Background and Purpose—Extracranial atherosclerosis, proximal to the carotid bifurcation and V3 segment of the vertebral artery, is considered to be an infrequent condition with a benign prognosis. However, its prevalence may be underestimated due to lack of data. We aimed to determine the prevalence of proximal extracranial plaques and stenosis in the common carotid artery, innominate and subclavian arteries, and proximal vertebral artery.

Methods—We performed a systematic analysis of intra- and extracranial arteries, the aortic arch, and the heart in 339 consecutive autopsies of patients with stroke; 259 patients had brain infarction; 80 patients had brain hemorrhage and were used as control subjects. Clinical history, risk factors, imaging data, and general autopsy reports were analyzed.

Results—Proximal extracranial plaques and stenosis were present in the arteries of 46.9% and 19.8% of patients, respectively, without a significant difference between brain infarction and brain hemorrhage groups. Proximal extracranial atherosclerosis occurred more frequently in the proximal vertebral artery than in other arteries (stenosis prevalence 12.7% versus 5.3% in the common carotid artery) and in patients with posterior circulation brain infarction (except for the posterior cerebral artery territory). More specifically, atherosclerosis in the proximal vertebral artery was significantly associated with posterior circulation brain infarction (age- and sex-adjusted OR, 2.31; 95% CI, 1.28 to 4.17 for plaques and 2.10; 95% CI, 1.01 to 4.38 for stenosis) using patients with isolated anterior circulation infarctions as control subjects.

Conclusions—Proximal extracranial atherosclerosis was frequent and was significantly associated with brainstem infarcts. These findings support the importance of a systematic workup, including the evaluation of proximal extracranial atherosclerotic lesions. (Stroke. 2009;40:713-718.)

Key Words: extracranial atherosclerotic disease ■ plaque ■ proximal extracranial atherosclerosis ■ stenosis ■ stroke

Extracranial atherosclerosis has privileged sites for lesion development, in particular, the carotid artery bifurcation.1-3 The natural history of extracranial atherosclerosis is well documented for lesions of the internal carotid artery origin (ICA0) as a result of prospective studies and large randomized trials evaluating surgical treatment.4-6 By comparison, for more proximal extracranial atherosclerosis (PEA), affecting the common carotid artery (CCA), the innominate or subclavian artery (I/SA), or the vertebral artery (VA), information on the prevalence and relationship with risk of stroke is scarce. Consequently, data on the optimal management of PEA are limited.

In the proximal location, atherosclerotic lesions have features in common with those of the ICAO with similar demographic characteristics and risk factors but seem to be associated with a much lower risk of brain infarction (BI).1,7 As a result, PEA is frequently underrecognized, documented with less acuity than internal carotid artery origin and carotid bifurcation extracranial atherosclerosis, or neglected. Although the benign reputation of PEA with regard to resultant stroke has been debated,8 the true incidence of BI resulting from a proximal atherosclerotic lesion has not been determined. The location can be difficult to explore by ultrasound and, as a consequence, the contribution of PEA to posterior circulation BI may have been underestimated. Our aim was to determine the autopsy prevalence of PEA in patients with fatal stroke.

Subjects and Methods

Patients with stroke were identified using the Multiple Atherosclerosis Site in Stroke autopsy database. Autopsies had been performed at La Salpêtrière Hospital in Paris, France, between November 1982 and February 1989, during which time the autopsy rate was 73%.9,10

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The methods have been reported previously. Clinical history, risk factors, imaging data, and autopsy reports were available for analysis. As reported previously, each autopsy report included a detailed anatomy of the extra- and intracranial arteries with systematic drawings of the site of occlusion and the site and extent of atherosclerotic plaques or stenosis. Autopsies were excluded if clinical data (including heart weight) were incomplete or if detailed reports on cerebral arteries were missing. PEA was defined by the presence of plaques or stenosis in the following arteries: the CCA, the I/SA, and the proximal VA (the vertebral artery origin [V Ao] and the V2 segment), excluding the ICAO. The percentage of the degree of stenosis at each site was determined macroscopically and then verified microscopically and was further classified in 4 grades: 0, 1 (stenosis 30% to 75%), 2 (stenosis 75% to 99%), or 3 (occlusion).

