Association of Small-Vessel Disease With Dilatative Arteriopathy of the Brain
Neuropathologic Evidence

Fernando Pico, MD; Julien Labreuche, BS; Danielle Seilhean, MD, PhD; Charles Duyckaerts, MD, PhD; Jean-Jacques Hauw, MD; Pierre Amarenco, MD

Background and Purpose—Clinical and imaging studies have reported an independent and intriguing association between intracranial arterial dilatative ectasia (IADE) and markers of small-vessel disease (SVD) such as lacune(s). We used a large brain-autopsy collection to investigate the relation between IADE and pathologically assessed cerebral SVD.

Methods—The entire arterial tree from the heart to the intracranial small intracerebral arteries was investigated in 381 consecutive autopsies from patients with stroke. Vascular risk factors, heart status (weight, coronary atherosclerosis, and myocardial infarction), prevalence and severity of atherosclerosis from heart to brain (aortic arch, carotid, vertebral, and intracranial arteries), dolichoectasia, cerebral SVD, and brain tissue lesions (lacune(s), état criblé) were evaluated. Analyses were adjusted for age, sex, and heart weight.

Results—Twenty-three (6%) of 381 patients had IADE, affecting mainly the basilar artery, with a median basilar artery diameter of 6 mm (range, 4 to 9 mm). Patients with IADE had a 2-fold increase in the prevalence of basilar artery plaques and ulcerated plaques in the aortic arch (both \( P < 0.006 \)), but there were no associations with coronary or cervical artery plaques. SVD was more frequent in IADE-positive than in IADE-negative patients (45% vs 18%; \( P = 0.004 \)). The adjusted odds ratio was 3.85 (95% confidence interval, 1.56 to 9.52). Cerebral amyloid angiopathy was not observed in IADE-positive patients.

Conclusions—Compared with stroke patients without IADE, those with IADE were more likely to have pathologic evidence of cerebral SVD and its consequences, independent of age, arterial hypertension, or diabetes mellitus. IADE and cerebral SVD may have unidentified biologic processes in common. (Stroke. 2007;38:1197-1202.)

Key Words: dolichoectasia • autopsy • atherosclerosis • lipohyalinosis • small-vessel disease • multilacunes • état criblé

Intracranial dilatative arteriopathy, also called intracranial arterial dolichoectasia (IADE), is defined as an increase in the length and diameter of the intracranial large arteries.1,2 IADE is found in 12% of patients with stroke and the pathophysiology is unknown.3,4 On autopsy, dolichoectatic arteries have an abnormally large external diameter with a thin arterial wall and sometimes bear an intraluminal thrombus or an atherosclerotic plaque.5 On microscopic examination, the main findings are in the media, with rarefaction of the elastic tissue and degeneration of the internal elastic lamina.6,7 Because they have risk factors in common, the relation between IADE and atherosclerosis is a matter of debate, atherosclerosis being either the cause or the consequence of dolichoectatic processes.4,5,8 In a large population of patients with brain infarction, we found no association between the prevalence and severity of carotid atherosclerosis on ultrasound examination and the presence of IADE on brain magnetic resonance imaging (MRI).8 No studies have investigated the relation between IADE and location of atherosclerosis from the heart to the brain, which could help us to understand the pathophysiology and may have practical implications, such as work-up and prevention in stroke patients with IADE.

Two studies have shown that stroke patients with IADE were more likely to have lacunar brain infarcts on brain imaging than stroke patients without IADE.8,9 We recently reported an independent association between IADE and MRI markers of small-vessel disease (SVD), such as multilacunes, leukoaraiosis, and dilatation of perivascular spaces (ie, état criblé).3 Although MRI scans show the consequences of cerebral SVD, they fail to show either the pathologic process underlying the signal changes or the nature of SVD. If
confirmed, simultaneous involvement of small intracerebral arteries and IADE could be due to a common pathologic cascade(s) or unknown risk factors.3,4

We carried out a case-control study to assess the pathology of the heart-to-brain arterial tree in patients with or without IADE, with a special focus on small intracerebral arteries. For this purpose, we used a large, brain-autopsy database because it included consecutive patients with stroke and a systematic evaluation of the brain and its arterial supply.

