Plasma Lipoproteins in Cortical Versus Lacunar Infarction

Robert J. Adams, MD, Richard M. Carroll, PhD, Fenwick T. Nichols, MD, Nancy McNair, MD, Daniel S. Feldman, MD, Elaine B. Feldman, MD, and William O. Thompson, PhD

We investigated the relation of plasma lipids to the risk for ischemic stroke by comparing clinical and biochemical characteristics of survivors of cortical (n=48) and lacunar (n=36) brain infarction. By analysis of variance, no differences were observed in the concentrations of total cholesterol, triglycerides, low density lipoprotein cholesterol, very low density lipoprotein cholesterol, or apoproteins A1 and B. Patients with lacunar infarction, however, had higher concentrations of high density lipoprotein (HDL)-cholesterol than patients with cortical stroke. This HDL-cholesterol difference was due primarily to a strikingly low HDL-cholesterol content in white patients with cortical stroke. These data suggest that previously demonstrated differences in HDL-cholesterol concentrations between patients with ischemic stroke and control subjects without stroke may apply to patients with cortical but not lacunar infarction. Separation of cerebral infarction into subtypes based on mechanism may help clarify lipid-related risk factors in cerebrovascular disease. (Stroke 1989;20:448-452)

A number of investigations of lipid-related risk factors in cerebrovascular disease have been reported.1-11 These studies have varied greatly in their definitions of cerebrovascular end points, assessments of concomitant risk factors, lipids analyzed, and findings. In the Framingham Study, the level of total serum cholesterol in persons over 65 years of age was inversely related to brain infarction; among lipoproteins, only low density lipoprotein (LDL)-cholesterol was identified, and the association was a negative one restricted to women.12 Other studies have suggested that increased concentrations of total cholesterol3,8 and/or triglycerides2,7 are related to risk for stroke. In more recent investigations, however, only a low concentration of high density lipoprotein (HDL)-cholesterol has been consistently implicated as an indicator of risk for brain infarction.5-7,9,11 While most previous studies have distinguished brain infarction from intracranial hemorrhage, further classification of ischemic stroke into subtypes based on presumed mechanism has generally not been attempted.

If the relation of plasma lipids to stroke risk parallels that of coronary artery disease, lipid abnormalities would be most likely encountered in patients with stroke due to large-vessel atherosclerosis rather than infarction caused by cardiac embolism or lacunar infarction. Clinical and radiographic data can be used to infer stroke mechanism during life.13 When patients with cortical artery distribution infarcts were compared to a cohort with "perforating artery" ischemic lesions (primarily lacunes) in a Japanese population, HDL-cholesterol concentration was found to be lower in the former group.14 These data suggest that separation of ischemic stroke into subtypes based on the relative likelihood of large-vessel atherosclerosis may help clarify lipid-related risk patterns in stroke. We performed a similar study in a racially mixed American population to determine if differences in the concentration of HDL-cholesterol (or other lipids) could be demonstrated between survivors of cortical infarction and a cohort of patients with isolated lacunar stroke.

Subjects and Methods

A prospective study was conducted over 18 months using the occurrence of stroke as the end point defining the study groups. Group I comprised patients evaluated by the Neurology Service at the Medical College of Georgia with cortical infarction. Inclusion criteria were 1) clinical evidence of stroke with cortical deficits (aphasia or nondominant hemi-
had a systemic malignancy were excluded.

Blood was placed on ice and processed within 1 hour. All plasma cholesterol and triglyceride analyses were carried out using Gilford System 103 autoanalyzer (Oberlin, Ohio) methodology. HDL-cholesterol concentration was measured in plasma supernatant following precipitation of very low density lipoprotein (VLDL) and LDL by dextran sulfate and magnesium. Plasma VLDL- and LDL-cholesterol concentrations were determined as follows. VLDL was isolated from the plasma by preparative ultracentrifugation at a plasma density of 1.006 g/ml at 40,000 rpm for 18 hours at 15° C using a Ti 50.3 rotor (Beckman Instruments, Palo Alto, California). The HDL + LDL-cholesterol concentration of the infranatant plasma was determined. VLDL-cholesterol concentration was calculated by subtracting the infranatant plasma HDL + LDL-cholesterol concentration from the total plasma cholesterol concentration. LDL-cholesterol concentration was calculated by subtracting the HDL-cholesterol concentration from the infranatant plasma HDL + LDL-cholesterol concentration.

