Adaptive common carotid arteries remodeling after unilateral internal carotid artery occlusion in adult patients

Nathalie Kubis\textsuperscript{a,b,*}, Arlette Checoury\textsuperscript{a}, Alain Tedgui\textsuperscript{b}, Bernard I. Lévy\textsuperscript{a,b}

\textsuperscript{a}Department of Clinical Neurophysiology Laboratory, Hôpital Lariboisière, 2 rue Ambroise Paré, 75010 Paris, France
\textsuperscript{b}INSERM Unit 541, Hôpital Lariboisière, 2 rue Ambroise Paré, 75010 Paris, France

Received 6 September 2000; accepted 11 January 2001

Abstract

Objective: This study was undertaken in human adults to examine modifications in common carotid internal diameter (ID), intima-media thickness (IMT), cross-sectional area (CSA) and wall shear stress (WSS) occurring both on the ipsilateral side of an internal carotid artery (ICA) occlusion and on the non-occluded contralateral side. Methods: Seventeen patients with unilateral ICA occlusion had repeated echo-Doppler examinations during 1 year and were compared to 12 volunteers with control non-occluded common carotid arteries (CCA). Results: The cause of ICA occlusion was atherosclerosis in nine patients, dissection in five, and undetermined in three. The results showed a significant reduction in ID on the occluded side (5.15\(\pm\)0.30 mm) compared with the non-occluded side (5.96\(\pm\)0.20 mm, \(P<0.05\)) and with control arteries (5.55\(\pm\)0.10, \(P<0.05\)). A significant reduction in blood flow was observed on the occluded side (404\(\pm\)58 ml/min) compared with the non-occluded side (703\(\pm\)51 ml/min, \(P<0.0001\)) and with controls (567\(\pm\)27 ml/min, \(P<0.0001\)). Wall cross-sectional area was found to be positively correlated to blood flow (\(r=0.35\), \(P<0.01\)), without any significant difference in mean CSA between both sides. Interestingly, wall shear stress values were identical on both sides whatever the cause of ICA occlusion, and did not differ from those in controls. Conclusions: Our results suggest that in humans, the internal diameter of the common carotid artery decreases in response to chronic decrease in blood flow, in order to maintain a constant wall shear stress even in pathological arteries. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Arteries; Hemodynamics; Regional blood flow; Remodeling; Ultrasound

1. Introduction

Chronic changes in blood flow through large arteries have been shown to produce adjustments of artery diameter. Flow restriction leads to arterial reduction [1], while increased blood flow leads to arterial enlargement [2]. Most of the studies dealing with the adaptive response of arteries to chronic changes in blood flow have been performed in animals, and rarely in humans. It has been demonstrated in experimental animals that these vascular adaptive responses to changes in blood flow tend to maintain a constant wall shear stress, the endothelium being the mechanically sensitive, signal transduction inter-

*Corresponding author. Tel.: +33-1-4463-1860; fax: +33-1-4281-3128.
E-mail address: levy@infobiogen.fr (N. Kubis).

Time for primary review 29 days.
documented in our Laboratory by using a combination of echo-Doppler scanning and continuous-wave Doppler scanning in 17 consecutive patients. The diagnosis was made either by echography-Doppler examination alone or in combination with angiography or magnetic resonance imaging angiography. The date of the occlusion was estimated to be related to the occurrence of a stroke [4]. All patients gave informed consent. None had significant contralateral stenosis. We did not exclude patients with plaques, defined as a prominent and clearly distinct elevation of the inner vessel wall having at least 1.5 mm in thickness but occupying less than 20% of the surface area. The following data were collected: body weight, height, body mass index, presence of diabetes mellitus defined as the current use of oral blood glucose lowering drugs or insulin or two fasting glycemas found over 7.6 mM, presence of hypertension defined as the current use of antihypertensive drugs or two separate measurements at rest of a systolic blood pressure of 160 mmHg or greater and of a diastolic blood pressure of 100 mmHg or greater, presence of hypercholesterolemia defined as the current use of hypocholesterolemic drugs or cholesterolemia over 6.5 mM at two different samplings and smoking habits measured as pack-years (average number of cigarettes smoked per day times the number of years the patient smoked). The etiology of the ICA occlusion, and of a subsequent stroke, was defined according to the TOAST classification [5], allowing us to separate patients into two groups: the patients with an atherosclerotic etiology and those with a non-atherosclerotic etiology. Blood pressure was systematically measured at the time of examination, and patients were questioned about any cardiological or neurological events that could have occurred since the last examination.

