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No effect of low-dose statins treatment on cerebral blood flow in humans with atherosclerotic cerebrovascular disease

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Abstract

Animal studies have suggested that the reduction in stroke risk observed with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) therapy is owing to an increase in basal cerebral blood flow (CBF). The purpose of the study was to determine if statin therapy was associated with increased CBF in humans with cerebrovascular atherosclerotic disease. Quantitative measurements of CBF were obtained on study entry in 97 patients with carotid artery occlusion enrolled in a prospective study of cerebral hemodynamics and stroke risk. This study represents a *post hoc* analysis of CBF measurements based on whether patients were receiving statin therapy at the time of CBF measurement. Global and regional CBF (including hemispheric, basal ganglia, and arterial borderzones), and baseline clinical, epidemiologic, and laboratory stroke risk factors were compared between the two groups. Nineteen of the 97 patients were on a statin agent on study entry. The statin group was younger, had significantly lower LDL levels and included more women. Statin therapy was not associated with higher baseline values of CBF in global or regional analyses. Mean middle cerebral artery territory CBF (±s.d.) ipsilateral to the occluded carotid artery was 37.6±12.7 mL/100 g min for the statin group (n = 19) compared with 38.6±12.7 mL/100 g min for the nonstatin group (n = 78). Contralateral values were 42.9±13.5 and 44.2±13.3 mL/100 g min for the statin and nonstatin groups, respectively. We conclude that the stroke risk reduction observed with statin therapy in humans likely involves mechanisms other than an increased basal CBF.

Keywords

atherosclerosis; CBF measurements; cerebral hemodynamics; cerebrovascular disease

Introduction

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is the rate-limiting enzyme involved in the synthesis of cholesterol by the liver. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are a class of agents, commonly known as statins, which deplete intracellular cholesterol in hepatocytes. This depletion leads to upregulation of hepatic low-density lipoprotein (LDL) cholesterol receptors and a lowering of serum LDL. These agents have been proven effective in clinical trials in reducing the incidence of heart attack, and unexpectedly, in reducing the incidence of stroke in patients with coronary artery disease

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(Sacks *et al*, 1996), hypercholesterolemia (Shepherd *et al*, 1995; Scandinavian Simvastatin Survival Study Group, 1995), or other coronary risk factors (Amarenco and Tonkin, 2004; Blauw *et al*, 1997; Heart Protection Study Collaborative, 2002).

This benefit appears to be independent of baseline cholesterol levels. The Cholesterol and Recurrent Events trial compared pravastatin versus placebo in 4,159 patients with prior myocardial infarction and normal serum cholesterol levels. Stroke incidence, a prespecified end point, was reduced by 31% in the treatment group (Sacks *et al*, 1996). Similar findings were reported in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm study, which randomized hypertensive patients with normal or below-normal cholesterol levels to atorvastatin or placebo (Sever *et al*, 2003). Data from these and other clinical trials supporting a cholesterol-independent effect include the following (Blauw *et al*, 1997): (1) the benefit with treatment starts almost immediately (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd *et al*, 1995); and (2) the risk reduction is not related to baseline cholesterol levels (Heart Protection Study Collaborative, 2002; Scandinavian Simvastatin Survival Study Group, 1995). A relationship between vascular risk reduction and the degree of cholesterol lowering has been observed, however (The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002).

There are many potential mechanisms through which statins may reduce stroke risk, including stabilization of atherosclerotic plaques and effects on thrombosis pathways (Delanty and Vaughan, 1997; Rosenson and Tangney, 1998). In animal studies, evidence has emerged that direct effects on endothelial nitric oxide synthase (eNOS, the enzyme that synthesizes nitric oxide (NO) from L-arginine) may be responsible for the cerebral protective effects observed in the clinical trials (Endres *et al*, 1998). Statin agents increase bioavailability of eNOS via stabilization of eNOS mRNA (Laufs *et al*, 1998). Nitric oxide is an important mediator of arterial tone in many vascular territories, including the cerebral circulation (Iadecola *et al*, 1994). Inhibition of eNOS reduces resting blood flow (Iadecola *et al*, 1994). Statins have been found to directly upregulate eNOS expression under cholesterol-clamped conditions (Laufs *et al*, 1998). Mice lacking eNOS are relatively hypertensive and show larger cerebral infarctions than normal mice (Huang *et al*, 1996). Inhibition or lack of eNOS reduces cerebral blood flow (CBF) and increases injury after focal ischemia, whereas administration of NO donors or L-arginine increases CBF and decreases ischemic injury (Huang *et al*, 1996; Morikawa *et al*, 1992; Zhang and Iadecola, 1994).