Apolipoproteins (Apos) A1 and B were quantified by radial immunodiffusion using plates purchased from Tago Diagnostics, Inc. (Burlingame, California). These Apos immunoassay plates contain antisera specific for Apo A1; the Apo B plates detect both Apo B-100 and Apo B-48. To avoid interference from lipids, the lipoproteins were dissociated with detergents during preincubation (Apo B) and during assay (Apo A1).

Statistical analyses included 1) comparison of group means for biochemical values and age using analysis of variance, 2) comparison of group clinical characteristics (nominal data) using \( \chi^2 \) analysis, and 3) multiple logistic regression to assess the relation of HDL-cholesterol concentration to clinical characteristics and stroke type (this analysis was performed by using significant \( p < 0.05 \) clinical variables and adding HDL-cholesterol concentration; significance was established using analysis of variance).

Results

The clinical characteristics of the two groups are shown in Table 1. There was no difference in age between groups, but the percentage of whites was significantly lower in the lacunar stroke group. The groups were comparable with respect to the other clinical characteristics. Among the lacunar stroke patients, the following syndromes were encountered: pure motor stroke in 29, clumsy hand-  

dysarthria in two, ataxic hemiparesis in two, pure sensory stroke in two, and sensorimotor stroke in

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean±SEM</th>
<th>Range</th>
<th>% male</th>
<th>% white</th>
<th>% HBP</th>
<th>% IHD</th>
<th>% DM</th>
<th>% smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>48</td>
<td>61±1.5</td>
<td>44-81</td>
<td>75</td>
<td>60</td>
<td>74</td>
<td>42</td>
<td>35</td>
<td>44</td>
</tr>
<tr>
<td>Lacunar</td>
<td>36</td>
<td>62±2.5</td>
<td>37-90</td>
<td>57</td>
<td>36*</td>
<td>72</td>
<td>33</td>
<td>36</td>
<td>36</td>
</tr>
</tbody>
</table>

HBP, hypertension; IHD, ischemic heart disease; DM, diabetes mellitus. *\( p < 0.05 \), different from cortical by \( \chi^2 \).
one; cranial CT confirmed lacunar infarction in 81% of the patients.

Biochemical values of the two groups are given in Table 2. Significant differences (p<0.05) were found only in HDL-cholesterol concentration; the cortical stroke group had a lower concentration than the lacunar stroke group. White stroke patients had lower HDL-cholesterol concentrations (37 mg%) than black patients (48 mg%). Apo A1 and Apo B (not shown) were analyzed in 50% of the patients; no significant differences were found between groups.

Drug effects were considered. Three patients were prescribed a thiazide diuretic and two were prescribed propranolol at the time of entry into the study. Since these numbers were small and the patients on these medications were distributed between the groups, the influence of drugs was considered insignificant and was not investigated further.

**Discussion**

Our principal findings were that HDL-cholesterol levels were lower in whites than in blacks among survivors of cortical and lacunar stroke and that a significant difference in HDL-cholesterol concentration was based on stroke type. Separation of cerebral infarction into cortical and lacunar subtypes and the exclusion of apparent cardioembolic strokes may have allowed differences to emerge even though the cohorts were relatively small. Selection of patients on the basis of relatively specific manifestations of cerebrovascular disease has been advocated by other investigators. Mathew et al. reported a higher incidence of hyperlipoproteinemia (primarily Type IV) in patients with large-artery extracranial disease than in patients with "intracranial small vessel lesions." However, the patients were classified on the basis of angiography, and the criteria for the detection of small-vessel disease were not described. Ueda et al. compared the characteristics of patients with transient ischemic attack (TIA) and extracranial carotid disease to patients with cerebral infarction and no extracranial disease (including 19% with lacunar infarcts); using this approach, cholesterol and triglyceride concentrations were found to be higher in patients with extracranial atherosclerosis. Other authors have documented an association between low concentrations of HDL-cholesterol (but not increased concentrations of total cholesterol and/or triglycerides) and the severity of carotid disease assessed by angiography or ultrasound.