Subjects and Methods
The Multiple Atherosclerosis Site in Stroke (MASS) study is an autopsy database of patients who died with neurological diseases at La Salpêtrière Hospital in Paris between November 1982 and February 1989. The autopsy rate during this period was 73%.10 Among 886 autopsies, 381 were of patients with stroke, including 83 with brain hemorrhage, 288 with brain infarction, and 10 with both brain hemorrhage and infarction, and 505 were of patients with other neurological diseases.11

Autopsy Process
Autopsies were performed according to French legislation and the published guidelines of the Neuropathology Department of la Salpêtrière for brain examination and its arterial supply.12–16 Medical reports were available for each case. In brief, after dissection of the aorta and its cervical branches, the cervical spine with the base of the skull was removed en bloc and subsequently fixed for at least 1 month and decalcified. Sections were then cut to examine the extracranial arteries throughout their length. Similarly, the configuration of the circle of Willis was assessed, and the arteries of the base of the brain were dissected along with their main branches. The arterial configuration and size and extent of arterial lesions were reported on a printed diagram according to a published classification.12–13 The brain was fixed in 10% formalin for at least 2 months. After sectioning of the midbrain at the level of the geniculate bodies, the brain was cut coronally at 1-cm intervals. The midbrain and cerebellum were cut perpendicular to the axis of the brain stem. On a printed diagram, brain lesions were drawn and samples identified. In each case, the sampling depended on the clinical data and pathologic examination. Basal ganglia and frontal white matter were sampled in most cases. Brain samples were always embedded in paraffin, whereas some other samples were embedded in celloidin. Stains included hematoxylin-eosin, Bodian coupled with Luxol fast blue, and Loyez hematoyxin for myelin. Arteries were embedded in paraffin and then stained with hematoxylin-eosin and Masson’s trichrome. Congo red staining was performed when amyloid angiopathy was suspected on clinical and pathologic grounds and was systematically performed in IADE-positive patients for the purpose of this study.

The MASS Computed Database
Based on autopsy files, we (P.A.) constructed a computer database, the primary goal of which was to analyze atherosclerotic and cardiac lesions in the stroke patients. Each autopsy file included a medical report with clinical risk factors, history, and biological and neuroimaging data; a general autopsy report with heart weight and cause of death; macroscopic examination of the brain and its arterial supply on printed diagrams with identification of arterial dolichoectasia, distribution of plaque stenosis, or occlusion of the extracranial and intracranial arteries (including the bony segments); and microscopic examination of the brain with information on lacunar infarct and état criblé (ie, dilatation of perivascular spaces).10,11 No information was available in the database about small-vessel status in 68 of 381 patients. The microscopic collection was reexamined by 2 investigators (F.P., J.-J.H.) who were blinded to IADE status and who assessed SVD status in 47 patients for whom adequate brain samples were available. Therefore, there were missing data for SVD status in 21 (6%) patients.

Definition of SVD and IADE
SVD was defined as the presence of sclerosis and hyalinosis (replacement of smooth muscle cells of small arteries <300 μm in diameter by fibroblasts and collagen, leading to hyaline thickening of the media), lipohyalinosis (wherein additional fibrinoid necrosis and sometimes lipid deposits were present), and isolated fibrinoid necrosis noted on microscopic examination.17 These diagnoses were made on hematoxylin-eosin–stained sections of basal ganglia and deep white matter, excluding the periventricular areas. Microatheroma, defined as atherosclerotic plaque involving the proximal perforating arteries (200–800-μm diameter), was not specifically assessed in this study. Lacunar infarcts were defined as lesions not exceeding 15 mm in their widest diameter and involving the territory of small, deep, perforating arteries. When multiple lacunar infarcts were present, the pattern of injury was described as multilacunes. État criblé was characterized by widening of the perivascular spaces of the lenticulostriate or the white matter small arteries (≤300 μm), in isolation, on microscopic examination.

IADE was defined as increased length and diameter of at least 1 of the following intracranial arteries: vertebral, basilar, carotid, or middle cerebral. IADE was pathologically diagnosed on gross examination (visual enlargement and tortuosity of intracranial large arteries; the Figure). To ensure the validity of the IADE diagnosis and to characterize its severity, the formalin-fixed specimen were reexamined by measuring the diameter of the basilar artery in IADE-positive patients and in an equivalent number of IADE-negative patients who were matched for age, sex, and year of death.

Statistical Analysis
The statistical analysis was based on 381 autopsies of patients with stroke. Data are presented as mean (SD) for continuous variables and percentage (count) for dichotomous variables. Patients with stroke were divided into 2 groups according to the presence or absence of IADE. We compared clinical and autopsy characteristics between the IADE-positive and IADE-negative patients with Student’s t test for continuous factors and the χ2 test for dichotomous factors. Fisher’s exact test was used when the expected cell frequency was <5. Associations of IADE with atherosclerosis, lacunar infarct, multilacunes, and état criblé were adjusted for 3 prespecified confounding factors (age, sex, and heart weight, taken as a surrogate for the presence of arterial hypertension) by logistic-regression analysis. The adjusted odds ratios (ORs) were calculated with their 95% CIs. Statistical testing was done at the 2-tailed α level of 0.05. Data were analyzed with the SAS software package, release 9.1 (SAS Institute).