Etiology was classified according to clinical data and pathological description. Stroke subtyping followed the Etude du Profil Génétique de l’Infarctus Cérébral classification: (1) atherothrombotic: ICAO stenosis >30% or ipsilateral stenosis >50% in the internal carotid artery siphon or middle cerebral artery (MCA); (2) cardioembolic: cardiac source of embolism (recent myocardial infarction, atrial fibrillation, intracardiac thrombus or tumor, valvulopathy, or endocarditis); (3) other cause: disseminated intravascular coagulation or other hematologic causes, inflammatory/infectious arterial disease (vasculitis), or intracranial or carotid dissection present; (4) coexisting causes: 2 or more possible etiologies as defined previously; and (5) unknown cause: no identifiable cause found. Patients with brain hemorrhage (BH) were used as a control group because they have been exposed to similar risk factors and were of a similar age to patients with BI at the time of their stroke.

**Terminology**

We used the term “atherosclerotic plaque” to describe the anatomic lesion of an artery produced by atherosclerotic disease. An atherosclerotic plaque may or may not induce an arterial stenosis with or without lumen narrowing. We used the term “plaque” to mean any anatomic plaque in the artery, including nonstenotic and stenotic plaques. We used the term “stenosis” to mean any plaque that induced a stenosis of the arterial lumen >30%. Consequently, a plaque that induced a stenosis <30% was classified as a nonstenotic plaque.

**Statistical Analysis**

We compared the prevalence of PEA in the BI and BH groups using logistic regression analysis adjusted for age and sex; the adjusted ORs with their 95% CIs were calculated using the BH group as the control group. We also used logistic regression analysis to study the association of PEA with several characteristics of the BI and BH groups combined (vascular risk factors; atherosclerosis in the aortic and coronary arteries, the intracranial internal carotid artery, and autopsy myocardial infarction). We investigated the association between PEA and vascular territory infarctions in the BI group using the χ² test or Fisher exact test when the expected cell frequency was <5. Because we found a higher prevalence of PEA in several posterior territory lesions, we computed the OR of posterior circulation BI associated with the presence of PEA using patients with isolated anterior circulation infarctions as the control group and logistic regression analysis adjusted for age and sex. Statistical testing was done at the 2-tailed α level of 0.05. Data were analyzed using the SAS package, Version 9.1 (SAS Institute, Cary, NC).

**Results**

Of 381 consecutive autopsies of patients with fatal stroke, 16 men and 26 women (mean age, 73 years; prevalence of atherothrombotic BI, 9.5%) were excluded because of incomplete clinical data, missing heart weight, or a missing detailed report on cerebral arteries (Figure 1). We included 259 patients with pathological evidence of BI and 80 patients with BH (mean age, 73 years, 56% [n = 191] of men). Ninety-one percent (n = 297) of patients died within the 3 months of stroke onset with a median delay of death of 15 days (interquartile range, 6 to 34 days) in patients with BI and 9 days (interquartile range, 2 to 23 days) in patients with BH (Mann–Whitney U test, P = 0.002).

**Prevalence of Proximal Extracranial Atherosclerosis**

The overall prevalence of plaques and stenosis in proximal extracranial arteries was 46.9% (95% CI, 41.6 to 52.2) and 19.8% (95% CI, 15.5 to 24.0), respectively; PEA occurred more frequently in the proximal VA with a stenosis prevalence of 12.7% (95% CI, 9.1 to 16.2) compared with 5.3% (95% CI, 2.9 to 7.7) in the CCA and 5.9% (95% CI, 3.4 to 8.4) in the I/SA (Table 1). By comparison, a stenosis prevalence of 29.8% (95% CI, 24.9 to 34.7) was found in the ICAO.

Table 2 shows the prevalence of proximal extracranial plaques and stenosis according to stroke subtype. We found no significant difference in PEA prevalence between patients with BI and those with BH with an adjusted OR of 1.43 (95% CI, 0.85 to 2.40) for plaques and 1.35 (95% CI, 0.69 to 2.64) for stenosis. Similar results were found for each arterial site.
with an adjusted OR of 1.26 (95% CI, 0.68 to 2.35) for CCA plaques, 0.80 (95% CI, 0.43 to 1.47) for I/SA plaques, and 1.67 (95% CI, 0.87 to 3.20) for proximal VA plaques. Among the 259 patients with BI, we found that the prevalence of proximal extracranial plaques and stenosis was significantly higher in atherothrombotic BI (both in anterior and posterior circulation) than in other BI subtypes (Table 2).

