Prevalence and Calcification of Intracranial Arterial Stenotic Lesions as Assessed With Multidetector Computed Tomography Angiography

Philip J. Homburg, MD; Gerben J.J. Plas, MD; Sietske Rozie, MD; Aad van der Lugt, MD, PhD; Diederik W.J. Dippel, MD, PhD

Background and Purpose—Intracranial arterial stenosis (ICAS) in patients with recent ischemic stroke is associated with a high risk of recurrent stroke. More insight into the pathophysiology of ICAS could help identify patients at high risk requiring more aggressive secondary prevention. We evaluated the prevalence, distribution, calcification, and the risk factors predisposing ICAS in a European stroke population.

Methods—Consecutive patients with a transient ischemic attack or ischemic stroke (n=786) were evaluated for the presence and distribution of ICAS (≥30% luminal narrowing) by CT angiography. ICAS were categorized as symptomatic or asymptomatic, and the presence of calcification was assessed. The association of traditional cerebrovascular risk factors and the erythrocyte sedimentation rate with ICAS was analyzed.

Results—In 178 of 786 patients (23%), 288 ICAS were observed. Most stenoses (n=194/288; 67%) were located in the posterior circulation arteries. In 59 of 786 patients (8%), ICAS were considered symptomatic. ICAS in the basilar artery and arteries beyond the circle of Willis were mainly noncalcified. In addition to age, gender, and several traditional cerebrovascular risk factors, erythrocyte sedimentation rate was independently associated with the presence of ICAS (OR, 1.20; 95% CI, 1.06–1.36) and with the presence of noncalcified ICAS in particular (OR, 1.20; 95% CI, 1.05–1.37).

Conclusions—ICAS was observed in a noteworthy number of European stroke patients. Particularly, the majority of ICAS was observed in the posterior circulation, possibly conferring worse prognosis. ICAS in distal arteries were mainly noncalcified. Association of noncalcified ICAS and erythrocyte sedimentation rate may indicate a prominent role for inflammatory factors in intracranial atherosclerotic disease. (Stroke. 2011;42:1244-1250.)

Key Words: atherosclerosis ■ atherosclerotic plaque calcification ■ computed tomography ■ intracranial stenosis ■ risk factors

Intracranial arterial stenosis (ICAS) in patients with TIA or ischemic stroke is associated with a high risk of recurrent stroke. Angioplasty and stenting are feasible procedures for revascularization of vessels affected by ICAS. However, insufficient evidence is available to recommend these treatments for the prevention of recurrent stroke in patients with ICAS in clinical practice. More insight into the prevalence, distribution, and calcification of ICAS lesions could help identify patients at high risk requiring more aggressive secondary prevention.

The prevalence of ICAS seems to vary among ethnic groups. Nevertheless, only limited studies have assessed the prevalence and associated risk factors for ICAS in European stroke patients. Moreover, the comparative value of studies available in European patients is limited by the use of multiple imaging modalities.

Also, little is known about the composition of ICAS lesions, which may point to a specific pathophysiological process. The pathophysiology of intracranial atherosclerosis is suggested to differ from that of the extracranial arteries. A prominent role for inflammatory factors is indicated in the atherosclerosis of the intracranial arteries. Consequently, the proatherogenic influence of inflammatory reactions could be manifested as an association between the erythrocyte sedimentation rate (ESR) and ICAS, as previously observed in a single study. In addition, an accelerated intracranial atherogenesis could be reflected in differences in plaque calcification.

Multidetector computed tomography angiography (MDCTA) is reliable for the evaluation of both extracranial and intracranial atherosclerotic disease. Moreover, the technique is available for detection of ICAS in most European
hospitals.13 As compared to digital subtraction angiography, MDCTA has been demonstrated to be effective in the detection of ICAS, with a sensitivity of 97% and a specificity of 99%.12 In addition, MDCTA allows differentiation between calcified and noncalcified atherosclerotic plaques.14

In the current study, we evaluated a large cohort of patients with TIA or ischemic stroke for the prevalence, distribution, and the calcification of ICAS lesions using MDCTA. Furthermore, the association of ICAS with the traditional risk factors for cerebrovascular disease as well as with ESR was investigated.

Materials and Methods

Study Population

From a prospective registry of 911 consenting patients with amaurosis fugax, TIA, or ischemic stroke (Rankin score <4 at discharge), we selected all patients (n=795) with a recent ischemic stroke or TIA but excluded patients with amaurosis fugax. Patients were enrolled from a specialized TIA/stroke outpatient clinic or the stroke unit. All patients were interviewed and examined by a vascular neurologist and underwent electrocardiography and laboratory analysis. Medical history and cerebrovascular risk factors were recorded. On admission, patients underwent MDCT of the brain and MDCTA Data Acquisition and Analysis.