Results
Of the 381 patients with stroke included in the MASS study, IADE was identified in 23 (6%) individuals. The percentage of brain infarction and intracerebral hemorrhage was similar in the IADE-positive and IADE-negative groups. The median time between stroke and death was 8 days (interquartile range, 3 to 31 days) in IADE-positive patients versus 13 days (interquartile range, 5 to 31 days) in IADE-negative patients (Mann–Whitney U test, P=0.35). The median diameter of the basilar artery was 6 mm (range, 4 to 9 mm) in IADE-positive versus 3 mm (range, 2 to 5 mm) in IADE-negative patients (Wilcoxon rank test, P<0.0001).

Description of Patients With IADE
Among the 23 IADE-positive patients, 12 were men and the median age was 78 years. Fourteen patients had a brain infarction, including 5 (36%) in the territory of a dolichoectatic artery. One had locked-in syndrome with an occlusive thrombus of the dolichoectatic basilar artery. Six patients had an intracerebral hemorrhage and 2 had a subarachnoid hemorrhage, including 1 by rupture of the dolichoectatic basilar
artery. Among 6 patients who had a brainstem compression by the dolichoectatic basilar artery, 4 also had brain infarction, 1 had an intracerebral hemorrhage, and 1 had a subarachnoid hemorrhage. The dolichoectatic process affected the basilar artery in 20 patients, the vertebral arteries in 13 patients, the carotid arteries in 11 patients, and the middle cerebral arteries in 5 patients.

Clinical and Anatomic Vascular Risk Factors
As shown in Table 1, IADE-positive patients were older than IADE-negative patients ($P=0.02$). No significant differences in other clinical and anatomic factors were found between the 2 groups. However, except for arterial hypertension, IADE-positive patients had fewer clinical risk factors than IADE-negative patients but tended to have higher heart weights.

Atherosclerosis Involvement
One IADE-positive patient and 27 IADE-negative patients were excluded from this analysis because detailed diagrams of the anatomy and extent of atherosclerosis in the cerebral arteries were not available. Table 2 shows the prevalence of atherosclerotic lesions in IADE-positive and IADE-negative patients. Although plaques in any segment of the intracranial and extracranial arteries were slightly more frequent in IADE-positive than in IADE-negative patients, the difference was not statistically significant. However, when the analysis was stratified according to various segments of the cerebral arteries, IADE-positive patients had more plaques in the basilar artery ($P=0.006$). After adjustment for age, sex, and heart weight, the OR of IADE associated with the presence of plaques in the basilar artery was 2.83 (95% CI, 1.15 to 6.95). We also found a positive association between IADE and the presence of ulcerated plaques in the aortic arch, which remained significant after multivariable analysis (adjusted OR, 3.13; 95% CI, 1.26 to 7.78).

Brain Tissue and Small-Vessel Lesions
As shown in Table 3, IADE-positive patients had a higher frequency of lacunar infarction (48% vs 27%) and multilacunes (35% vs 16%) than IADE-negative patients. After adjustment for age, sex, and heart weight, multilacunes remained significantly associated with IADE (Table 3).

Illustrative case: 66-year-old hypertensive male smoker. In July 1983, the patient had right-sided hemiplegia. The computed tomography scan showed only leukoaraiosis. He was then treated with aspirin, and on May 2, 1984, he died of a massive right putaminal and ventricular hemorrhage. Basilar, vertebral, and internal carotid arteries were dolichoectatic with enlarged diameters and thin walls and were free of any atherosclerotic lesions (A). There were multiple, small, deep infarcts (multilacunar state) and dilatation of perivascular spaces (état criblé) on celloidin-fixed section (Loyez stain for myelin; B). Microscopic examination of the brain showed SVD with lipohyalinosis (C) and hyalinosclerosis (D) (hematoxylin-eosin stain). No amyloid angiopathy was detected on Congo red-stained sections.
fibrinoid necrosis was observed in neither IADE-positive nor IADE-negative patients. No case of cerebral amyloid angiopathy was detected on Congo red–stained sections in the IADE-positive group.

**Statistical Power Calculation**

We calculated the smallest difference (expressed as an OR) that our sample size allowed us to detect between IADE-positive and IADE-negative stroke patients at the 5% nominal significance level with 80% power and assuming an exposure frequency of 30% in IADE-negative stroke patients. On the basis of this calculation, without missing data, we could detect an OR of 3.3 with 23 IADE-positive and 358 IADE-negative stroke patients.