The strongest evidence for an association between eNOS upregulation with statin therapy and stroke protection via increased basal blood flow is derived from animal studies by Endres *et al* (1998). They showed that simvastatin selectively and directly upregulated eNOS, and that this was associated with increased basal CBF and protection against ischemic injury in normocholesterolemic mice. Infarct volumes after 2 h of filamentous middle cerebral artery (MCA) occlusion and 22 h of reperfusion were smaller and neurologic deficits less in simvastatin-treated mice than in controls (significant at 0.2, 2, and 20 mg/kg doses). Simvastatin treatment had no effects on blood flow or stroke protection in eNOS-deficient mice.

The purpose of this study was to determine if statin use is associated with a higher baseline level of CBF in humans with atherosclerotic cerebrovascular disease. We reviewed clinical and hemodynamic data from patients enrolled in the St Louis Carotid Occlusion study (STLCOS), a prospective study of hemodynamics and stroke risk (Grubb *et al*, 1998; Powers *et al*, 2000). On study enrollment, patients underwent measurements of cerebral blood flow and all current medications were recorded.

Materials and methods

This study represents a *post hoc* analysis of clinical and hemodynamic data obtained from 117 patients with complete atherosclerotic carotid artery occlusion enrolled in the STLCOS, a masked prospective study of cerebral hemodynamics and stroke risk. The details of the overall study design of the STLCOS can be found in previous publications describing the analysis of baseline clinical, hemodynamic, and epidemiological stroke risk factors (Derdeyn *et al*, 1998) and the primary outcome analysis (Grubb *et al*, 1998). This study was approved by our Institutional Research Board and Radioactive Drug Research Committee.

Subjects

At enrollment, and just before positron emission tomography (PET) examination, each patient underwent neurological evaluation including detailed questioning regarding any symptoms. Focal ischemic symptoms in the territory of the occluded carotid artery were categorized as cerebral transient ischemic attack (< 24 h duration), cerebral infarct (> 24 h duration), or retinal event (any duration) and as single or recurrent episodes. Times from the first and the most recent ischemic symptoms were recorded. The presence or absence of 17 known risk factors for stroke was recorded (Derdeyn *et al*, 1998). All current medications were recorded. A study physician investigator reviewed pertinent medical records, computed tomography or magnetic resonance scans, and angiograms. Specific clinical, imaging, and angiographic data were recorded on a standardized form. All current medications and dosages were recorded.

Patients were followed by the study coordinator for the duration of the study by telephone contact every 6 months with the patient or next of kin. The interval occurrence of any symptoms of cerebrovascular disease, other medical problems and functional status was determined. The occurrence of any symptoms suggesting a stroke was thoroughly evaluated by one designated (and masked) physician-investigator based on history from the patient or eyewitness and review of medical records. This investigator remained masked to the PET data. All living patients were followed for the duration of the study.

Hemodynamic and Metabolic Measurements

Details of the hemodynamic PET studies have been published in prior analyses of these data (Derdeyn *et al*, 2002). Positron emission tomography studies on patients with carotid occlusion were performed on study entry. Venous and arterial catheters were placed for intravenous radiotracer administration and for arterial blood gas analyses and arterial time-activity curve determination, respectively. All PET studies were performed on one of two scanners (ECAT 953B or ECAT EXACT HR, Siemens/CTI, Knoxville, TN, USA) in two-dimensional mode. A transmission scan was performed before radiotracer administration using germanium-68/gallium-68 rotating rod sources.