MDCTA was performed with a 16-slice MDCT scanner (Sensation 16; Siemens) or a 64-slice MDCT scanner (Sensation 64; Siemens) with a standardized protocol.16,17 Intracranial arteries were evaluated on a stand-alone workstation (Leonardo; Siemens Medical Solutions) with multiplanar reformatting and maximum intensity projection images of 4-mm thickness (Figure 1). Because symptomatic ulceration with superimposed thrombus of intracranial atherosclerotic plaques is also present in low-grade stenosis, we defined ICAS as ≥30% luminal narrowing.18 The degree of stenosis was measured according to the WASID criteria on oblique multiplanar reformatting images perpendicular to the central lumen line.19 Stenoses were classified as 30% to 49%, 50% to 69%, and 70% to 99%. The internal carotid arteries, the anterior cerebral arteries, the medial cerebral arteries, the vertebral arteries, the basilar artery, and the posterior cerebral arteries were analyzed.

Blinded to clinical information, 2 trained observers (P.J.H. and G.J.J.P.) independently analyzed the presence of ICAS according the WASID method in the first 50 patients. After 4 weeks, the first observer analyzed the same 50 patients. Good interobserver agreement (κ=0.79; 95% CI, 0.55–1.02) and intraobserver agreement (κ=0.79; 95% CI, 0.60–0.99) were observed.

A calcified ICAS lesion was defined as any intracranial stenosis (≥30%) containing plaque calcifications (≥130 Hounsfield units). Symptomatic ICAS was defined as any intracranial stenosis (≥30%) in an artery supplying the involved region of the brain, taking into account the configuration of the circle of Willis.

Statistical Analysis

Differences between variables were tested with the χ² test, Fisher exact test, Mann-Whitney U test, or a nonparametric rank test when appropriate. The association of traditional cerebrovascular risk factors and ESR with the presence of ICAS was determined using regression analysis. The risk factors significantly associated with ICAS (P<0.05) in the univariable regression analysis, which were not directly interrelated, were included in a multivariable regression model. Associations were expressed as OR with 95% CI. The analysis was repeated for the presence of noncalcified ICAS lesions, calcified ICAS lesions, and symptomatic ICAS in patients. For the
analyses were performed using SPSS 15.0. \( P<0.05 \) was considered statistically significant.

### Results

#### Prevalence, Distribution, and Calcification of ICAS

Most patients were male \((n=513; 56\%)\) and the mean age was \(62\pm 14\) years. Baseline characteristics of patients with and without ICAS are illustrated in Table 1. The presence and severity of ICAS in different arteries are shown in Table 2. ICAS \(\geq 30\%\) was observed in 178 patients \((23\%)\). ICAS \(\geq 50\%\) was present in 77 patients \((10\%)\), and ICAS \(\geq 70\%\) was present in 21 patients \((3\%)\). In total, 288 ICAS \((\geq 30\%)\) were observed.

In 184 of 288 ICAS \((64\%)\), the degree of stenosis ranged from \(30\%\) to \(49\%\), from \(50\%\) to \(69\%\) in 83 of 288 ICAS \((29\%)\), and from \(70\%\) to \(99\%\) in the remaining 21 of 288 ICAS \((7\%)\). Occlusions were present in 52 arteries. Interestingly, the majority of ICAS \((n=194/288; 67\%)\) was located in the posterior circulation. Stenoses \(\geq 70\%\) occurred mainly in the posterior circulation of the brain. Exclusively noncalcified ICAS lesions were observed in 126 patients \((16\%)\). In total 221 of 288 ICAS, lesions \((77\%)\) were noncalcified. ICAS lesions in the anterior cerebral artery, medial cerebral artery, and basilar artery were exclusively noncalcified. Calcified ICAS lesions were predominantly present in the proximal arteries (internal carotid artery and vertebral artery; \(n=64\)), whereas only 3 calcified ICAS lesions were identified in the posterior cerebral artery. In 59 patients \((8\%)\), a total of 63 symptomatic ICAS \(\geq 30\%\) was observed. Symptomatic ICAS of \(\geq 50\%\) was present in 18 of the patients \((3\%)\). Overall, symptomatic ICAS comprised 39 stenoses in the anterior circulation and 24 stenoses in the posterior circulation.

#### Risk Factors Associated With ICAS

Multivariable analysis revealed an independent association between ICAS and age, male gender, Asian ethnicity, hypertension, diabetes mellitus, LDL cholesterol, and ESR (Table 3). Risk factors independently associated with noncalcified ICAS lesions and calcified ICAS lesions are provided in Table 4. Age, male gender, hypertension, diabetes mellitus,
LDL cholesterol, and ESR remained independently associated with noncalcified ICAS lesions, whereas only age was independently associated with calcified ICAS lesions. The median time since symptom onset and clinical and laboratory analysis was 5 days.1–14 The association of ESR with ICAS remained present after adjustment for time between onset of symptoms (OR, 1.22; 95% CI, 1.08–1.36). Interestingly, ESR increased with degree of intracranial stenosis (Figure 2). Age, Asian ethnicity, hypertension, and ESR were independently associated with symptomatic ICAS.