**Discussion**

In this autopsy study, we found that IADE-positive patients with fatal stroke were more likely than those without IADE to have a disorder of the arterial tree, including ulcerated plaques of the aortic arch, basilar plaques, and SVD. These associations were independent of known vascular risk factors such as age, sex, and heart weight (taken as a surrogate for arterial hypertension). No IADE-positive patient had diabetes mellitus in this series.

**Frequency of IADE**

In this series of patients with fatal stroke, we found a 6% prevalence of IADE, which is less than the 12% found in a previous MRI study of 510 distinct stroke patients in the GENIC study. This difference may be explained by differences in the diagnostic criteria used in the 2 studies. The strong association between IADE and lacunar infarction and the low case-fatality rate for lacunar infarcts make it less likely that these patients will die of their stroke. Therefore, our sample of 23 patients with IADE and fatal stroke should be regarded as cases different from those of the entire spectrum of IADE.

**IADE and Large-Artery Atherosclerosis**

The pathologic patterns of atherosclerosis and dolichoectasia are distinct. Atherosclerosis primarily involves the intima of the cerebral arteries, whereas dolichoectasia primarily affects the media and adventitia.

**TABLE 1. Clinical and Anatomic Vascular Risk Factors in Stroke Patients With and Without IADE**

<table>
<thead>
<tr>
<th>Clinical factors</th>
<th>IADE+ (n=23)</th>
<th>IADE− (n=358)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean±SD</td>
<td>78±11</td>
<td>72±12</td>
<td>0.02</td>
</tr>
<tr>
<td>Men, % (n)</td>
<td>52 (12/23)</td>
<td>55 (195/358)</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>65 (15/23)</td>
<td>57 (199/352)</td>
<td>0.42</td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>0 (0/23)</td>
<td>15 (51/352)</td>
<td>0.06*</td>
</tr>
<tr>
<td>Smoking, % (n)</td>
<td>4.4 (1/23)</td>
<td>16 (55/352)</td>
<td>0.22*</td>
</tr>
<tr>
<td>Obesity, % (n)</td>
<td>4.4 (1/23)</td>
<td>9.9 (35/352)</td>
<td>0.71*</td>
</tr>
<tr>
<td>Dyslipidemia, % (n)</td>
<td>4.4 (1/23)</td>
<td>7.4 (26/352)</td>
<td>1.00*</td>
</tr>
<tr>
<td>Atrial fibrillation, % (n)</td>
<td>13 (3/23)</td>
<td>28 (87/352)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cardiovascular history, % (n)</td>
<td>8.7 (2/23)</td>
<td>22 (79/352)</td>
<td>0.19*</td>
</tr>
<tr>
<td>Stroke history, % (n)</td>
<td>4.4 (1/23)</td>
<td>20 (71/355)</td>
<td>0.10*</td>
</tr>
</tbody>
</table>

**Autopsy factors**

| Heart weight, g, mean±SD                              | 458±114      | 417±102       | 0.06  |
| Silent and nonsilent myocardial infarction, % (n)     | 44 (10/23)   | 39 (136/346)  | 0.69  |
| Cardiac valvulopathy, % (n)                           | 23 (5/22)    | 12 (40/342)   | 0.17* |

Proportions and continuous variables were compared with the \( \chi^2 \) (or Fisher’s exact*) test and Student’s \( t \) test, respectively.