Each PET study consisted of three separate physiologic studies. During each, arterial blood samples were drawn by hand or automatically to convert quantitative regional radioactivity data to quantitative physiologic measurements. Additional arterial samples were drawn at intervals during the examination for determination of PaCO2 stability, mean arterial oxygen content, and carboxyhemoglobin content. Cerebral blood flow was measured using a bolus intravenous injection of oxygen-15-labeled water (Herscovitch *et al*, 1983; Raichle *et al*, 1983). Cerebral blood volume was measured after inhalation of air containing trace amounts of carbon monoxide labeled with oxygen-15 (Martin *et al*, 1987). Oxygen extraction fraction (OEF) and the cerebral rate of oxygen metabolism was measured after one or two breaths of oxygen-15-labeled oxygen in combination with data from the cerebral blood volume and CBF measurements (Mintun *et al*, 1984; Videen *et al*, 1987).

Image Processing and Data Analysis

All images were reconstructed using filtered back projection and scatter correction with a ramp filter at the Nyquist frequency. They were then filtered with a three-dimensional Gaussian filter to a uniform resolution of 16 mm full width at half maximum. These images were subsequently transformed to stereotactic atlas space using a lateral skull film obtained in the scanner and the transmission scan (Fox *et al*, 1985).

For each patient, 32 separate spherical regions of interest, 19 mm in diameter, were placed in each cerebral hemisphere, including 7 in each MCA territory. Cortical regions included gray and white matter. All regions of interest were placed automatically using stereotactic coordinates (Powers and Raichle, 1985). Areas of prior infarction were identified by two investigators by review of cerebral rate of oxygen metabolism images as well as computed tomography or magnetic resonance examinations. Neither the regions within these areas nor the corresponding contralateral regions were used for analysis. The mean OEF and CBF in each cerebral hemisphere were calculated from the remaining regions. Cerebral blood flow data were calculated for global, hemispheric, MCA territory, basal ganglia, arterial borderzones, and lobar regions. Lobar regions were defined as regions of interest that included both cortical and subcortical tissue in frontal, temporal, parietal, and occipital lobes.

Statistical Analysis

For this study, the patients were divided into two groups based on whether they were receiving statin therapy at the time of enrollment and baseline PET study. Global, hemispheric, and regional CBF values, and 17 baseline clinical, epidemiologic, and laboratory risk factors were compared between the two groups using Student's *t*-tests and χ^2 analysis. Baseline medications were compared between groups. The effect of statin therapy on the risk of ipsilateral stroke, any stroke, and death was analyzed by $\chi^2$and Fisher's exact analysis.

Results

Complete quantitative CBF measurements were obtained in 97 of the 117 patients enrolled in the STLCOS. Nineteen of the 97 patients were on a statin agent at the time of enrollment and baseline PET measurements of CBF and OEF (Table 1). Clinical, laboratory, and epidemiologic characteristics of both groups of patients are shown in Table 2. Patients on statin agents ($n = 19$) were younger, more likely to be female and had lower LDL levels. Other baseline characteristics were similar between the statin group and the nonstatin group ($n = 78$).

Analysis of global CBF and other brain regions, such as the cortical borderzones or basal ganglia also failed to show a statistical difference (Table 3). Cerebral blood flow in the statin group was consistently lower than the nonstatin group. Global CBF was 39.3 mL/100 g min in the statin group (standard deviation (s.d.), 13.5) and 40.7 mL/100 g min (s.d., 11.6) in the nonstatin group ($P = 0.63$). Basal ganglia CBF was 42.6 mL/100 g min (s.d., 16.0) in the statin group and 43.7 mL/100 g min (s.d., 12.4) in the nonstatin group ($P = 0.75$). Cerebral blood flow measured in the cortical borderzone regions was 36.4 mL/100 g min (s.d., 12.1) in the statin group and 38.1 mL/100 g min (s.d., 10.8) in the nonstatin group ($P = 0.56$). Lobar CBF (gray and white matter) was 37.9 mL/100 g min (s.d., 12.6) in the statin group and 39.3 mL/100 g min (s.d., 11.5) in the nonstatin group ($P = 0.65$).