2.2. Echo-Doppler examination

An Acuson Computed Sonography 128XP/10c equipped with a 2–7-MHz multifrequency linear probe was used for the ultrasonic examination. The electrocardiographic signal was simultaneously recorded to synchronize the image capture to the R wave, to measure end-diastolic diameters, and to minimize variability of measurements during the cardiac cycle.

Measurements were performed on both CCA. The following data were measured: internal diameter (ID), intima-media thickness (IMT) and mean blood velocity (Vm). Wall cross-sectional area (CSA), blood flow (BF) and wall shear stress (WSS) were calculated as follows: CSA = π×IMT×(IMT+ID); BF = Vm×(π×ID/2)^2; WSS = 4(η)Vm/(ID/2), η being the blood viscosity estimated at 0.035 Poise.

Details of the procedure have been described elsewhere [6]. Briefly, on a longitudinal two-dimensional ultrasound image of the CCA, the near and far wall were displayed as two bright lines separated by a hypoechogetic space. The inner lumen diameter or internal diameter was assessed as the distance between the intima–lumen interface at the near wall and the lumen–intima interface at the far wall. IMT was measured, avoiding plaques, at the far wall of the CCA, 1–2 cm proximal to the bulb, as the distance between the leading edge of the first bright line on the far wall (lumen–intima interface) and the leading edge of the second bright line (media-adventitia interface). Moreover, IMT was analysed secondarily with an automated computerized analyzing system (Io Data Processing, Paris, France): a short sequence of real-time images of a longitudinal view of the part of the CCA proximal to the bulb was recorded on a videotape, and repeated frozen longitudinal images were captured at the far wall and averaged [7,8]. All systolic and mean blood velocities were recorded as the mean of the last three cardiac cycles, the angle between the ultrasound beam and the longitudinal vessel axis kept between 55 and 59°.

Clinical examination and echo-Doppler measurements were repeated three to four times by the same examiner, except for two patients who were lost of follow-up, in order to control that measurements were all realized in patients in a steady state. Patients were compared to controls defined as subjects with no vascular risk factors, no treatment and a normal echo-Doppler examination.

2.3. Statistical analysis

Numerical data were expressed as mean±S.E.M.. Unpaired two-tail t-test was used to compare body mass indexes and the ratios of WSS between patients and control subjects. Two-way ANOVA were constructed with data of ID, IMT, CSA, BF and WSS to evaluate the effects of CCA occlusion. Linear regression analyses were used to evaluate the relationship between measured blood flow and ID, IMT, CSA or WSS values. A value of P<0.05 was considered as significant.

3. Results

3.1. Clinical results

Seventeen patients were included in our study (14 men and 3 women). The age ranged between 40 and 70 years (mean 54 years, median 52.5 years). Mean body mass index was of 40±1 kg/m^2. Cardiovascular risk factors were diabetes mellitus for four patients, hypertension for six, hypercholesterolemia for seven and smoking habits for 13. The right side was occluded in 11 patients. According to the TOAST classification, nine patients had atherosclerotic disease and five were identified as having carotid artery dissection. Among these five latter patients, two suffered from fibromuscular dysplasia diagnosed on angiography. ICA occlusion remained of undetermined etiology in three patients.
In four patients, the time of ICA occlusion could not be determined because it had remained asymptomatic and was discovered after a systematic investigation. The delay between stroke and admission in our study for the 13 other patients ranged between half a month and 93 months (mean 35 months, median 25 months).

All patients except two had an antiplatelet therapy regimen which was administered after the stroke or after the discovery of the ICA occlusion. Of these two exceptions, one patient was under anticoagulant therapy because of concomitant saphenous phlebitis and the other had no treatment until healing of acute gastric ulceritis. Five patients were receiving angiotensin converting enzyme inhibitor antihypertensive therapy at the time of the discovery of the ICA occlusion and three were receiving statins.

There was no cardiac event for any of the 17 patients, but one had a recurrence of stroke after 1 year.

