, and finally to noninvasive measurement of endothelium-dependent flow-mediated dilatation of the brachial or digital arteries [3]. Limitations of the different tests used have recently been nicely reviewed with a call for the development of a noninvasive and more reliable method for assessment of endothelial dysfunction and vascular health [4].

Various studies showed that the presence of endothelial dysfunction in peripheral arteries or the coronary circulation is independently associated with different cardiovascular combined end points, including cerebrovascular events [5–7]. Notably, the study by Targonski et al. [8•] showed

Table 1. Function of a normal endothelium

Control of vasomotor tone
Regulation of nutrient trafficking
Control of leukocyte adhesion and migration
Regulation of smooth muscle cell migration and multiplication
Regulation of platelet adhesion and aggregation
Balance between coagulation and anticoagulation
Balance between antifibrinolytic and profibrinolytic effects
Control of inflammation
Antioxidant effects
Neovascularization

that the presence of coronary endothelial dysfunction in patients without obstructive coronary atherosclerosis is associated with a fourfold increased risk of cerebrovascular events independent of known risk factors for stroke. These results suggest that a healthy endothelium represents a key protective factor against cerebrovascular events. Endothelium-derived NO was shown to be a critical factor for cerebrovascular health [9]. The importance of endothelial dysfunction in the pathogenesis of stroke is further highlighted by the fact that different treatment strategies that decrease the risk of cerebrovascular events also improve endothelial dysfunction [10,11]. The present review summarizes various treatment options for endothelial dysfunction and points out currently available evidence for their role in the prevention of cerebrovascular events.

Treatment

- There is no gold standard therapy for endothelial dysfunction. Moreover, there is currently no study that demonstrates an association between the improvement of endothelial function and reduction of stroke with any intervention. However, given that endothelial dysfunction is associated with all currently known cardiovascular risk factors, it is not surprising that treatment or elimination of these cardiovascular risk factors (eg, blood pressure–lowering therapy, smoking cessation) in general also translates into improvement of endothelial function. In addition to traditional cardiovascular risk factor modification, some specific dietary supplements, lifestyle modification strategies, and nonpharmacologic and pharmacologic therapies were shown to lead to an improvement in endothelial function. Notably, some of these treatment modalities have been shown to reduce the risk of cerebrovascular events as well. Nonetheless, it still remains to be determined whether an improvement of endothelial function also translates directly into clinical improvement in a patient's prognosis [3].
- Taken together, our current understanding is that it may reasonable to conclude that modifications of lifestyle with the additional of statin and aspirin may be recommended as measures to improve endothelial function and stroke prevention.

Dietary supplements

Folic acid

- A small randomized crossover study of patients with coronary artery disease showed that folic acid supplementation resulted in improvement of peripheral endothelial dysfunction [12]. Endothelial function was also improved in patients with familial hypercholesterolemia [13]. Moreover, in a large prospective observational study of 43,732 healthy men, there was an inverse relationship between dietary folate intake and the risk of ischemic stroke [14]. Nonetheless, the results of the randomized controlled VISP (Vitamin Intervention for Stroke Prevention) trial that compared the effect of high doses of folic acid, pyridoxine (vitamin B_6), and cobalamin (vitamin B_{12}) to the effect of low doses of these vitamins failed to show a reduction in the risk of recurrent stroke over a 2-year period [15]. Moreover, the recently presented results

of the NORVIT (Norwegian Vitamin Trial) suggest that combined supplementation of high-dose pyridoxine and folic acid may even increase the risk of stroke in survivors of myocardial infarction [16].

Antioxidants

- With a few exceptions, acute administration of vitamin C was shown to reverse endothelial dysfunction of patients with cardiovascular risk factors and/or overt atherosclerosis [17]. In contrast, the effect of vitamin E on endothelial function remains controversial [18]. Nonetheless, human studies failed to show any benefit on stroke prevention with use of vitamin E or vitamin C [19].
- Other antioxidants that have been shown to improve endothelial function include glutathione [20] and *N*-acetylcysteine [21]. However, the benefits of glutathione [22] and *N*-acetylcysteine [23] on stroke have been limited to experimental models.

L-Arginine

- Conflicting data exist on the utility of L-arginine supplementation. In one study, long-term oral L-arginine supplementation for 6 months improved patients' symptoms of angina, coronary endothelial function, and plasma endothelin concentrations [24]. In another randomized, double-blind, placebo-controlled crossover trial of patients with established coronary artery disease and angina, flow-mediated brachial artery dilation, treadmill exercise time, and quality-of-life scores improved with a specially formulated nutrition bar rich in L-arginine [25]. However, a different study showed no benefit of L-arginine supplementation on endothelial function [26].
- No clinical trial has yet evaluated the effect of L-arginine supplementation on the risk of stroke. A recent systematic review of available data on experimental stroke showed that L-arginine was ineffective at reducing lesion volume in transient stroke, permanent stroke, or both [27]. In one study, L-arginine even significantly increased infarct volume [28].