Discussion

In the current study, ICAS ≥30% was observed in 178 patients (23%) with a recent ischemic stroke or TIA. The majority of all ICAS was located in the posterior circulation arteries. Symptomatic ICAS ≥30% was observed in 59 patients (8%). Calcified ICAS lesions were predominantly observed in the proximal intracranial arteries (internal carotid artery and vertebral artery), whereas ICAS lesions in the distal intracranial arteries (basilar artery, anterior cerebral artery, medial cerebral artery, and posterior cerebral artery) were mainly noncalcified. A number of traditional risk factors including age, male gender, Asian ethnicity, hypertension, diabetes mellitus, and LDL cholesterol were independently associated with the presence of ICAS in multivariable analysis. An independent association was also observed between ESR and ICAS. Equivalent traditional risk factors and ESR were also associated with noncalcified ICAS lesions. However, age was the only risk factor associated with calcified ICAS lesions.

Prevalence and Distribution of ICAS

The comparability of studies on the prevalence of ICAS in stroke patients is limited because of the variation in the symptoms (OR, 1.22; 95% CI, 1.08–1.36). Interestingly, ESR increased with degree of intracranial stenosis (Figure 2). Age, Asian ethnicity, hypertension, and ESR were independently associated with symptomatic ICAS.

Table 3. Univariable and Multivariable Analysis of Risk Factors Associated With Intracranial Arterial Stenosis

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 y)*</td>
<td>1.65 (1.43–1.90)</td>
<td>1.65 (1.40–1.94)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.34 (0.96–1.89)</td>
<td>1.55 (1.05–2.29)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2.90 (1.47–5.73)</td>
<td>2.68 (1.20–5.98)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Multivariable Analysis of Risk Factors Associated With Exclusively Noncalcified Intracranial Arterial Stenosis Lesions, Calcified Intracranial Arterial Stenosis Lesions, and Symptomatic Intracranial Arterial Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Noncalcified ICAS (n = 126; 16%)</th>
<th>Calcified ICAS (n = 52; 7%)</th>
<th>Symptomatic ICAS (n = 59; 8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 y)*</td>
<td>1.37 (1.15–1.63)</td>
<td>2.09 (1.56–2.82)</td>
<td>1.37 (1.07–1.75)</td>
</tr>
<tr>
<td>Male</td>
<td>1.56 (1.01–2.40)</td>
<td>1.29 (0.68–2.45)</td>
<td>1.60 (0.87–2.92)</td>
</tr>
<tr>
<td>Asian</td>
<td>2.02 (0.88–4.62)</td>
<td>2.52 (0.76–8.36)</td>
<td>3.69 (1.49–9.14)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.74 (1.02–2.96)</td>
<td>1.84 (0.79–4.31)</td>
<td>3.04 (1.23–7.49)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.13 (1.32–3.42)</td>
<td>1.37 (0.67–2.81)</td>
<td>1.52 (0.80–2.86)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)*</td>
<td>1.29 (1.07–1.57)</td>
<td>1.25 (0.94–1.67)</td>
<td>1.08 (0.83–1.41)</td>
</tr>
<tr>
<td>ESR (per 10 mm/h)*</td>
<td>1.20 (1.05–1.37)</td>
<td>1.09 (0.88–1.35)</td>
<td>1.23 (1.04–1.46)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ESR, erythrocyte sedimentation rate; ICAS, intracranial arterial stenosis; LDL, low-density lipoprotein; OR, odds ratio; TIA, transient ischemic attack.

*Ratio per unit increase.
studied populations, definition of ICAS, and used imaging modalities. Thus far, large studies on the prevalence, distribution, and risk factors predisposing ICAS have been mainly performed in Asian stroke populations.\textsuperscript{20–22} Relatively high prevalence of 26% to 54% was observed in studies of different Asian populations of stroke patients. In contrast, limited studies have evaluated the prevalence of ICAS in Europe.\textsuperscript{4,5,6} In a multicenter European study by Weimar et al.,\textsuperscript{6} using various imaging modalities, symptomatic ICAS of $\geq 50\%$ was observed in 6.5\% of the evaluated stroke patients. In contrast, the results of the present study reveal a lower prevalence of symptomatic ICAS $\geq 50\%$ in European stroke patients (3\%). The difference in prevalence can be partly explained by the inclusion of a higher proportion of patients with TIA and the exclusion of patients with severe ischemic stroke (Rankin score $<4$ at discharge) in the current study.