Twenty-four control common carotid arteries were concomitantly examined in 12 subjects (7 men and 5 women). The range of age spanned from 39 to 56 years (mean 51±1 years, median 52 years). Mean body mass index was of 38±1 kg/m².

Body mass index was not statistically different in patients compared with control subjects (40±1 vs. 38±1, respectively).

3.2. Echography-Doppler results

The permeability of the origins of both CCA was verified by echography and Doppler examination. We did not observe a hemodynamic stenosis in any patient which could have interfered with more distal measurements.

We observed a significant reduction in common carotid artery ID on the occluded internal carotid artery side (5.15±0.30 mm) compared with the contralateral side (5.96±0.20 mm) and ID from subjects without any occlusion (5.55±0.10 mm) (P<0.05). On the same way, we found a significantly lower blood flow on the occluded side (404±58 ml/min) compared with the contralateral side (703±51 ml/min) and with control carotids (567±27 ml/min) (P<0.0001). However, there was no statistical significant difference in mean wall shear stress between the occluded side (18.3±1.7 dyn/cm²), the non-occluded side (20.7±1.7 dyn/cm²) and in control carotids (19.6±0.7 dyn/cm²) (Table 1). As blood viscosity may vary according risk factors and treatment, we verified that the ratio of WSS obtained on the occluded side and WSS on the contralateral side in each patient was not significantly different from the ratio of WSS obtained on the right side and WSS on the left side in control subjects. Indeed, we found no significant difference in the ratio of WSS in patients and in control subjects (0.98±0.10 vs. 0.95±0.02 respectively).

We found no statistically significant difference in IMT, whether we used manual or automated measurements, between the occluded side, the non-occluded side and the control carotids (0.65±0.10 mm, 0.58±0.14 mm and 0.55±0.02 mm, respectively). Similarly, we found no difference between the occluded side, the non-occluded side and the control carotids in wall cross-sectional area (12.15±1.19 mm², 12.25±1.05 mm² and 10.70±0.50 mm² respectively) (Table 1).

Linear regression analyses showed that there was a significant positive linear relationship between BF and ID (r=0.72, P<0.0001) (Fig. 1a), and between BF and CSA (r=0.35, P<0.01) (Fig. 1b), whereas we found no correlation between BF and IMT (r=0.07, NS) (Fig. 1c). Interestingly, no correlation was observed between BF and WSS, indicating that WSS values remained constant whatever the changes in BF (r=0.13, NS) (Fig. 1d). Moreover, in order to analyze more precisely the relationship between BF and CSA, we calculated further the relationship between ID and IMT on the one hand and the relationship between ID and CSA on the other hand: we found a significant positive linear relationship between IMT and ID (r=0.31, P<0.02) and a significant positive linear relationship between CSA and ID (r=0.70, P<0.001) (data not shown).

4. Discussion

The main finding of our study is the absence of variation in wall shear stress of the CCA upstream to the ICA occlusion, compared with the contralateral CCA, despite a significant ipsilateral reduction in blood flow. We found a

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Occluded side in patients</th>
<th>Contra1ateral side in patients</th>
<th>Carotids in control subjects</th>
<th>Two-way ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID (mm)</td>
<td>5.15±0.30</td>
<td>5.96±0.20</td>
<td>5.55±0.10</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>0.65±0.10</td>
<td>0.58±0.14</td>
<td>0.55±0.02</td>
<td>NS*</td>
</tr>
<tr>
<td>CSA (mm²)</td>
<td>12.15±1.19</td>
<td>12.25±1.05</td>
<td>10.70±0.50</td>
<td>NS</td>
</tr>
<tr>
<td>BF (ml/min)</td>
<td>404±58</td>
<td>703±51</td>
<td>567±27</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>WSS (dyn/cm²)</td>
<td>18.3±1.7</td>
<td>20.7±1.7</td>
<td>19.6±0.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Values are represented as mean±S.E.M.
*NS, non-significant.
positive significant relationship between blood flow and internal diameter, and between blood flow and cross-sectional area, suggesting an adaptive vascular response to decreased blood flow in order to maintain a constant WSS. Interestingly, this result was obtained despite the heterogeneity of the studied population.

Changes in blood flow in both CCA in response to unilateral ICA occlusion have been previously reported in human studies [9], but those authors did not evaluate other hemodynamic or structural parameters.