Mean CBF measured in the MCA territory ipsilateral or contralateral to the occluded carotid artery was similar between groups (Table 3). The upper 95% confidence limit for the difference of means was 5.4 mL/100 g min for both hemispheres. The lower 95% confidence limits for the difference in the means were 7.4 and 8.1 mL/100 g min for ipsilateral and contralateral hemispheres, respectively. The data for OEF are given in Table 4.

There was no difference in outcome between the two groups over the course of the longitudinal study. One of the 19 patients on statins on enrollment died during the course of the study, compared with 13 of the patients not on statin agents ($P = 0.29$). Ischemic stroke in the territory ipsilateral to the occluded carotid artery occurred in three of the statin patients and six of the nonstatin patients ($P = 0.40$). Four of the statin patients and 20 of the nonstatin patients reached the end point of any stroke or death ($P = 0.88$).

Discussion

Statin therapy was not associated with a higher baseline CBF in this nonrandomized cohort of 97 patients. An increase of up to 5.4 mL/100 g min could have been present, given the 95% confidence limit for the difference of the means. There are several reasons why statins may not result in a measurable increase in baseline CBF in humans. The lower doses of statin agents used in humans may be responsible for the absent or at least lower magnitude of CBF change. In the animal study of Endres *et al* (1998), the protective effect was dose dependent with greater benefit at higher doses (0.2, 2, and 20 mg/kg doses). Absolute basal CBF was increased by 31% after 14 days of daily 20 mg/kg doses of simvastatin (15±75 mL/100 g min compared with 117±7 mL/100 g min for controls). Other possibilities include species differences between rats and humans and the presence of atherosclerotic disease. The presence of underlying hemodynamic impairment is unlikely to explain the lack of an effect on CBF, as no difference was seen between statin or nonstatin groups in ipsilateral or contralateral CBF or OEF values.

We focused on CBF measurements made in the MCA core territory ipsilateral and contralateral to the occluded carotid artery. The ipsilateral MCA regions would be most likely to have some degree of autoregulatory vasodilation and might exhibit a different response to statin therapy than the contralateral MCA regions. No effect was seen in either hemisphere. No differences were observed between groups in analysis of whole brain CBF or other regional analyses.

This was a *post hoc* analysis of a prospective observational study. Patients were not randomized to statin therapy. There were three significant baseline differences between the two groups of patients: age, gender, and serum LDL levels. Two of these three factors bias the statin group for higher levels of CBF. The statin group was significantly younger than the group not on statins. Cerebral blood flow decreases with advancing age (Naritomi *et al*, 1979). In addition, there were more women in the statin group. Female gender is also associated with higher levels of global CBF (Rodriguez *et al*, 1988). The lower serum LDL observed in the statin group confirms that most patients were likely taking their stated medications.

Several limitations of this study must be noted. The recorded doses of statin agents were lower than those used in more recent clinical trials of statin agents showing a reduction in stroke risk. The duration of statin therapy, before enrollment or after enrollment, was not recorded. The total number of patients in this analysis, particularly the group on statin agents, is small and our ability to detect small changes in CBF between groups is limited. The study cohort is limited to patients with atherosclerotic carotid occlusion and may not be representative of the patients in whom the stroke risk reduction was demonstrated. Two different PET scanners were employed over the course of this study, however sensitivity and resolution of the scanners was similar.

In conclusion, we found no evidence for a higher baseline CBF in patients with atherosclerotic cerebrovascular disease on current statin therapy, despite the bias in the statin group for higher CBF. It is possible that some slight increase in CBF occurs with statin therapy. It is unlikely that this effect is responsible for the stroke risk reduction. Other effects of statin agents are more likely to be responsible for the stroke risk reduction observed with statin therapy.