Observed prevalence and distribution of ICAS are also influenced by the applied imaging modality.\textsuperscript{23} In general, transcranial Doppler is more operator-dependent and obtained results vary according to operator skills. Moreover, transcranial Doppler is suggested to be less sensitive than CTA for the detection of ICAS in the posterior circulation.\textsuperscript{23,24} However, in Asian patients with TIA and ischemic stroke, the anterior circulation seems to be the predilection site in the distribution of ICAS irrespective of the imaging modality.\textsuperscript{25–27} Distribution of ICAS reported in European stroke patients has been less consistent. Using either digital subtraction angiography or ultrasonography for primary detection, Mazighi et al.\textsuperscript{4} observed a higher prevalence of ICAS in the anterior and posterior circulations. In contrast, using transcranial Doppler/duplex ultrasonography in 99\% of the studied patients, Weimar et al.\textsuperscript{6} reported a similar distribution of ICAS in the anterior and posterior circulations. In contrast, using Doppler/duplex ultrasonography in 99\% of the studied patients, Weimar et al.\textsuperscript{6} observed a higher prevalence of ICAS in the anterior (77\%) versus the posterior (23\%) circulation. Using MDCTA in current study, the majority of ICAS (67\%) was located in the posterior circulation. The lower proportion of ICAS in the posterior circulation in the previous European studies may be attributable to a detection bias, because investigators have mainly relied on ultrasonography. Of note, detection of ICAS in the posterior circulation may be an important prognostic determinant because these lesions have been associated with a high risk of recurrent stroke.\textsuperscript{1,28,29}

Composition of ICAS Lesions

Thus far, limited imaging studies have evaluated the composition of ICAS lesions. CT brain studies have reported a predominant presence of calcification in the proximal arteries but did not combine the evaluation of ICAS and plaque calcification with MDCTA.\textsuperscript{30,31} Our findings confirm the presence of calcified ICAS lesions in the proximal intracranial arteries. However, a majority of noncalcified ICAS lesions was demonstrated in the distal arteries, which would be neglected on CT of the brain. This implicates that absence of calcification on CT of the brain does not exclude the presence of ICAS in the distal arteries. In line with the results of the current study, a previous postmortem histological analysis of atherosclerotic plaque composition in the medial cerebral artery has demonstrated calcification in only a minority of the specimens (31 of 111; 28\%).\textsuperscript{32} The low prevalence of calcified ICAS lesions on MDCTA in the distal intracranial arteries suggests a different pathophysiology of atherosclerotic disease in the proximal and distal intracranial arteries. The intracranial arteries show significantly greater antioxidant enzyme activities than the extracranial arteries.\textsuperscript{8} The greater activity of antioxidant enzymes in intracranial arteries may contribute to a greater resistance to atherogenesis. This antiatherogenic activity decreases significantly in older age, coinciding with accelerated atherogenesis.\textsuperscript{8} Consequently, with age, intracranial arteries may respond with accelerated atherogenesis as their antioxidant protection decreases more significantly than that of the extracranial arteries. In the current study, the higher prevalence of extracranial stenosis in patients with ICAS supports the loss of protective antioxidant capacity in the extracranial arteries at a younger age. In line with this observation, higher plasma C-reactive protein levels have been previously noted in patients with extracranial stenosis as compared to those with isolated medial cerebral artery stenosis.\textsuperscript{33}

Furthermore, with age, plasma LDL becomes more susceptible to oxidation.\textsuperscript{34} The oxidative modification of LDL therefore may play a key role in this atherogenic process through inflammatory reactions.\textsuperscript{35,36} The presence of mainly noncalcified ICAS lesions in the basilar artery and arteries beyond the circle of Willis in the current study might be a reflection of this accelerated atherogenesis.

Risk Factors Associated With ICAS

A number of traditional risk factors for atherosclerotic disease have been previously related to ICAS.\textsuperscript{3,9,37} In addition, high-sensitivity C-reactive protein, a marker of inflammation, is associated with recurrent ischemic events in the territory of the stenotic artery in stroke patients with ICAS.\textsuperscript{5} Also, ESR was shown to be independently associated of with the presence of ICAS in a South Asian stroke population.\textsuperscript{10} In the present study of European patients, ICAS lesions were associated not only with the traditional risk factors including hypertension, diabetes, and LDL cholesterol but also with ESR. Importantly, the association of ESR with ICAS remained significant even after adjustment for the time since onset of symptoms. Thereby, the contribution of the acute phase reaction as a cause of ESR elevation was made less probable. As a result, an independent association was identified between ESR and LDL cholesterol with the presence of ICAS and, more importantly, with the presence of noncalcified ICAS lesions in patients with a recent TIA or ischemic stroke. These findings may indicate a prominent role for inflammation in intracranial atherogenesis.\textsuperscript{35,36}

Study Limitations

The design of the present study is cross-sectional. The prognostic values of the presence, distribution, and calcification of ICAS lesions in patients with ischemic stroke or TIA remain to be determined in follow-up studies. The pathophysiological mechanisms initiating intracranial atherosclerosis were not evaluated. However, the predisposing risk factors and degree of calcification of ICAS support the current...
hypothesis on the delayed development of intracranial atherosclerosis.

In the current study, the association of ICAS with the ESR was investigated as a marker of inflammatory processes in the atherosclerosis of the intracranial arteries. However, the ESR is only an indirect indicator of inflammatory processes and could be increased because of comorbidity. We did not exclude patients with comorbidity associated with ESR elevation to avoid additional bias. Evaluation of additional inflammatory markers such as high-sensitivity C-reactive protein and interleukins could have provided additional data on the role of inflammatory processes in intracranial atherosclerosis. Finally, the ESR was only measured at a single time point and during the acute phase in some of the patients.