Lifestyle modification

The type of diet

- The Mediterranean diet has been shown to have beneficial effect on peripheral endothelial function in diabetic [29] and hypercholesterolemic patients [30].
- A prospective cohort study looking at the effect of different dietary patterns found that a dietary style characterized by higher intakes of red and processed meats, refined grains, and sweets increased stroke rate, whereas a diet higher in fruits and vegetables, fish, and whole grains protected against stroke [31].

Weight loss

- Weight loss has been shown to improve endothelial dysfunction in obese women [32] and in children [33].
- To this day, no study has looked specifically at the relationship between weight loss and stroke risk reduction.

Physical exercise

- Exercise training was shown to prevent age-associated endothelial dysfunction and to improve endothelial dysfunction in previously sedentary middle-aged and older healthy men [34]. In patients with coronary artery disease, regular aerobic exercise was shown to improve coronary endothelial function [35].
- A meta-analysis of 23 studies looking at the overall association between physical activity and stroke incidence and mortality found that moderate or high levels of exercise are associated with a reduced risk of stroke [36].

Smoking cessation

- Cigarette smoking was demonstrated to be associated in a dose-related fashion with peripheral endothelial dysfunction. Smoking cessation was found to result in improvement of endothelial function in asymptomatic young adults [37].
- The risk of stroke in patients who stopped smoking was found to approach that of nonsmokers over the course of a few years [38].

Pharmacologic therapy

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins)

- There is strong evidence from both experimental and clinical studies that treatment with statins enhances endothelial NO bioavailability and improves endothelial function, an effect that seems to be at least partly mediated by lipid-independent effects of this class of drugs [39]. Notably, experimental studies in a normocholesterolemic murine model demonstrated that prophylactic treatment with statins increased cerebral blood flow, reduced cerebral infarct size, and improved neurologic function via an NO-mediated mechanism [40]. Numerous large-scale randomized clinical trials have shown that statins reduce the risk of stroke in patients with established coronary artery disease or in individuals who are considered at risk for cardiovascular events [41]. Based on the encouraging results of these trials, the Stroke Council of the American Heart Association/American Stroke Association issued an advisory statement indicating that the majority of patients with a history of ischemic stroke or transient ischemic attack of atherosclerotic origin could benefit from statin therapy. Moreover, initiation of statin therapy during hospitalization for first ischemic stroke is probably justified [42]. However, results of the ongoing SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial will have to provide definite information about the role of statins in patients with stroke but no history of other vascular disease. Nonetheless, given that hypercholesterolemia is not an established risk factor for stroke and given the favorable lipid-independent effects of statins on endothelial function, statin-induced improvement of endothelial function represents a likely mechanism contributing to the beneficial effect of statins on the risk of cerebrovascular events observed in large clinical trials.

Angiotensin-converting enzyme inhibitors

- Angiotensin-converting enzyme inhibitors have been shown to improve endothelial function in both patients with coronary artery disease and in patients at risk for atherosclerosis [43,44]. The proposed mechanism for improvement of endothelial function includes enhancing NO bioavailability by decreasing angiotensin II and increasing bradykinin levels.
- There is a paucity of trials looking specifically at the effect of angiotensin-converting enzyme inhibitors on prevention of stroke independent of the effect on blood pressure lowering [45]. In the HOPE (Heart Outcomes Prevention Evaluation) trial, by analyzing the end point of stroke separately from the primary composite end point of cardiovascular death, myocardial infarction, and stroke, ramipril was shown to have a significant protective effect on stroke risk [46]. The benefit of ramipril was thought to go beyond the small attained improvement in blood pressure [47].

Angiotensin II receptor blockers

- Several studies showed the benefit of angiotensin II receptor blockers on endothelial function in both patients with coronary artery disease and in patients at risk for atherosclerosis [48,49].
- In the LIFE (Losartan Intervention For Endpoint reduction for hypertension study) trial, losartan treatment resulted in fewer cardiovascular deaths, myocardial infarctions, and stroke when compared with atenolol. This effect was due to reduction in stroke risk driving the primary composite end point in favor of losartan. The conclusion was that the benefit of blocking the angiotensin II receptor goes beyond the blood pressure–lowering effect of losartan [50].

Estrogen replacement therapy

- The effect of estrogen replacement therapy on endothelial function in postmenopausal women is controversial [51,52]. Unfortunately, estrogen replacement therapy was found to be associated with an increased stroke risk in several studies [53••,54••]. Discrepancies between these randomized studies and earlier observational studies are difficult to reconcile but different hypotheses have been advanced [55].

Aspirin

- The role of aspirin in the reduction of the risk of cerebrovascular events is well established [56]. Preliminary studies demonstrated that acute administration of aspirin may improve peripheral endothelial function in humans [11].

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