The only other study to directly compare cortical infarction (presumably related to atherosclerosis) and lacunar infarction (in which the role of atherosclerosis is uncertain) was the study of Murai et al. In this Japanese cohort, HDL-cholesterol concentration was lower in patients with cortical infarcts than in patients with lacunar lesions or those without apparent stroke. Our findings confirm this difference in a cohort of Americans and suggest a larger difference between the two stroke types in Caucasians than in blacks. We were unable to account for this difference in HDL-cholesterol concentration on the basis of patient characteristics such as age or the incidence of HBP.

We believe that the importance of our study is our comparison of the risk factors of these two common ischemic stroke subtypes. Our selection process, although not providing absolute assurance of correct classification, was adequate to eliminate cases of intracranial hemorrhage and most cases of cardioembolic infarction. The clinical criteria we applied for defining lacunar infarction and our high rate of CT confirmation suggest that our lacunar stroke group contained primarily, if not exclusively, patients with lacunar lesions without coincident cortical infarction.

We also looked at the stroke patients in our series who received ultrasonography (combined B-mode and Doppler) of their extracranial carotid arteries. Of 19 patients with cortical stroke, 16 showed evidence of significant carotid disease compared with only four of 11 patients with lacunar stroke similarly studied. Our two groups thus represent populations distinguished in part by their likelihood of having large-vessel atherosclerosis.

Recent stroke data registries have recognized the importance of lacunar infarction disease and have separated this clinical stroke type from others, including large-artery thrombosis. It is not clear, however, how the risk factor profiles for these two distinct manifestations of cerebrovascular disease differ. Based on data from a population in south Alabama similar to ours, HBP is more common in patients with lacunar stroke, but the incidence is nearly as high among patients with large-artery stroke. Crouse et al. recently analyzed risk factors for extracranial carotid artery atherosclerosis identified by B-mode ultrasonography and confirmed the importance of both HBP and low HDL-cholesterol concentration as independent risk factors for the development of cervical carotid artery disease. HBP was equally common in our groups. These studies sug-

---

**Table 2. Lipid Concentrations of Study Population of 84 Patients With Stroke**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Total cholesterol</th>
<th>Triglycerides</th>
<th>VLDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>48</td>
<td>204±8.8</td>
<td>221±24.3</td>
<td>26±3.0</td>
<td>139±7.3</td>
<td>39±2.1</td>
</tr>
<tr>
<td>Lacunar</td>
<td>36</td>
<td>218±12.4</td>
<td>188±2.3</td>
<td>25±3.5</td>
<td>147±11.5</td>
<td>47±3.7</td>
</tr>
</tbody>
</table>

Data are mean±SEM mg/dl. VLDL, very low density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol.

*p<0.05, different from cortical by analysis of variance.
gest that HBP is more often a common, rather than a distinguishing, characteristic for patients with large- and small-vessel disease. Whether the degree or duration of HBP is an important factor is unknown because these studies, as well as our own, did not stratify HBP as to chronicity and/or severity.

To what extent do these two groups represent distinct clinical "phenotypes" with critical differences in risk profiles? This question is difficult to answer from currently available data. Systematic stroke data banks have not reported on the coincidence of large-vessel disease and lacunar lesions, suggesting that the presence of both types of lesions in the same patient, by clinical and CT criteria at least, may be uncommon.

Only recently have neuropathologic studies paid special attention to lacunar disease. From the work of Fisher and others, several causes of lacunar lesions can be identified. Occlusion of penetrating arteries can be caused by 1) lipohyalinosis and/or fibrinoid necrosis, 2) microatheroma or "lipid macrophage plaque," 3) middle cerebral artery (MCA) stem or proximal division large-vessel atherosclerosis, or 4) embolic occlusion of the proximal MCA. Although the presence of a cardioembolic source, a "giant lacune," or distal MCA territory infarction on CT may suggest one of the latter two mechanisms, it is usually not possible to know clinically which process is involved. The relative importance of these different causes of lacunar disease, as well as the coincidence of lacunar lesions with non-MCA large-vessel cerebral atherosclerosis, is not known. Even in a relatively well selected lacunar cohort, individuals with different risk profiles may be present.

Lipohyalinosis, fibrinoid necrosis, and microatheroma may represent various points along a continuum of HBP damage to small vessels of the brain. If so, the primary relevant factor pertaining to lacunar stroke is HBP.