Conclusions

It has been suggested that atherosclerosis in the extracranial carotid artery is the primary source of ischemic stroke in white patients. We observed a low prevalence of ICAS in the current study population of predominantly white ethnicity. However, most ICAS were observed in the posterior circulation, a location associated with a high risk of recurrent stroke. Mainly noncalcified ICAS lesions were observed in distal intracranial arteries. A strong association of LDL cholesterol and ESR was identified with the presence of ICAS and, more importantly, with the presence of noncalcified ICAS lesions in patients with a recent TIA or ischemic stroke. Accordingly, in intracranial atherogenesis, a prominent role is indicated for inflammation. Further research on noninvasive analysis of plaque components in ICAS lesions could improve understanding of the pathophysiology of intracranial atherosclerosis. The additional evaluation of intraplaque hemorrhage using high-resolution MRI, which is likely to convey strong prognostic value for recurrent stroke, may be of particular interest.

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Disclosure

None.

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应用多排 CT 血管造影评估颅内动脉狭窄的发生率和钙化情况

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背景和目的：缺血性卒中的患者若伴有颅内动脉狭窄（ICAS）则卒中再发的风险较高。为了能在及时对患者采取更为积极的二级预防，则需进一步观察 ICAS 的病理生理特征。为此，我们对欧洲缺血性卒中患者 ICAS 的患病率、分布特征、钙化情况以及诱发因素进行了评估。

方法：利用 CT 血管造影（CTA）对 786 例短暂性脑缺血发作（TIA）或缺血性卒中患者 ICAS（其管腔狭窄 ≥30%）的分布情况和分布特征进行评估。将 ICAS 按照有症状或无症状以及其是否存在钙化情况进行分类。分析 ICAS 与传统脑血管病危险因素及红细胞沉降率（ESR）之间的关联。

结果：在 786 名患者中，有 178 人（23%）存在共 288 处 ICAS，大多数狭窄（n=194/288; 67%）位于后循环的动脉；786 名患者中有 58 人（8%）的 ICAS 是有症状性的。发生在基底动脉和 Willis 环远端的 ICAS 多是非钙化性的。除了年龄、性别和传统的脑血管病危险因素外，红细胞沉降率与 ICAS 的发生具有独立的相关性（OR, 1.20; 95% CI, 1.06-1.36），尤其是与非钙化性 ICAS (OR,1.20; 95% CI, 1.05-1.37)。

结论：在欧洲的缺血性卒中患者中，ICAS 的发生率是值得关注的。特别是大多数 ICAS 发生在后循环动脉，提示预后更差。在 Willis 环远端的动脉中，ICAS 主要是非钙化性的。红细胞沉降率和非钙化性 ICAS 关系表明炎症因子可能在颅内动脉粥样硬化疾病中有着重要的作用。

关键词：动脉粥样硬化，动脉粥样硬化斑块钙化，计算机断层扫描，颅内狭窄，危险因素

(Stroke. 2011;42:1244-1250. 吉林大学第一医院神经内科 孙欣 译 杨弋 吴江 校)
MDCTA 还可以有效的区分钙化性和非钙化性动脉粥样硬化斑块 [14]。

在目前的一项研究中，为了了解 ICAS 病变的患病率、分布特征和钙化情况，我们利用 MDCTA 评估了大量患有短暂性脑缺血发作 (TIA) 或缺血性卒中的患者。并且，我们对 ICAS 和脑血管疾病的传统危险因素（如红细胞沉降率 [ESR]）的相关性也进行了研究。

### 材料和方法

#### 研究对象

从 911 名患有一过性黑曚、TIA 或缺血性卒中的患者中 (出院时 Rankin 评分 <4)，我们选取了 795 名近期患 TIA 或者缺血性卒中但不包括一过性黑曚的患者作为研究对象。患者都是在专业 TIA/缺血性卒中门诊登记的。所有患者都要接受神经血管专家的检查，并行心电图和实验室检查。病史和脑血管危险因素都会被记录下来。患者入院时，还要在同一时间接受脑部多排 CT 扫描 (MDCT) 和颈动脉以及颅内动脉的 MDCTA 扫描。有 3 例患者由于 MDCTA 扫描图像欠佳无法进行可靠评价，6 例患者由于颅内动脉在扫描重建区之外而被排除。研究最终分析了剩余的 786 例患者中。

#### 危险因素

我们应用一种计算方法来确定患者的种族，这一方法是基于患者和患者父母的出生地以及他们的姓和名来确定的 [15]。为了实现本次研究的主要目标，我们区分了亚裔和非亚裔人口。缺血性心脏病史定义为曾患慢性心力衰竭、心绞痛、心肌梗死或曾接受冠状动脉旁路移植术。高胆固醇血症的定义为空腹胆固醇 >5.0 mmol/L 或曾应用过治疗高胆固醇血症的药物。高血压定义为在两次为时 15 分钟的无创性连续血压测量时，收缩压 >140 mmHg 和 / 或舒张压 >90 mmHg，或应用治疗高血压的药物。糖尿病定义为空腹血糖 >7.9 mmol/L，糖化血红蛋白 >6.5%，或应用治疗糖尿病的药物。实验室的分析包括总胆固醇、高密度脂蛋白胆固醇、低密度脂蛋白 (LDL) 胆固醇水平、甘油三酯、血糖以及 ESR。

