The Significance of the Cerebral Collateral Capacity in Patients with Carotid Atheroma


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Objectives: to identify the echodensity, stenosis of carotid plaques and cerebral collateral capacity that were associated with various ipsilateral presentations (retinal, cerebrovascular, asymptomatic).

Design: cross-sectional study.

Materials: forty-four patients, with 44 plaques associated with various presentations, were studied.

Methods: the duplex images of the plaques were analysed echomorphologically in a computer by means of Grey Scale Median (GSM) [hypoechoic (low GSM), hyperechoic (high GSM)]. The percentage (%) reduction of the mean velocity in the middle cerebral artery (PRMCA) on transcranial Doppler, during clamping in carotid endarterectomy, was evaluated to distinguish the competent cerebral collateral supply (low PRMCA) from the non-competent one (high PRMCA).

Results: the retinal symptoms were associated with plaques of low median GSM (0), severe median stenosis (90%) and low median PRMCA (0.31) as contrasted with the cerebrovascular symptoms (17, 84%, 0.47, respectively) and asymptomatic status (32, 83%, 0.4, respectively) (p = 0.038 (GSM), p = 0.67 (stenosis), p = 0.15 (PRMCA)). The retinal and the cerebrovascular symptoms were distinct in terms of PRMCA (p = 0.045).

Conclusions: the retinal symptoms were produced by hypoechoic and possibly embologenic plaques, whereas the cerebrovascular ones possibly by the combination of carotid embolism and a non-competent cerebral collateral circulation. Asymptomatic status was associated with the absence of any relevant mechanism.

Key Words: Carotid plaque echodensity; Duplex; Degree of stenosis; Cerebral collateral circulation; TCD.

Introduction

An overview analysis of studies in patients with transient ischaemic attacks or minor ischaemic strokes associated with an occluded carotid artery revealed that the annual ipsilateral rate of subsequent stroke was 2.1%. This rate reached the level of 9.5% in patients with a compromised cerebral blood flow as measured by positron emission tomography, single-photon emission CT, transcranial Doppler, or stable xenon CT. In all studies of the above review the cerebral blood flow relied mostly on the collateral circulation since the internal carotid arteries were occluded. These findings demonstrated the significance of the impaired cerebral collateral circulation in the pathogenesis of stroke.

In addition, a longitudinal study of asymptomatic patients with carotid atheroma has demonstrated that hypoechoic and severely stenosed plaques were associated with a higher rate of incident stroke. This observation stressed the importance of the embolic and the haemodynamic impact of carotid atheroma on the pathogenesis of stroke.

The aim of this cross-sectional study was to determine the attributes of (1) the carotid plaques (in terms of ultrasonic characteristics and degree of stenosis) and (2) the cerebral collateral flow that were associated with the various neurovascular manifestations [retinal (amaurosis fugax), cerebrovascular (hemispheric transient ischaemic attack, stroke) and asymptomatic status]. It was hoped that the recognition of these attributes might elucidate the degree of the contribution of the embolic and haemodynamic mechanism in the pathogenesis of the above-mentioned clinical manifestations.

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Significance of Cerebral Collateral Circulation

Materials and Methods

Patients and design of the study

Forty-four carotid bifurcation plaques (stenosis range: 65%–99%) in patients scheduled for carotid endarterectomy (44 patients, 36 men and eight women, mean age: 70.2 years, range: 40–80), associated with retinal symptomatic conditions (amaurosis fugax (AF), n = 14/44, 32%, i.e. hemispheric transient ischaemic attack (HTIA), n = 11/44 and stroke n = 3/44) and asymptomatic status (9/44, 20%) on the ipsilateral retinal or hemispheric side, were studied. Each endarterectomised plaque and its ipsilateral retinal or cerebral side were treated as independent cases (units of the study) and defined the side of interest on each patient. The selection of the material was performed so that the symptomatic sides sustained the symptom 3–4 months prior to their recruitment. The exclusion of patients with symptoms sustained more than 4 months from recruitment was based on the fact that a plaque may change haemodynamically and echomorphologically over a period of time. In the present study the intention was to “incriminate” the plaque under investigation for the development of symptoms. In addition, the exclusion of patients with symptoms sustained more than 4 months from recruitment was in accordance with the exclusion criteria for carotid endarterectomy (operation within the 120 days from the symptom - North American Symptomatic Carotid Endarterectomy Trial Collaborators). The exclusion of patients with symptoms sustained less than 3 months from recruitment was based on the fact that in this case (less than 3 months from the symptom) the cerebral collateral circulation might be diminished (an event-related phenomenon), whereas on the third month it tends to approach the pre-event level.