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Table 1

Statin agents and dosages recorded on enrollment

Daily dose	10mg	20mg	30mg	40mg
Simvastatin	3	3		
Lovastatin	1	6		3
Pravastatin		1		
Fluvastatin		2		

Table 2

Baseline stroke risk factors between groups

	Statins (n = 19)	Nonstatins (n = 78)	P *value*
Age (years)	61.1+/-8.6	65.4+/-8.5	0.048
Male	10 (53%)	60 (78%)	0.041
Hemoglobin	13.2+/-1.4	12.7+/-1.4	0.25
Drinks (week)	2.6+/-4.7	5.9+/-13.7	0.29
Fibrinogen	386+/-55	370+/-88	0.48
High-density lipoproteins	46.5+/-16.1	41.5+/-11.2	0.12
Low-density lipoproteins	130+/-39.7	154+/-45.3	0.049
Triglycerides	218+/-122	210+/-157	0.83
Prior symptoms	14 (74%)	54 (70%)	0.99
Amaurosis	3	12	
Stroke	5	29	
Transient ischemic attack	6	12	
Ischemic optic neuropathy	0	1	0.57
Hypertension	11 (58%)	50 (65%)	0.61
Prior myocardial infarction	3 (16)%	17 (22%)	0.53
Diabetes	4 (22%)	22 (29%)	0.50
Smoking			
Never	2	11	
Exsmoker	10	34	
Pipe (cigar)	0	3	
Cigarette	7	29	0.77
Family history	4 (21%)	17 (22%)	0.99
Medications			
Antiplatelet	13 (68%)	59 (75%)	0.55
Coumadin	7 (37%)	24 (30%)	0.55
Calcium channel blocker	5 (26%)	30 (38%)	0.28
Angiotensin-converting enzyme inhibitor	6 (32%)	19 (24%)	1.00
Beta blocker	5 (26%)	14 (18%)	0.73
Alpha blocker	0	3 (4%)	1.00
Pentoxifyllin	1 (5%)	6 (8%)	1.00
Dipyridamole	1 (5%)	2 (3%)	0.46

Table 3

Global and regional CBF values in mL/100g min

	Statins (n = 19)	Nonstatins (n = 78)	P *value*	Lower 95% C.I difference of means	Upper 95% CI difference of means
Ipsilateral MCA (s.d.)	37.6 (12.7)	38.6 (12.7)	0.74	-7.4	5.4
Contralateral MCA	42.9 (13.5)	44.2 (13.2)	0.67	-8.1	5.4
Global	39.3 (13.4)	40.7 (11.6)	0.63	-7.6	4.7
Ipsilateral hemisphere	37.4 (13.4)	38.3(11.3)	0.77	-7.0	5.2
Contralateral hemisphere	41.0 (13.5)	43.0 (12.5)	0.56	-8.5	4.6
Basal ganglia	42.6 (16.0)	43.7 (12.4)	0.75	-7.9	5.7
Borderzone	36.4 (12.1)	38.1 (10.8)	0.56	-7.4	4.1
Lobar	37.9 (12.6)	39.3 (11.5)	0.65	-7.5	4.7

CBF, cerebral blood flow; CI, confidence intervals; MCA, middle cerebral artery; s.d., standard deviation.

Ipsilateral MCA indicates the CBF measured in the seven regions of interest placed in the core MCA territory ipsilateral to the occluded carotid artery.

Contralateral MCA is measured in the opposite hemisphere.

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Table 4

Middle cerebral artery territory OEF values

	Statins (n = 19)	Nonstatins (n = 77)	P *value*	Lower 95% CI difference of means	Upper 95% CI difference of means
Ipsilateral OEF	0.449	0.438	0.74	-0.046 (-16%)	0.066
s.d	+/-0.12	+/-0.11			
Contra OEF	0.421	0.410	0.4	-0.036 (-17%)	0.058
s.d.	+/-0.09	+/-0.09			

CI, confidence intervals; OEF, oxygen extraction fraction; s.d., standard deviation.