**Proximal Extracranial Atherosclerosis and Atherosclerosis Profile**

Of the vascular risk factors, only sex was significantly associated with proximal extracranial plaques or stenosis (data not shown). Prevalence of proximal extracranial plaques was higher in men (52.9%) than in women (39.2%, \( P = 0.007 \)). A similar difference was observed in the prevalence of proximal extracranial stenosis (23.6% versus 14.9%, \( P = 0.038 \)).

Table 3 shows that the presence of proximal extracranial plaques was positively associated with atherosclerosis (plaques and stenosis) in the intracranial internal carotid artery, ICAO, coronary artery, and in pathological evidence of silent myocardial infarction. Patients with proximal extracranial stenosis had more ICAO atherosclerosis than those with no proximal extracranial stenosis (plaques, 76.6% versus 56.6%, respectively, \( P = 0.011 \); stenosis, 53.7% versus 23.9%, respectively, \( P < 0.001 \)) and more coronary atherosclerosis than those with no proximal extracranial stenosis (plaques, 86.9% versus 69.4%, respectively, \( P = 0.017 \); stenosis, 50.8% versus 34.5%, respectively, \( P = 0.044 \)).

**Table 1. Prevalence of Proximal Extracranial Atherosclerotic Disease by Site and Severity (All Patients; n=339)**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Any Artery</th>
<th>CCA</th>
<th>I/SA</th>
<th>VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>180 (53.1)</td>
<td>260 (76.7)</td>
<td>271 (79.9)</td>
<td>259 (76.4)</td>
</tr>
<tr>
<td>Nonstenotic plaques</td>
<td>92 (27.1)</td>
<td>61 (18.0)</td>
<td>48 (14.2)</td>
<td>37 (10.9)</td>
</tr>
<tr>
<td>Stenosis 30% to 74%</td>
<td>42 (12.4)</td>
<td>18 (5.3)</td>
<td>14 (4.1)</td>
<td>22 (6.5)</td>
</tr>
<tr>
<td>Stenosis 75% to 99% or with occlusion</td>
<td>25 (7.4)</td>
<td>0 (0.0)</td>
<td>6 (1.8)</td>
<td>21 (6.2)</td>
</tr>
</tbody>
</table>

**Table 2. Prevalence of Proximal Extracranial Plaques and Stenosis by Stroke Subtype**

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>No. of Patients</th>
<th>Proximal Extracranial Plaques</th>
<th>Proximal Extracranial Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain infarction</td>
<td>259</td>
<td>127 (49.0)</td>
<td>54 (20.8)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>62</td>
<td>41 (66.1)†</td>
<td>26 (41.9)§</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>94</td>
<td>42 (44.7)</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>23</td>
<td>11 (47.8)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Coexisting causes</td>
<td>38</td>
<td>22 (57.9)</td>
<td>11 (29.0)</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>31</td>
<td>10 (32.3)</td>
<td>6 (19.4)</td>
</tr>
<tr>
<td>Brain hemorrhage*</td>
<td>80</td>
<td>32 (40.0)</td>
<td>13 (16.3)</td>
</tr>
</tbody>
</table>

*Computed using logistic regression analysis adjusted for age and sex.

**Association of Proximal Extracranial Atherosclerosis With Vascular Territory Infarctions**

Among the 259 patients with BI, the vascular territory involved was not determined pathologically for 5 patients. For the remaining 254 patients with BI, the vascular territories involved were as follows: anterior cerebral artery, 20.5% (n=52) of patients; anterior choroidal artery, 9.8% (n=25); basilar artery (BA, pons and mesencephalon), 16.5% (n=42); MCA, 74.8% (n=190); posterior cerebral artery (PCA), 24.0% (n=61); posterior inferior cerebellar artery, 9.8% (n=25); superior cerebellar artery, 3.9% (n=10); and VA (medulla), 2.4% (n=6). One hundred four patients (40.9%) had multiple vascular territory lesions.

The prevalence of proximal extracranial plaques did not differ between patients with and without anterior circulation, MCA, or PCA infarctions (Figure 2). The prevalence of proximal extracranial stenosis was significantly lower in patients with MCA infarctions than in those with non-MCA infarctions (16.3% versus 31.3%, respectively, \( P = 0.01 \)). Overall, no significant difference in PEA prevalence was found between patients with and without posterior circulation lesions.