Asymptomatic patients were considered to be those who had never experienced a symptom on the side of interest. In the final analysis, symptoms on the contralateral side and in vertebrobasilar system were outside the scope of the study. The assignment of symptoms was performed by a neurologist who was unaware of the duplex findings and was in accordance with the recommendations of the Committee for the Classification of Cerebrovascular Disease III. Recruitment of patients was performed during their routine preoperative duplex scanning in our vascular laboratory. The ultrasonic characteristics and degree of stenosis of the carotid plaques under study were evaluated on presentation.

Patients with cardioembolic conditions: atrial fibrillation, aortic or mitral valve pathologies, recent (less than 6 weeks from the neurovascular event) myocardial infarction, prosthetic cardiac valves and heart failure, were excluded by a cardiologist on clinical and electrocardiographic grounds. Lacunar symptomatology (pure motor hemiplegia, pure sensory stroke, motor-sensory stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome and absence of cortical dysfunction) and cerebral haemorrhage, diagnosed by a neurologist on clinical and brain CT grounds, were additional exclusion criteria. Lacunae and cerebral haemorrhages are not attributable to carotid atheroma.

These conditions (presence of a carotid plaque, exclusion of cardioembolism, lacunar symptomatology and cerebral haemorrhage) ensured the implication of carotid atheroma as the most likely cause in the pathogenesis of the neurovascular symptomatology.

The flow in the middle cerebral artery (MCA) on the side of interest was monitored with transcranial Doppler (TCD) during the carotid endarterectomy and the percentage (%) reduction of the mean velocity in the MCA (PRMCA) during clamping was noted to distinguish the competent cerebral collateral capacity (low PRMCA) from the non-competent one (high PRMCA). The carotid endarterectomies were performed under general anaesthesia. In all of them an arterial radial line was inserted for the continuous monitoring of the systemic blood pressure. General anaesthesia was induced with intravenous infusion of Fentanyl. Neuromuscular blockade was maintained with intravenous infusion of Atracurium Besylate. During surgery, the endotracheal anaesthesia was maintained with Enflurane in nitrous oxide/oxygen. Mechanical ventilation was adjusted to achieve mild vasodilatation. All the above ensured the standardisation of the cerebral blood flow measurements.

Ultrasonographic evaluation: the grading of internal carotid artery stenosis

The severity of carotid stenosis was assessed on duplex scanning upon recruitment, using the ATL HDI 3000 scanner (Advanced Technology Laboratories, Bothell, Washington, U.S.A.). This entailed a haemodynamic evaluation of the index stenotic vessel based on standard criteria. This evaluation was performed by one experienced operator (TJT) who was unaware of the clinical profile of the patients at the time of the scanning and was fully familiar with the protocol of the grading of carotid stenosis.

Ultrasonic characteristics of carotid plaques

Following duplex scanning, capturing and digitisation in a computer of the plaque images, their ultrasonic
characteristics were evaluated by means of the Grey Scale Median (GSM). Hypoechoic plaques were associated with low values of GSM, whereas hyperechoic ones with high values of GSM. The above cited echocanalysis was performed on presentation by the same experienced operator (TJT) who also evaluated the degree of stenosis.

Cerebral collateral flow on transcranial Doppler

TCD settings
The flow in the middle cerebral artery (MCA) ipsilateral to the plaque under study was monitored with transcranial Doppler (TCD) in each patient during the carotid endarterectomy by one experienced operator (TJT) at a depth of 50–60 mm via the transtemporal window with a 2 MHz transducer. The equipment used was a Translink 9900, Rimed™. The settings of the device were pre-selected and kept unaltered during the monitoring of all cases for standardisation purposes.

Cerebral collateral flow detected on TCD
During the intraoperative monitoring the percentage (%) reduction of the mean velocity in the MCA (PRMCA) was recorded per patient 2 min after the clamping of the internal carotid artery distal to the diseased segment to distinguish the competent cerebral collateral flow (low PRMCA) from the non-competent one (high PRMCA). The timing of 2 min was selected to allow the recruitment of collateral circulation to become manifested. This method evaluated all the available collaterals.