#### MDCT和MDCTA数据采集和分析

MDCTA 是按照标准试验设计方案，应用 16 排螺旋 CT 扫描仪 (Sensation 16; Siemens) 或者 64 排螺旋 CT 扫描仪 (Sensation 64; Siemens) 来完成的 [16,17]。颅内动脉的评估是在一个独立的工作站 (Leonardo; Siemens Medical Solutions) 上使用多平面重组和 4 mm 厚的最大强度投影图像来完成的（图 1）。由于低度狭窄时会发生颅内动脉粥样硬化斑块溃疡与血栓相叠加的情况，因此我们将 ICAS 定义为管腔狭窄 ≥30% [18]。狭窄的程度是根据 WASID 标准中的多维重组图像到管腔中央线的垂直距离来进行测量的 [19]。狭窄被划分为 30%-49%、50%-69% 和 70%-99%，并分别对颈内动脉、大脑前动脉、大脑中动脉、椎动脉、基底动脉和大脑后动脉进行分析。

在不知道临床资料的情况下，两名训练有素的研究员 (P.J.H. 和 G.J.J.P.) 依据 WASID 方法，独立的
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**ICAS** 定义为任何颅内狭窄 (≥30%) 导致的颅内血管分布区域供血的异常。

### 统计分析

参数之间的差异是根据情况适当的采用 \( \chi^2 \) 测试、Fisher 精确检验、Mann-Whitney U 检验或非参数的秩和检验。使用回归分析确定传统脑血管病危险因素和红细胞沉降率与 ICAS 之间的关系。在多变量回归模型中钙化性卒中危险因素和 ICAS 并没有直接关联，但在单因素回归分析中，二者则显著相关 (\( P<0.05 \))。相关性用优势比 (OR) 及其 95% 的可信区间 (CI) 表示。这种分析方法反复应用在出现非钙化性 ICAS 病变、钙化性 ICAS 病变和症状性 ICAS 的患者中。在分析的过程中，我们认为完全没有钙化的 ICAS 病变为非钙化性 ICAS 病变，而出现任何钙化的 ICAS 病变则被认为是钙化性 ICAS 病变。统计分析采用 SPSS 15.0, \( P<0.05 \) 则其关联具有统计学意义。

### 结果

ICAS 的患病率、分布和钙化情况

大部分的患者为男性 (513 例，56%)，平均年龄为 62±14 岁。患者有无 ICAS 的基线特征见表 1。ICAS 在不同动脉的分布和严重程度见表 2。在这些患者中发现 178 名患者 (23%)ICAS≥30%，77 名患者 (10%)ICAS≥50%，21 名患者 (3%)ICAS≥70%。共有 288 处 ICAS≥30%。

在这个 288 处 ICAS 中，狭窄程度在 30%-49% 有 184 处 (64%)，50%-69% 的有 83 处 (29%)，剩余的 21 处 (7%) 狭窄程度在 70%-99% 之间。共有 52 根动脉出现闭塞。有趣的是，大多数 ICAS(194/288, 67%) 出现在后循环。狭窄≥70% 主要出现在后循环。
在126名(16%)患者中发现非钙化性病变，其中528处ICAS中，有211处(77%)非钙化性病变。大脑前动脉、大脑中动脉、基底动脉中的ICAS都是非钙化性的。钙化性ICAS主要出现在近端动脉(颈内动脉和椎动脉)，而只有3例钙化性ICAS出现在远端动脉。在59名(8%)患者中，分别发现在大脑前动脉、大脑中动脉、基底动脉中的ICAS都是非钙化性的。钙化性ICAS主要出现在近端动脉(颈内动脉和椎动脉，64例)，而只有3例钙化性ICAS出现在远端动脉。在59名(8%)患者中，分别发现63处症状性ICAS，其管腔狭窄≥30%。而管腔狭窄≥50%的患者中，有18人(3%)发现症状性ICAS。总的来说，症状性ICAS有39处为前循环狭窄，24处为后循环狭窄。

