Is There a Side Predilection for Cerebrovascular Disease?

Sergio A. Rodríguez Hernández, Abraham A. Kroon, Martin P.J. van Boxtel, Werner H. Mess, Jan Lodder, Jelle Jolles, Peter W. de Leeuw

Abstract—In studies on carotid artery intima-media thickness and stroke, researchers implicitly assume that cerebrovascular abnormalities show a symmetrical distribution. To evaluate whether there is a difference in intima-media thickness between the 2 carotids, we compared left and right common carotid artery intima-media thickness as measured by B-mode ultrasonography in a group of 102 untreated hypertensive patients. This yielded a significant difference between both sides (left, 0.75±0.11 mm; right, 0.71±0.11 mm; P<0.001). This was associated with a higher cross-sectional area of the intima-media complex and a higher flow velocity at the left side. Arterial diameters, however, were not different. We also assessed whether there is a side preference with respect to cerebrovascular accidents. To this end, we explored our population-based Stroke Registry of 1843 subjects and indeed found a significantly higher incidence of nonlacunar cerebrovascular stroke at the left side, whereas lacunar infarcts were symmetrically distributed. Our findings suggest a predilection for cerebrovascular disease at the left side, which may be related to greater hemodynamic stress and intimal damage in the left carotid artery. (Hypertension. 2003;42:56-60.)

Key Words: carotid arteries ▪ atherosclerosis ▪ cerebral arteries ▪ stroke

An increase in carotid artery intima-media thickness (IMT) not only coincides with other risk factors such as hypercholesterolemia, hypertension, and diabetes mellitus but also correlates independently with clinical end points such as myocardial infarction and peripheral atherosclerosis.1–7 Recent data have confirmed the relationship between IMT and stroke, especially of the nonlacunar subtype.8 Thus, an increase in IMT can be considered as a marker of cardiovascular risk. Usually, one averages measurements from the left and right common carotid artery for the determination of IMT.9 However, it is not known whether this is justified, as differences may exist in IMT between both arteries. Indeed, during routine assessment, we frequently noted a left-right difference in IMT. Other studies also suggest differences between left and right IMT,5,9 but it is not clear whether there is a systematic increase in favor of one side. This prompted us to systematically compare left and right IMT in a group of hypertensive patients who had been referred to our hospital for evaluation of their elevated blood pressure. Although an increased IMT of the internal carotid artery correlates well with the risk of both myocardial infarction and stroke, a higher IMT of the common carotid artery (CCA) is a good predictor of stroke incidence as well as prevalent stroke.10,11 Moreover, Cupini and coworkers8 demonstrated that CCA IMT values are higher in patients with nonlacunar stroke than in those with lacunar stroke, thereby lending further support to the notion that an increased IMT is a marker of atherosclerotic (ie, nonlacunar) cerebrovascular complications rather than of microvascular (lacunar) lesions. For these reasons and because they are easier to perform and more reproducible, we restricted our measurements in the current study to the CCA.

Because an increased IMT may develop in response to high shear forces,12 any difference between the left and right carotid artery IMT may reflect a differential effect of hemodynamic stress. Taking this a bit further, one could hypothesize that a left-right difference in the effects of hypertension on the cerebral vasculature may lead to an asymmetrical distribution of strokes as well. To examine this possibility, we also performed a retrospective analysis of the Maastricht Stroke Registry, which contains data on all stroke patients admitted to our hospital since 1988. This was done to assess whether there is a side preference in the occurrence of nonlacunar stroke in patients known to have been hypertensive before their stroke.

Methods

Study 1: IMT Measurements

Patients were selected from the hypertension outpatient clinic of the Department of Internal Medicine of the University Hospital of Maastricht. As part of the local protocol, IMT measurements were performed in all patients. For the current analysis, we selected 102...
untreated hypertensive patients in whom no known cause for their hypertension could be detected, who did not have any symptoms suggestive of cerebrovascular disease or prior stroke and who otherwise were also free of apparent cardiovascular complications. This specific population was chosen because hypertension is a major determinant of IMT and stroke\textsuperscript{13,14} and because the absence of cardiovascular complications would render secondary changes of IMT less likely. Blood pressure was measured before each IMT measurement after 5 minutes of rest in sitting position. Measurements of the IMT of the posterior wall as well as of lumen diameters of the left and right CCA were obtained 1 cm proximal to the bulb from an anterolateral and posterolateral view (SONOS 5500; Agilent-Philips; linear array transducer, 3 to 11 MHz). The left and right arteries were investigated in random order.