**Table 3. Association of Proximal Extracranial Plaques With Atherosclerosis in Aortic, Carotid, and Intracranial Internal Carotid Arteries and in Myocardial Infarction (All Patients; n=339)**

<table>
<thead>
<tr>
<th>Proximal Extracranial Plaques</th>
<th>Absent (n=180)</th>
<th>Present (n=159)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial ICA plaques</td>
<td>76 (42.2)</td>
<td>129 (81.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial ICA stenosis &gt;30%</td>
<td>40 (22.2)</td>
<td>61 (38.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>ICAO plaques</td>
<td>32.8 (59)</td>
<td>71.7 (114)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICAO stenosis &gt;30%</td>
<td>22.2 (40)</td>
<td>38.4 (61)</td>
<td>0.001</td>
</tr>
<tr>
<td>Coronary plaques</td>
<td>110 (64.3)</td>
<td>124 (82.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Coronary stenosis &gt;50%</td>
<td>50 (29.2)</td>
<td>71 (47.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Ulcerated plaques in aortic arch</td>
<td>36 (20.0)</td>
<td>43 (27.0)</td>
<td>0.331</td>
</tr>
<tr>
<td>Ulcerated plaques in abdominal or thoracic aortas</td>
<td>36 (20.0)</td>
<td>29 (18.2)</td>
<td>0.492</td>
</tr>
<tr>
<td>Symptomatic myocardial infarction</td>
<td>30 (16.7)</td>
<td>30 (18.9)</td>
<td>0.953</td>
</tr>
<tr>
<td>Silent myocardial infarction</td>
<td>28 (15.6)</td>
<td>49 (30.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*PA her seg MT, ICAO stenosis >50% (n=61).
infarctions with an adjusted OR of 1.20 (95% CI, 0.72 to 2.00) for proximal extracranial plaques and 1.25 (95% CI, 0.67 to 2.36) for proximal extracranial stenosis. However, PEA did occur more frequently in patients with BI involving the BA, posterior inferior cerebellar artery, superior cerebellar artery, and VA vascular territories (Figure 2) with adjusted ORs of 2.19 (95% CI, 1.18 to 4.05) for proximal extracranial plaques and 1.93 (95% CI, 0.98 to 3.81) for proximal extracranial stenosis. Figure 3 shows that the association between PEA and posterior circulation infarctions differed according to the arterial site involved; only atherosclerosis in the proximal VA was significantly associated with posterior circulation infarction with an age- and sex-adjusted OR of 2.31 (95% CI, 1.28 to 4.17) for plaques and 2.10 (95% CI, 1.01 to 4.38) for stenosis using patients with isolated anterior circulation infarction as the control group. Among the 36 patients with proximal VA lesions, 31 had posterior or anterior tandem lesions, mainly BA and ICAO for the posterior and anterior circulation, respectively (see Figure 4).

Discussion

This autopsy study is the first to show that PEA occurs frequently (with a prevalence of almost 50%) in patients with fatal stroke. Proximal VA plaques and stenosis were significantly associated with posterior circulation infarctions. PEA also occurred more frequently in patients with brainstem and cerebellar ischemic strokes (ie, involving the superior cerebellar artery, BA, and posterior inferior cerebellar artery territories), but not in those with PCA territory infarctions. Atherosclerosis is a widespread process as illustrated by the positive association we found between atherosclerosis in the proximal arteries and atherosclerosis in the ICAO and the coronary artery. In patients with PEA and stenotic lesions >30%, ICAO stenosis was documented in more than 53.7% of cases, and similar findings were obtained for coronary atherosclerosis with coronary stenosis present in 50.8% of patients with stenotic lesions in proximal arteries. Like in other studies, we found a male predominance in patients with PEA.14,15 In previous autopsy studies, patients with PEA were

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Prevalence of proximal extracranial plaques according to the vascular territory involved in the brain infarction. ACA indicates anterior cerebral artery; AchA, anterior choroidal artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery. *P*<0.05.

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3.** Age- and sex-adjusted ORs for the association between posterior circulation brain infarctions and the presence of proximal extracranial atherosclerotic disease. Black squares indicate the ORs for all posterior circulation lesions; gray squares indicate the ORs for lesions of the superior cerebellar artery, posterior inferior cerebellar artery, VA, and BA. 95% CIs are plotted.
much older than patients with carotid bifurcation atherosclerosis. In this study, however, we found no association between PEA and age or any other patient characteristic. However, given that the review of the medical charts was retrospective, the prevalence of other vascular risk factors may have been underestimated. This cohort was collected in the 1980s, when current treatments for vascular risk factors were not yet established. Although these treatments may alter the prevalence of atherosclerotic lesions, they are unlikely to alter the pathophysiology of the disease.