Remodeling in response to chronic changes in blood flow has been intensively investigated in animal experimental studies [1,2,10]. Pourageaud et al. [11] showed that rat mesenteric arteries undergo hypo- and hypertrophic
remodeling in low- and high-blood flow situations respectively. Analysis of signaling pathways of mechanical stresses in the vascular wall have also been the subject of numerous studies, using in vitro cell culture or organ culture models [12–15]. However, this kind of study in clinical research is impossible. Nevertheless, we performed the first study to the best of our knowledge that explored non-invasively the consequences of unilateral ICA occlusion on vessel caliber and WSS in human adults, with and without atherosclerosis. Ultrasonographic assessment was chosen because of its non-invasive nature, allowing accuracy and repeatability of internal diameter, wall thickness, as validated by Pignoli et al. [16] and mean blood velocity. These parameters were used for calculation of blood flow and wall shear stress. No other mean of investigation gather all these conditions in vivo.

Circumferential tensile stress associated with arterial blood pressure and wall shear stress associated with blood flow are the two mechanical stresses to which the vessel wall is permanently subjected [13]. Any chronic changes in these stresses have been shown to lead to vascular remodeling. In our study, the difference in response in common carotid arteries was only due to the variations in chronic blood flow, since arterial blood pressure values did not change.

Internal diameter values were smaller on the occluded side than on the non-occluded side. This was observed in all non-atherosclerotic patients and in seven out of nine atherosclerotic patients. Langille and O’Donnell [3] showed in rabbits that the decrease in CCA internal diameter ipsilateral to the occlusion is only observed when the endothelium is intact. Endothelial dysfunction evaluated on the basis of impaired endothelium-dependent relaxation, has been well documented in atherosclerotic patients [17]. However, our study suggests that the endothelium-dependent remodeling in response to chronic change in blood flow was well maintained in 7 out of 9 (78%) atherosclerotic patients.

In order to examine whether modifications of the internal diameter resulted from vasomotor tone modulation or from structural changes, we measured the intima-media thickness and we calculated the cross-sectional area, in order to take into account the modifications in internal diameter. Although there was no significant correlation between blood flow and intima-media thickness, we found a highly significant positive relationship between blood flow and cross-sectional area. This result suggests that structural rather than vasomotor tone modifications occurred in response to chronic change in blood flow. Indeed, if reduction in carotid diameter on the occluded side was due to vasomotor tone, IMT should increase with decreased diameter, but CSA should remain unchanged. Yet, on the contrary, we found both positive significant relationships between IMT and internal diameter (P<0.02), and between CSA and internal diameter (P<0.001).

In our study, the absence of significant differences in IMT or CSA between both sides may be related to the fact that in our atherosclerotic patients, the vascular wall was increased on the occluded side because of the underlying pathology, and thus hide a possible difference between both sides in the total group of patients. Indeed, IMT and CSA are not univocal in interpretation but can be considered as the consequence of two potential additional phenomena. Increased intima-media thickness of the CCA has been largely described in human vascular diseases, and mainly interpreted as an indicator of coronary disease [18,19], and risk factor for myocardial infarction and stroke [20]. Besides, it has been shown in animal experimental studies that a chronic increase in blood flow induces smooth muscle cell proliferation and results in a larger cross-sectional area [10,21]. Thus, increased cross-sectional area, and indirectly intima-media thickness which is the most often used parameter in human studies, can also be considered as an adaptive consequence of hemodynamic modifications. In a large series of patients aged over 55 years [22], Bots et al. observed a CCA internal diameter enlargement with a concomitant increase in intima-media thickness up to 1.2 mm, and hypothetized that increased intima-media thickness would not only reflect atherosclerosis, that otherwise would reduce internal diameter, but would be at least in part, a consequence of hemodynamic modifications.

In conclusion, using a non-invasive technique, in this study of seventeen unilateral occluded internal carotid arteries, of atherosclerotic and non-atherosclerotic etiology, we assessed the ability of the common carotid artery to decrease in response to the chronic reduction in blood flow. This allowed for the maintenance of wall shear stress at a constant value.

Acknowledgements

The authors wish to thank France Woomant for clinical assistance, Yacine Aggoun for helping in data analysis, and Stéphanie Lehoux for critical reading of the manuscript.

References