End-diastolic B-mode images of the IMT were analyzed off-line with an automated edge-tracking method (M'ath, version 2.0.1).\textsuperscript{15,16} The average IMT was measured over a length of 10 mm, and the mean of both the anterolateral and posterolateral view at each side was calculated and used for further analyses. In addition, flow velocity indexes, that is, mean velocity (cm/s), pulsatility index (PI), and resistance index (RI), were derived from the Doppler spectrum. PI and RI were calculated as follows: \( \text{PI} = \frac{(S-D)/MN} {S} \) and \( \text{RI} = \frac{(S-D)/S} {S} \), in which \( S \) and \( D \) indicate systolic and diastolic velocity (cm/s), respectively, and MN mean velocity (cm/s). The cross-sectional area of IMT (CSA–IMT) was calculated according to the formula \( \text{CSA–IMT} = 3.14 \times \text{IMT} \times (\text{IMT} + D) \), in which \( D \) is lumen diameter (mm).\textsuperscript{9}

Measurements were performed in random order by 4 experienced operators, none of whom was aware of the purpose of the study. In addition, they were unaware of the left/right randomization of the images. Although patients were informed about the purpose of the IMT measurements, they did not know that this comprised evaluation of a left-right difference in IMT.

**Study 2: Stroke Registry**

The Maastricht Stroke Registry is a large database containing the clinical, functional, and outcome data of all patients that have been admitted to our hospital with a stroke.\textsuperscript{13} The Registry started in 1988 and at the time of this study had data on 1843 patients. We explored the Registry and compared the prevalence of first-ever territorial cerebral infarcts and cardio-embolic stroke in both hemispheres. In addition, we looked at side differences for small deep lacunar infarcts, because this type of infarct would not be expected to occur more frequently on one side. Definitions to classify stroke subtypes have been described before\textsuperscript{13} and are based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.\textsuperscript{17} Analyses were performed for the whole group of patients with first-ever stroke as well as for the subgroup of patients who were known to be hypertensive.

The study was approved by the Medical Ethics Committee of Maastricht University Hospital and performed according to the institutional guidelines. All subjects or, if necessary, the next of kin, gave written informed consent to use patient data for this type of scientific evaluation.

**Statistical Analysis**

Differences in IMT between the left and right CCA were determined by means of \( t \) tests for paired samples. The concordance between left and right IMT was analyzed by linear regression. Bland-Altman analysis was used to assess systematic differences between both sides.\textsuperscript{18} Proportional differences between stroke subgroups were determined by means of \( \chi^2 \) tests. Data are shown as mean±SD, unless indicated otherwise. A probability value \(<0.05\) was considered statistically significant.

**Results**

**Study 1**

The mean age of the 102 hypertensive subjects was 56±11 years, 60% were men, and body mass index averaged 29±6 kg/m\(^2\). Office systolic and diastolic blood pressures were 165±7 and 94±8 mm Hg, respectively. A close relationship was found between the IMT of both sides (regression equation \( y=0.5755x+0.2844\); \( R^2=0.4528; P<0.001\); Figure 1, left panel). Table 1 shows the IMT of the left and right carotid artery: 0.75±0.11 mm and 0.71±0.11 mm, respectively (\( P<0.001\)). The mean left-right difference was 0.03±0.09 mm, with no systematic deviation at any level of average IMT (Figure 1, right panel). Although both left and right IMT tended to increase with age and with the level of systolic blood pressure, none of the relationships reached statistical significance in simple regression analysis. However, when patients were divided in quartiles by age, the left-right difference appeared to increase with age in subjects younger than 60 years; thereafter, the difference became again smaller (Figure 2). There was no significant difference in lumen diameter between both carotids (Table 1). Differences in IMT between the left and right side remained significant after correction for the luminal diameter. As shown in Table 1, the cross-sectional area of the intima-media complex was greater at the left side as well. Mean blood flow velocities in the left and right carotid artery at the side where the IMT measurements were done were 41.1±9.4 cm/s versus 39.3±9.8 cm/s, respectively (\( P=0.004\)). No differ-

**TABLE 1. Echo Doppler Characteristics of Left and Right Common Carotid Artery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Left</th>
<th>Right</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT, mm</td>
<td>0.75±0.11</td>
<td>0.71±0.11</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Lumen, mm</td>
<td>7.5±1.0</td>
<td>7.6±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>PI</td>
<td>1.18±0.39</td>
<td>1.19±0.40</td>
<td>NS</td>
</tr>
<tr>
<td>RI</td>
<td>0.64±0.09</td>
<td>0.64±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Mean velocity, cm/s</td>
<td>41.1±9.4</td>
<td>39.3±9.8</td>
<td>0.004*</td>
</tr>
<tr>
<td>CSA-IMT, mm(^2)</td>
<td>10.6±3.0</td>
<td>9.9±2.7</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

IMT indicates intima media thickness; PI, pulsatility index; RI, resistance index; CSA-IMT, cross sectional area of IMT; and NS, not significantly different.