PEA lesions were located in the CCA, the I/SA, and the proximal VA in 23.3%, 20.1%, and 23.6% of cases, respectively. Nonstenotic plaques were found predominantly in the CCA and the I/SA, whereas PEA stenoses were found mainly in the proximal VA. The prevalence of proximal VA stenosis reached 12.7%, double that in the CCA and the I/SA and 2.3 times lower than that in the ICAO. We found a lower prevalence of atherosclerotic lesions in the VAO and V2 segment than reported previously in autopsy series. Huntchinson et al reported VAO stenosis in 39.6% of 48 patients with fatal stroke and Hennerici et al found VAO stenosis in 43% of 426 angiograms. VAO lesions are often considered to be benign and rarely associated with downstream BI. Moufarrij et al reported a low event rate in a small cohort of 89 patients with ≥50% stenosis in at least one VAO; within a mean follow-up of 4.6 years, 19 patients had a possible vertebrobasilar transient ischemic attack, and among 23 patients who had a stroke, only 2 infarctions were located in the posterior circulation. In our series, however, VAO stenosis was significantly associated with posterior circulation infarctions with an age- and sex-adjusted OR of 2.10 (95% CI, 1.01 to 4.38); this suggests that the proximal VA may be an important site of atherosclerosis and that its investigation should be included in the workup of BI. Previous studies may have failed to demonstrate this association because of the small number of patients involved. Further prospective studies are clearly needed to evaluate fully the risk of BI associated with proximal VA stenosis.

Surgical procedures for CCA or I/SA lesions require thoracotomy, which is associated with high morbidity. The risk–benefit ratio for proximal VA revascularization either by surgical or endovascular procedure is not established. The latest study of endovascular treatment (percutaneous transluminal angioplasty and stenting) for symptomatic VA stenosis failed to show a benefit over the best medical treatment; however, the randomized trial included only 16 patients, which precluded any meaningful conclusions to be drawn. In this context, our results support further evaluation of interventional procedures, either surgical or endovascular, for the treatment of proximal VA lesions involving a sufficient number of patients to enable the benefits and risks to be determined accurately.

Our study was limited by the recruitment biases of autopsy studies, and the findings should be confirmed in series of patients with nonfatal stroke. Patients with fatal stroke are more likely to have had severe strokes, which accounts for the high prevalence of cardioembolic strokes found in our study. Furthermore, cardioembolic strokes are the leading cause of PCA infarctions, which may explain in part the heterogeneity found in the relationship between PEA and posterior circulation infarctions. The high prevalence of posterior infarcts may explained, at least in part, the overrepresentations of vertebral PEA lesions.

In patients with anterior circulation infarctions, PEA in the CCA appeared not to be a frequent cause of BI. The lower prevalence of PEA lesions in patients with MCA infarctions may partly explained by a higher prevalence of cardioembolic strokes or atherosclerotic lesions of the ICA. Indeed, ICAO stenoses were more frequent in MCA strokes (38.4% versus 23.4% for non-MCA strokes, P=0.03); similar findings were noted for cardioembolic strokes (43.2% versus 18.8% for non-MCA strokes, P<0.001). Overall, PEA occurred more frequently in patients with BI than in patients...
without BH, but the difference did not reach formal statistical significance. The strength of this relationship was probably underestimated in our series because of inadequate statistical power. It is also possible that patients with BH are not an ideal control group for evaluating the influence of PEA on the risk of BI, because the 2 groups have risk factors in common.

A more appropriate control group would have been patients who had died as a result of another neurologic disease, but unfortunately, the detailed anatomy of the extra- and intracranial arteries was not recorded systematically and was only available in 30.1% (n=152) of patients; in this group, the prevalence of PEA plaques and stenosis was 11.2% (95% CI, 6.2 to 16.2) and 2.6% (95% CI, 0.1 to 6.6), respectively.

PEA is a marker for severity of widespread atherosclerotic disease, because it is also associated with intracranial, extracranial, aortic, and coronary atherosclerosis. Furthermore, our findings support the fact that a causal relationship between ostial lesions of the proximal VA and BI should be investigated in future studies.

**Acknowledgments**

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**Disclosures**

None.

**References**


Autopsy Prevalence of Proximal Extracranial Atherosclerosis in Patients With Fatal Stroke

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