The differences in HDL-cholesterol concentration found in our study and that of Murai et al suggest a factor related to HDL-cholesterol that is not shared by the stroke groups. We believe it plausible that this factor may in part determine which patients with HBP develop large-vessel atherosclerosis and which have manifestations primarily limited to the penetrating arteries. The differences in HDL-cholesterol concentration in our study cannot be accounted for by other illness, age, smoking (which lowers HDL-cholesterol concentration), or medications. Although HBP, clinically apparent IHD, and smoking are predictive of stroke, presence of these risk factors did not discriminate between cortical and lacunar stroke in our cohort.

IHD, however, remains a potential confounding variable. Detection of asymptomatic coronary artery disease requires special investigations that were not part of our study. Although clinically apparent IHD did not account for the differences in HDL-cholesterol concentration in our study, we cannot eliminate the possibility that our groups may have differed in the presence or severity of undetected coronary artery atherosclerosis.

We also considered the potential effects of the timing of blood sampling on our results. The majority of our patients were studied 2–30 days after their stroke (mean±SD 9±9 days for the cortical and 11±11 days for the lacunar stroke groups). Stressful events such as myocardial infarction and surgery are associated with a decrease in total cholesterol concentration over several weeks after the event. Two studies have examined the acute effects of stroke on plasma lipid concentration. Hollander et al reported a steady decline in total cholesterol concentration over the first 4 weeks after cerebral infarction, but HDL-cholesterol content was not measured. The more recent study of Mendez et al assessed cholesterol and lipoprotein concentrations 1, 7, and 90 days after cerebral infarction and TIA. Significant decreases in total and LDL-cholesterol, but not HDL-cholesterol, contents were observed on Day 7 in the patients with cerebral infarction; the authors suggest that sampling soon after infarction may underestimate premorbid levels of cholesterol and LDL-cholesterol and suggest that the finding of low HDL-cholesterol concentration in their and other studies, some of which waited 8–12 weeks after ictus before sampling, is not explained by the timing of biochemical measurements. In addition, other studies have used the presence of predisposing carotid atherosclerosis prior to a major ischemic event and have also found low HDL-cholesterol concentrations in patients with significant carotid artery disease.

Could the type of stroke have a differential effect? The data of Mendez et al argue against this. The authors found that TIA patients, whose stress presumably was less than that of patients who experienced infarction, also had minor variations in HDL-cholesterol content similar to those of patients with infarction. The HDL-cholesterol concentration difference between our groups exceeds the variations seen in either of their groups.

The observed differences in HDL-cholesterol content are not explained by a racial imbalance between our groups. When only the white patients are considered, the difference between the cortical (33 mg%) and lacunar stroke groups (46 mg%) remained significant (p<0.0002) despite a reduction in sample sizes. We also used multiple logistic regression to analyze the effect of stroke type and race, the two significant variables by univariate analysis, on HDL-cholesterol content. Although both stroke type and race significantly affect HDL-cholesterol level, the interaction between these variables was not significant (p=0.114).

Our analysis indicates that while the HDL-cholesterol concentration difference was primarily the result of a strikingly low mean for white patients with cortical stroke, evidence from this sample is not sufficient to conclude that HDL-cholesterol values are uniquely low for white, as opposed to
black, patients with cortical stroke. The trend suggests, however, that racial differences in HDL-cholesterol level by stroke type might emerge from a similar study of a larger cohort.

The race difference we observed is consistent with previous studies. Blacks are known to have higher HDL-cholesterol concentrations than whites. The difference between groups was not seen among blacks whose mean HDL-cholesterol values (48 mg/dl) were identical. Why this difference was not seen in blacks requires further investigation.

We conclude that patients with cortical infarction have lower HDL-cholesterol concentrations than patients with lacunar stroke. This difference suggests that a factor related to lipid metabolism may in part determine risk for these different expressions of cerebrovascular disease.

Acknowledgments

The authors express appreciation to Ms. Pam House and Ms. Becky Mueller for preparation of the manuscript.

References


KEY WORDS • cerebral infarction • lacunar infarction • cholesterol • lipids
Plasma lipoproteins in cortical versus lacunar infarction.
R J Adams, R M Carroll, F T Nichols, N McNair, D S Feldman, E B Feldman and W O Thompson

(*Stroke*. 1989;20:448-452
doi: 10.1161/01.STR.20.4.448
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/20/4/448

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/