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PRMCA = \frac{\text{MVMCA}_{\text{preclamp}} - \text{MVMCA}_{\text{postclamp}}}{\text{MVMCA}_{\text{preclamp}}} \times 100,
\]

where PRMCA is the percentage (%) reduction of the mean velocity of the middle cerebral artery, MVMCA_preclamp is the mean velocity of the middle cerebral artery prior to clamping, MVMCA_postclamp is the mean velocity of the middle cerebral artery subsequent to clamping.

Validation of the PRMCA
The mean stump pressure in mmHg (MSP) of the internal carotid artery (ICA) upon clamping of the common and external carotid artery, just before the ICA clamping, was evaluated in 15 cases. This was performed by means of a manometer connected through a saline-filled tubing to a 21-gauge needle which was inserted in the common carotid artery distal to its clamp and proximal to the carotid bifurcation and the significantly diseased segment. The gauge zero reference was established at the head level of the patient and the measurement has taken place 2 min after clamping. At the same time the mean radial artery blood pressure in mmHg (MBP) was recorded by means of a gauge plastic cannula and the ratio of

\[
\frac{\text{MSP}}{\text{MBP}}
\]

was calculated. The rationale behind the use of this ratio was to offset the effect of the systemic blood pressure on the stump pressure. This method evaluated all the collaterals apart from the ipsilateral ophthalmic artery.

A linear inverse relationship was found between the

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\text{PRMCA} \quad \text{and} \quad \frac{\text{MSP}}{\text{MBP}}
\]

\((n = 15 \text{ cases, Pearson’s correlation, } p = 0.005, r = -0.68)\) (Fig. 1).

The fact that the ophthalmic artery was not included into the assessment of the cerebral collateral circulation by means of the stump pressure
Table 1. Characteristics of the various clinical groups in terms of GSM, ipsilateral stenosis and PRMCA.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>n</th>
<th>GSM median (IQR)</th>
<th>Ipsilateral stenosis (%) median (IQR)</th>
<th>PRMCA median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal</td>
<td>21</td>
<td>0 (15)</td>
<td>90 (10)</td>
<td>0.31 (0.29)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>14</td>
<td>17 (19.5)</td>
<td>84 (13.7)</td>
<td>0.47 (0.5)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>9</td>
<td>32 (39)</td>
<td>83 (10)</td>
<td>0.4 (0.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(p = 0.038^*)</td>
<td>(p = 0.67^*)</td>
</tr>
</tbody>
</table>

Retinal symptom: amaurosis fugax; cerebrovascular symptom: transient ischaemic attack and stroke.

GSM: grey scale median; PRMCA: percentage (%) reduction of the mean velocity in the middle cerebral artery at clamping in carotid endarterectomies.
IQR: interquartile range.

\(*\) Kruskal–Wallis test.

Results

The median values and the interquartile range (in parenthesis) for ipsilateral stenosis, contralateral stenosis, GSM, PRMCA and blood pressure at clamping in our material were: 85% (10), 55% (62.5), 0.4 (0.2) and 85 mmHg (10), respectively.

Table 1 summarises the characteristics of the three clinical groups (retinal, cerebrovascular and asymptomatic) in terms of GSM, ipsilateral stenosis of the plaques and PRMCA. Pearson’s correlation was performed between the PRMCA and (1) the ipsilateral and (2) the contralateral stenosis to establish their relation. The accepted level of statistical significance was 5%.

**Statistical analysis**

The statistical package SPSS for Windows (release 9) was used for data analysis. The Kruskal–Wallis test and the Mann–Whitney \(U\)-test were performed to distinguish the three clinical groups: retinal, cerebrovascular, asymptomatic, in terms of GSM, ipsilateral stenosis of the plaques and PRMCA. Pearson’s correlation was performed between the PRMCA and (1) the ipsilateral and (2) the contralateral stenosis to establish their relation. The accepted level of statistical significance was 5%.