* \( t \) test for paired samples.
The preferential occurrence of cerebrovascular pathology at the left side could be due to hemodynamic effects related to the specific anatomy of the carotid vessels. Whereas the right common carotid artery arises from the brachiocephalic trunk (generally at a right angle to the flow of the innominate artery), the left one stems directly from the aortic arch and runs more in an even line with the ascending aorta. As a corollary, energy transfer from systolic emptying forces may be greater in the left carotid than in the right one, where part analysis revealed that the difference in IMT between both carotids tends to increase up to an age of about 60 years and to decline again thereafter. The latter phenomenon may be due to selection bias, because we deliberately excluded in our first study patients with overt cerebrovascular disease, and it may be that those with the highest IMT difference already had symptoms. Although the clinical significance of the asymmetry in IMT is not yet apparent, the phenomenon should be taken into account when evaluating the association between the results of IMT measurements and the occurrence of cardiovascular complications. Presently, it is common practice to use the average of the left and right carotid IMT in such associations, but the relationships may run a steeper course when only the left one is used for analysis.

Whether an increased IMT in hypertensive patients is indicative of an endothelial abnormality or merely reflects medial hypertrophy remains a matter of debate.21,22 Certainly, hypertension is a major determinant of CCA IMT, as demonstrated in various studies.20,22,23 Since medial hypertrophy typically is an adaptive response to an elevated pressure, a larger IMT at a certain segment of the vasculature in a hypertensive patient would point toward a higher transmural pressure gradient at that site if indeed IMT predominantly represents medial structures. In that case, one would also expect a greater number of lacunar infarcts in the same vascular territory because these lesions are related to microvascular disease for which hypertension is a risk factor. This, however, is not borne out by our findings, which showed a symmetrical distribution of lacunar infarcts. Therefore, our data suggest that the left-right difference in IMT should probably be interpreted in terms of intimal changes rather than medial hypertrophy. Nevertheless, whether the increased IMT in the left carotid artery is due to greater intimal hyperplasia or to more extensive medial hypertrophy, both conditions could be viewed as a sequel of increased hemodynamic stress at that side. If these differential effects of hemodynamic forces were to be a general phenomenon, one could then expect a side preference for the occurrence of nonlacunar stroke as well. This is, indeed, supported by our observation of an anatomic predilection of nonlacunar strokes in the left hemisphere. Nonlacunar strokes can be divided into atherosclerotic and cardio-embolic subtypes. Generally, lacunar strokes are caused by local obstruction and not by embolism, whereas most cardio-embolic strokes occur in the absence of carotid disease. Therefore, the similarity between cardioembolic and atherosclerotic strokes with regard to predilection to the left hemisphere in our study suggests again a role for hemodynamic factors. These may cause more cardiac emboli to enter the left carotid system and more often affect the left carotid artery structure.

The current study shows that in untreated essential hypertensive patients, a difference exists between IMT of the left and right common carotid artery, with higher values on the left side. Although the difference is small, it is statistically significant and of the same magnitude as that observed during aggressive lipid-lowering therapy.19 Also, cross-sectional area (as a marker of vascular mass) of the intima-media complex was larger on the left than on the right side. In most published studies, IMT values are seldom reported for the left and right carotid separately. However, in reports in which data are actually given for both sides, the IMT of the left CCA tends, on average, to be larger than on the right.9,20 Further differences between left and right arteries could be found with respect to PI and RI (Table 1). Results were similar for all 4 observers.

### Study 2

The median age of all patients (n=1843) in this database was 72 years (range, 25 to 99), 51% of patients were men, and 50% had known hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥90 mm Hg).

Lacunar infarcts appeared to be symmetrically distributed (Table 2). In contrast, for nonlacunar strokes, we found a predilection for side: both atherosclerotic and cardio-embolic (Table 2). In most cases, a difference exists between IMT of the left and right carotid artery, the left one stems directly from the aortic arch and runs more in an even line with the ascending aorta. As a corollary, energy transfer from systolic emptying forces may be greater in the left carotid than in the right one, where part

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**Figure 2.** Mean difference and 95% confidence intervals for difference between left and right IMT by quartiles of age. Q1–Q4 indicates quartile 1 to 4; *P*<0.01 compared with quartile 1.