### 表3 颅内动脉狭窄和危险因素相关性的单变量和多变量分析

<table>
<thead>
<tr>
<th>颅内动脉狭窄和危险因素相关性的单变量和多变量分析</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄 (每10岁)*</td>
<td>1.65(1.43-1.90)</td>
<td>1.65(1.40-1.94)</td>
</tr>
<tr>
<td>男性</td>
<td>1.34(0.96-1.89)</td>
<td>1.55(1.05-2.29)</td>
</tr>
<tr>
<td>亚洲人</td>
<td>2.90(1.47-5.73)</td>
<td>2.68(1.20-5.98)</td>
</tr>
<tr>
<td>机制</td>
<td>1.79(1.24-2.60)</td>
<td>...</td>
</tr>
<tr>
<td>腹部</td>
<td>1.51(0.96-2.37)</td>
<td>...</td>
</tr>
<tr>
<td>脑磷脂等磷脂 (mmol/L)*</td>
<td>1.25(0.79-1.96)</td>
<td>...</td>
</tr>
<tr>
<td>第一管分析</td>
<td>1.14(0.74-1.76)</td>
<td>...</td>
</tr>
</tbody>
</table>

OR，优势比；CI，可信区间。
* 每一单位增长的比率。

### 表4 危险因素与非钙化性ICAS、钙化性ICAS和有症状性ICAS相关性的多变量分析

<table>
<thead>
<tr>
<th>危险因素与非钙化性ICAS、钙化性ICAS和有症状性ICAS相关性的多变量分析</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄 (每10岁)*</td>
<td>1.37(1.15-1.63)</td>
<td>2.09(1.56-2.82)</td>
<td>1.37(1.07-1.75)</td>
</tr>
<tr>
<td>男性</td>
<td>1.56(1.01-2.40)</td>
<td>1.29(0.86-2.54)</td>
<td>1.60(0.87-2.92)</td>
</tr>
<tr>
<td>亚洲人</td>
<td>2.02(0.88-4.62)</td>
<td>2.52(0.76-8.36)</td>
<td>3.69(1.49-9.14)</td>
</tr>
<tr>
<td>高血压</td>
<td>1.74(1.02-2.96)</td>
<td>1.84(0.79-4.31)</td>
<td>3.04(1.23-7.49)</td>
</tr>
<tr>
<td>糖尿病患者</td>
<td>2.13(1.32-3.42)</td>
<td>1.37(0.67-2.81)</td>
<td>1.52(0.80-2.86)</td>
</tr>
<tr>
<td>腹部磷脂 (mmol/L)*</td>
<td>1.29(1.07-1.57)</td>
<td>1.25(0.94-1.67)</td>
<td>1.08(0.83-1.41)</td>
</tr>
<tr>
<td>脑磷脂等磷脂 (mmol/L)*</td>
<td>1.20(1.05-1.37)</td>
<td>1.09(0.88-1.35)</td>
<td>1.23(1.04-1.46)</td>
</tr>
</tbody>
</table>

OR，优势比；CI，可信区间。
* 每一单位增长的比率。

### 讨论

目前的研究表明，ICAS≥30%的患者中，有178例(23%)近期患缺血性卒中或TIA。而ICAS大多位于后循环动脉。症状性ICAS≥30%的患者为59例(8%)。钙化性ICAS则主要存在于远端颅内动脉(颈内动脉和椎动脉)，而在远端颅内动脉(包括基底
动脉、大脑前动脉、大脑中动脉和大脑后动脉）的 ICAS 病变则主要是非钙化性的。在进行多变量分析的时候，发现 ICAS 的产生和一些传统危险因素（如年龄、男性、亚洲人种、高血压、糖尿病、低密度脂蛋白胆固醇）有关。研究还发现了红细胞沉降率和 ICAS 的产生存在着独立的相关性。然而，对于钙化性 ICAS，年龄是唯一具有相关性的危险因素。

ICAS 的患病率和分布情况
由于研究对象、ICAS 的定义和所采用的成像方法不同，故针对卒中患者进行的 ICAS 患病率的对比研究是有一定局限性的。目前为止，大量关于 ICAS 患病率、分布情况和危险因素的研究集中在亚洲卒中人群中[20-22]。通过对不同亚洲人群的卒中患者进行研究发现，ICAS 具有相对较高的患病率，约为 26%-54%，与此相反，只有有限的研究可以用来评估 ICAS 在欧洲的患病率[4-6]。Weimar 等人[6]应用多种成像技术在欧洲进行了多中心的研究，发现现有 6.5% 的卒中患者为有症状性 ICAS，其管腔狭窄≥50%。相对而言，本研究结果表明，欧洲卒中患者中发现有症状性 ICAS（管腔狭窄≥50%）只占 3%。


ICAS 病变的构成
目前，ICAS 病变的构成已经可以通过现有的成像技术进行推断。脑 CT 的研究结果表明钙化主要发生在近端动脉，但是目前尚未应用 MDCTA 对 ICAS 和斑块钙化进行过联合评估[30,31]。我们的研究结果证明钙化的 ICAS 病变主要存在于近端颅内动脉，大多数非钙化性的 ICAS 病变则主要存在于远端动脉，然而在脑 CT 扫描时，远端动脉通常容易被忽略。所以脑 CT 的研究并不能排除远端动脉存在 ICAS 的可能。与我们目前的研究结果一致的是，在一个早期关于欧洲人群中动脉粥样硬化斑块组成的尸检病理分析中证实，只有少数样本存在钙化 (38/111；28%)[32]。