**Comparison of the distributions of GSM and stenosis**

Corresponding to the clinical groups: retinal, cerebrovascular and asymptomatic, demonstrated that the GSM was statistically different between these groups (Kruskal–Wallis test, chi square = 6.54, df = 2, \(p = 0.038\)) but stenosis was not (Kruskal–Wallis test, chi square = 0.77, df = 2, \(p = 0.67\)) (Table 1).

The GSM was different between: (1) the retinal and the cerebrovascular group (Mann–Whitney \(U\)-test: 90, \(p = 0.045\)), (2) the retinal and the asymptomatic group (Mann–Whitney \(U\)-test: 50, \(p = 0.03\)) but not between...
A previous study demonstrated an inverse correlation between the plaque GSM and the number of emboli detected on transcranial Doppler in the ipsilateral (to the plaque) middle cerebral artery. Based on this finding, one might expect that the plaques associated with amaurosis fugax (hypoechoic in the present study, Table 1) might be more embolic than the plaques associated with transient ischemic attacks and stroke (plaques of intermediate echodensity in the present study, Table 1). The previously mentioned study, though, failed to discriminate the plaques associated with amaurosis fugax and transient ischemic attacks or stroke based on the embolic activity. It also suggested that both of the above mentioned clinical presentations (amaurosis fugax and transient ischemic attacks or stroke) might be embolic in origin but other factors might discriminate them. One of those might be the impairment of cerebral collateral flow, as the present study demonstrated.

In addition, the present study demonstrated that the GSM constitutes the discriminator between the retinal symptomatology and the asymptomatic status. Taking into consideration the inverse correlation between the plaque GSM and the embolic count detected on TCD in the ipsilateral middle cerebral artery as has been previously suggested, it might ensue that amaurosis fugax (which is associated with hypoechoic plaques, Table 1) is an embolic manifestation and the asymptomatic status (which is associated with hyperechoic plaques, Table 1) is characterised by an absence of the embolic activity.

The current study demonstrated that the GSM and the PRMCA were the discriminators between the retinal and cerebrovascular symptomatology.

**Discussion**

The current study demonstrated that the GSM and the PRMCA were the discriminators between the retinal and cerebrovascular symptomatology.
As to the impact of the severity of carotid stenosis on the status of cerebral collaterals (open or not), Morgenstern et al. demonstrated a direct relationship between the degree of carotid stenosis and the recruitment of the cerebral collaterals, suggesting that the severe carotid stenosis opens the collaterals through the low cerebral flow state it produces. However, in another study, Gibbs et al. demonstrated an absence of association between those variables, suggesting that the cerebral collateral circulation is a distinct entity, functioning independently of carotid stenosis.

The present study demonstrated a moderate linear relationship between the degree of the ipsilateral carotid stenosis and the cerebral collateral supply ($p = 0.001, r = -0.47$), suggesting that the cerebral collateral status depends not only on the severity of carotid stenosis but also on other factors (i.e. collateral artery hypoplasia). Indeed, Riggs and Rupp demonstrated that the classic circle of Willis can be found only in 20% of cases.

Previous research has shown that the degree of the contralateral carotid stenosis was unrelated to the velocity of the middle cerebral artery during the cross-clamp in carotid endarterectomies. This is in agreement with the present study (contralateral stenosis-PRMCA relationship, $p = 0.16, r = 0.42$). The reason might be that in the present study the median values for contralateral stenosis was less than those of the ipsilateral stenosis (55% and 85%, respectively) and therefore the contralateral stenosis was inadequate to influence the collateral circulation.

The present study examined the effect of the carotid plaque characteristics (echomorphology and degree of stenosis) and the cerebral collateral flow on the development of cerebrovascular symptomatology and formulated a hypothetical mechanism for the interpretation of the results. It might be interesting to apply this methodology to prospective natural history studies of asymptomatic patients with carotid plaques having as an end point the development of stroke attributable to carotid atheroma. For the evaluation of the cerebral collateral capacity, the percentage (%) reduction of the mean velocity of the middle cerebral artery on transcranial Doppler during the clamping phase of carotid endarterectomy could be replaced with the CO$_2$ reactivity test on transcranial Doppler or flow studies on positron emission tomography. It is hoped that studies of this nature might identify groups of patients with a high and a low risk of stroke. The end result will be the better refinement of the criteria for carotid endarterectomy, which will offer benefits both to the vascular specialists and to the patients.


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