**TABLE 2.** Distribution of Stroke Subtypes in the Maastricht Stroke Registry

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Number</th>
<th>Left (%)</th>
<th>Right (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar</td>
<td>721</td>
<td>357 (49.9)</td>
<td>364 (50.1)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>319</td>
<td>188 (58.9)*</td>
<td>131 (41.1)</td>
</tr>
<tr>
<td>Atherosclerotic</td>
<td>803</td>
<td>463 (57.7)*</td>
<td>340 (42.3)</td>
</tr>
<tr>
<td>All strokes</td>
<td>1843</td>
<td>1008 (54.7)</td>
<td>835 (45.3)</td>
</tr>
</tbody>
</table>

*P*<0.001 for left/right difference.

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Discussion

The preferential occurrence of cerebrovascular pathology at the left side could be due to hemodynamic effects related to the specific anatomy of the carotid vessels. Whereas the right common carotid artery arises from the brachiocephalic trunk (generally at a right angle to the flow of the innominate artery), the left one stems directly from the aortic arch and runs more in an even line with the ascending aorta. As a corollary, energy transfer from systolic emptying forces may be greater in the left carotid than in the right one, where part

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of the flow vector energy will be reduced by the innominate artery. This is further supported by our observation that mean flow velocity was significantly higher in the left than in the right carotid artery. Consequently, high or oscillating shear forces, which are strong determinants of adaptive intimal thickening, will be different in both arteries. Whereas intimal thickening at sites of high shear stress does not in itself proceed to atherosclerosis, marked oscillations in the direction of wall shear may enhance atherogenesis at more distally located sites. From a different perspective, however, we also need to consider the possibility that blood flow through the aortic arch could play a role, as ulcerated plaques at this side may cause embolic stroke.

To the best of our knowledge, no data have been published with regard to side predilection of cerebrovascular disease. Taken together, however, our 2 studies support the notion that such a predilection exists. Whereas study 1 suggests that the higher IMT in the left carotid reflects greater hemodynamic stress in the left cerebrovascular system, the results from study 2 suggest (by extrapolation) that the higher frequency of left-sided stroke may be the consequence of this greater sensibility of the left cerebrovascular system to hypertensive stress.

Limitations

Obviously, several limitations apply to our 2 studies. First, the increased IMT at the left side probably reflects a higher hemodynamic stress in large conduit arteries but not necessarily in small resistance arteries. Our observation that lacunar infarcts do not show a side preference provides indirect support for the hypothesis that greater hemodynamic stress manifests itself primarily at the level of the greater arteries. Second, our IMT studies have focused only on the CCA. Although several studies have shown that a thicker intima-media complex of the internal carotid artery is a valid marker of atherosclerotic complications, a higher IMT of the CCA remains a good predictor of stroke incidence, and patients with brain infarction have a greater IMT of the far wall of both common carotid arteries than control subjects. For these reasons and because they are easier to perform and more reproducible, we restricted our measurements in the current study to the CCA. Third, one could argue that the differences in the site of strokes may have resulted from admission bias in this particular cohort of patients: left hemispheric infarcts may be more symptomatic and rated by physicians as more severe. However, the initial stroke severity in our Registry was similar between left and right hemispheric infarcts, which make such a bias less likely. Finally, we compared stroke rates in a different population than the one in which we obtained IMT measurements, and, contrary to study 1, only half of the patients in study 2 had hypertension. Although this may confound the potential influence of hypertension on stroke in the study 2 population, our data are still in accordance with the assumption that the cerebral vasculature is more susceptible to damage at the left side. In addition, we want to emphasize that the higher IMT in the left CCA and the more frequent occurrence of stroke in the left hemisphere do not necessarily reflect a common pathophysiological mechanism or even a cause-and-effect relationship. Only prospective follow-up studies would be able to assess whether a higher IMT at one side predicts future stroke in the same vascular territory. Moreover, despite the fact that some investigators have found significant associations between CCA IMT and atherosclerosis elsewhere in the carotid system, so far no evidence is available that changes in IMT are causally related to plaque formation and stroke. Nevertheless, the current results allow us to conclude that the left cerebrovascular system probably is affected adversely more from the hypertensive process than the right one.

Perspectives

We have shown an increased susceptibility of the left cerebral vessels in hypertensive patients. Further prospective studies investigating the relationship of IMT and stroke in the same cohort are necessary to evaluate whether an increased IMT at the left side predisposes to nonlacunar infarcts at the same side. Furthermore, our findings may set the stage for an early, differential preventive strategy for left or right carotid artery disease. This may be highly relevant, as the left hemisphere is dominant in most people.

Acknowledgments

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References


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