**TABLE 2. Prevalence of Atherosclerosis in 353 Consecutive Autopsies of Stroke Patients With or Without IADE**

<table>
<thead>
<tr>
<th>Atherosclerotic plaques in the cerebral arteries</th>
<th>IADE+ (n=22)</th>
<th>IADE− (n=331)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any segment of cerebral arteries</td>
<td>91 (20/22)</td>
<td>77 (256/331)</td>
<td>0.18*</td>
</tr>
<tr>
<td>Any segment of intracranial arteries</td>
<td>68 (15/22)</td>
<td>58 (192/331)</td>
<td>0.35</td>
</tr>
<tr>
<td>Siphon and termination of ICA or MCA</td>
<td>50 (11/22)</td>
<td>45 (150/331)</td>
<td>0.67</td>
</tr>
<tr>
<td>V4 segments of vertebral artery</td>
<td>19 (4/21)</td>
<td>20 (67/329)</td>
<td>1.00</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>59 (13/22)</td>
<td>31 (102/330)</td>
<td>0.006 (0.02†)</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>23 (5/22)</td>
<td>8.8 (29/331)</td>
<td>0.05* (0.05†)</td>
</tr>
<tr>
<td>Any segment of extracerebral arteries</td>
<td>73 (16/22)</td>
<td>67 (223/331)</td>
<td>0.60</td>
</tr>
<tr>
<td>ICA origin and CCA</td>
<td>64 (14/22)</td>
<td>62 (204/331)</td>
<td>0.85</td>
</tr>
<tr>
<td>Origin and V2 segments of vertebral artery</td>
<td>27 (6/22)</td>
<td>23 (76/331)</td>
<td>0.64</td>
</tr>
<tr>
<td>Subclavian arteries</td>
<td>36 (8/22)</td>
<td>18 (61/331)</td>
<td>0.05 (0.08†)</td>
</tr>
<tr>
<td>Coronary artery plaques</td>
<td>91 (20/22)</td>
<td>71 (219/308)</td>
<td>0.05 (0.20†)</td>
</tr>
<tr>
<td>Coronary artery stenosis</td>
<td>55 (12/22)</td>
<td>36 (111/308)</td>
<td>0.08 (0.27†)</td>
</tr>
<tr>
<td>Ulcerated plaques in aortic arch</td>
<td>50 (11/22)</td>
<td>22 (70/325)</td>
<td>0.006 (0.01†)</td>
</tr>
<tr>
<td>Ulcerated plaques in the abdominal or thoracic aorta</td>
<td>36 (8/22)</td>
<td>18 (59/331)</td>
<td>0.05* (0.10†)</td>
</tr>
<tr>
<td>Abdominal or thoracic aortic aneurysm</td>
<td>9.1 (2/22)</td>
<td>4.2 (14/331)</td>
<td>0.26*</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; MCA, middle cerebral artery; and CCA, common carotid artery. \( P \) values were computed with the \( \chi^2 \) or Fisher’s exact* test.

†\( P \) values were calculated by logistic regression, adjusted for age, sex, and heart weight.
large- and medium-size arteries, whatever their location, whereas dolichoectasia involves mainly the media of intracranial arteries. The 2 diseases have several vascular risk factors in common, such as old age, male sex, and hypertension, which may explain their coexistence. In our previous case-control study, performed in 510 stroke survivor patients, we found no relation between IADE and carotid atherosclerosis as assessed by the presence of plaque and intima-media thickness on ultrasound examination. In this autopsy study, we confirmed the lack of association between IADE and ulcerated plaques in the aortic arch has not been reported. The aorta is 2 to 4 times more likely to show evidence of severe atherosclerosis than are the cervical arteries, and the presence of ulcerated plaques in the aortic arch is poorly correlated with that of carotid stenosis.

**IADE and SVD**

The present study is the first to assess the pathology of small intracerebral arteries in IADE patients with stroke. We confirm the strong, independent association between IADE and multilacunes that we reported previously in the GENIC study, and we further show that the underlying changes in intracranial arteries in IADE patients with stroke. We found no relation between IADE and carotid atherosclerosis.10

<table>
<thead>
<tr>
<th></th>
<th>IADE+ (n=23)</th>
<th>IADE− (n=358)</th>
<th>P</th>
<th>OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small vessel disease, % (n)</td>
<td>45 (10/22)</td>
<td>18 (61/338)</td>
<td>0.004†</td>
<td>3.85 (1.56–9.52)</td>
</tr>
<tr>
<td>Lacunar infarction, % (n)</td>
<td>48 (11/23)</td>
<td>27 (97/358)</td>
<td>0.03</td>
<td>2.42 (0.99–5.89)</td>
</tr>
<tr>
<td>Multilacunes, % (n)</td>
<td>35 (8/23)</td>
<td>16 (58/358)</td>
<td>0.04†</td>
<td>2.85 (1.11–7.32)</td>
</tr>
<tr>
<td>État crible, % (n)</td>
<td>23 (5/22)</td>
<td>13 (44/338)</td>
<td>0.19†</td>
<td>1.78 (0.62–5.17)</td>
</tr>
</tbody>
</table>

*Sclerosis, hyalinosis, or lipohyalinosis of small arteries <300 μm and arterioles.

P values were computed with the χ² or Fisher’s exact test. ORs were calculated by logistic regression, adjusted for age, sex, and heart weight.

In conclusion, intracranial arterial dolichoectasia was associated with cerebral SVD, mainly hyalinosclerosis, independent of age, arterial hypertension, and diabetes mellitus. This finding suggests that these media-involving arteriopathies have biological processes in common.

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Disclosures
None.

References
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