通过 MDCTA 检测发现，在远端颅内动脉中 ICAS 病变钙化发生率较低，这意味着动脉粥样硬化类的疾病在远端和近端颅内动脉可能具有不同的病理特征。颅内动脉的抗氧化酶活性要高于颅外动脉[8]，这使颅内动脉对动脉粥样硬化具有更强的抵抗能力。而这种抗动脉粥样硬化的能力在老年人中要明显降低，这与动脉粥样硬化加速形成的过程的阶段刚好是一致的。随着年龄的增长，颅内动脉会由于抗氧化酶活性的明显减低而比颅外动脉更易产生动脉粥样硬化。在近期的研究中发现，若 ICAS 患者其颅外动脉狭窄的发病率较高，则多是由于较早的出现了颅外动脉抗氧化酶活性降低，从而导致了动脉粥样硬化发生。与这一发现相一致的是，与孤立的大脑中动脉狭窄相比，颅外动脉狭窄患者的血浆 C 反应蛋白的含量要明显增高，这一情况已经得到了广泛的关注[33]。

此外，随着年龄的增长，血浆低密度脂蛋白更易被氧化[34]。因此，血浆低密度脂蛋白氧化修饰可能通过炎症反应在动脉粥样硬化形成的过程中起到了重要的作用[35,36]。因此，在基底动脉和 Willis 动脉环远端的动脉中，多数的非钙化性 ICAS 病变很可能是动脉粥样硬化加速形成的一个反应。

和 ICAS 相关的危险因素
一些导致动脉粥样硬化疾病的传统危险因素很早就被认为与 ICAS 有关[3,9,37]。此外，作为炎症标志的超敏 C 反应蛋白，也被认为与伴有 ICAS 的缺血性卒中患者的脑卒中再发有关，其再发主要发生在狭窄动脉的供血范围内[5]。另外，在南亚的卒中人群中还发现红细胞沉降率和 ICAS 的发生率是具有独立相关性的[10]。在这次欧洲患者的研究中，我
们也发现了ICAS病变不但和高血压、糖尿病、低密度脂蛋白胆固醇等这类传统的危险因素有关，还和红细胞沉降率有关。更为重要的是，即使是在症状出现后的一段时间内，红细胞沉降率和ICAS仍然存在着较为显著的关系，由此可见，红细胞沉降率的升高不能仅仅理解为是一种急性期反应。所以，红细胞沉降率和低密度脂蛋白胆固醇与ICAS的发生率有关的，而且更重要的是其与近期患TIA和缺血性卒中患者的非钙化ICAS病变的发生率密切相关。这些研究结果表明炎症在颅内动脉粥样硬化的过程中起到了重要的作用[35,36]。

研究的局限性

本研究是一项横断面研究，我们在随访研究中确定缺血性卒中或TIA患者ICAS病变的发生率，分布情况和钙化的预后价值。颅内动脉粥样硬化的病理生理机制没有在最初进行研究，但研究发现的ICAS的危险因素和钙化程度支持颅内动脉粥样硬化在后期进展这一假说。

在本研究中，ICAS和红细胞沉降率的关系提示了炎症反应影响颅内动脉粥样硬化的形成。然而，红细胞沉降率在炎症过程中只是一个间接的指标，而且会由于并发症的原因而升高。为了避免研究偏倚，我们不排除患者的并发症和颅内动脉粥样硬化的关系。更多的关于诸如超敏C反应蛋白和红细胞介素等这类其他炎症因子的评价也为我们提供了更多的数据，来研究炎症在颅内动脉粥样硬化过程中的作用。最后，对于研究中的一些患者我们只在某一个单一的时间点上和急性期检测了红细胞沉降率。而且会由于并发症的原因而升高。为了避免研究偏倚，我们不排除患者的并发症和颅内动脉粥样硬化的关系。更多的关于诸如超敏C反应蛋白和红细胞介素等这类其他炎症因子的评价也为我们提供了更多的数据，来研究炎症在颅内动脉粥样硬化过程中的作用。最后，对于研究中的一些患者我们只在某一个单一的时间点上和急性期检测了红细胞沉降率。

结论

研究认为在白种人中，颈动脉颅外段的动脉粥样硬化是形成脑缺血性卒中的主要原因[38]。在本研究中，我们发现ICAS在白种人中只有较低的患病率。而且我们发现大部分的ICAS都位于后循环，也就是缺血性卒中发率较高的区域[1,28,29]。

非钙化性ICAS病变主要位于颅内动脉的远端。ICAS病变的发生与低密度脂蛋白胆固醇和红细胞沉降率显著相关，尤其是与TIA或缺血性卒中患者的非钙化ICAS病变密切相关。因此，炎症是颅内动脉粥样硬化的一个重要因素。应用无创性技术对ICAS病变的斑块成分的深入研究，能够使我们更多的了解颅内动脉粥样硬化的病理生理特征。使用高分辨率磁共振成像对斑块内出血进行更进一步的研究，将能够更好的预测卒中的再发[39]。

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