Wall stress of the cervical carotid artery in patients with carotid dissection: a case-control study

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- Spontaneous internal carotid artery (ICA) dissection (sICAD) results from an intimal tear located around the distal carotid sinus. The mechanisms causing the tear are unknown. This case-control study tested the hypotheses that head movements increase the wall stress in the cervical ICA and that the stress increase is greater in patients with sICAD than in controls. Five patients with unilateral, recanalized, left sICAD and five matched controls were investigated before and after maximal head rotation to the left and neck hyperextension after 45° head rotation to the left. The anatomy of the extracranial carotid arteries was assessed by magnetic resonance imaging and used to create finite element models of the right ICA. Wall stress increased after head movements. Increases above the 80th and 90th percentile were located at the intimal side of the artery wall from 7.4 mm below to 10 mm above the cranial edge of the carotid sinus, i.e., at the same location as histologically confirmed tears in patients with sICAD. Wall stress increase did not differ between patients and controls. The present findings suggest that wall stress increases at the intimal side of the artery wall surrounding the distal edge of the carotid bulb after head movements may be important for the development of carotid dissection. The lack of wall stress difference between the two groups indicates that the carotid arteries of patients with carotid dissection have either distinct functional or anatomical properties or endured unusually heavy wall stresses to initiate dissection.

- Stroke; carotid sinus; finite element analysis; cervical dissection

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Exclusion criteria. The following exclusion criteria were used: 1) cigarette smoking, either current (smoking within the last 5 yr) or past (smoking cessation since >5 yr) (28); 2) hypertension, defined as a history of antihypertensive treatment or a history of systolic blood pressure > 18.7 kPa (140 mmHg) or diastolic blood pressure > 10.6 kPa (80 mmHg) or both (22); 3) diabetes mellitus, defined as a history of fasting venous plasma glucose concentration on at least two separate occasions > 7.8 mmol/l or glucose concentration > 11.1 mmol/l at 2 h after oral ingestion of 75 g glucose; 4) history of dyslipidemia, defined as serum cholesterol concentration > 5 mmol/l, serum low-density lipoprotein (LDL) cholesterol concentration of > 2.6 mmol/l, serum high-density lipoprotein (HDL) cholesterol concentration of < 1.0 mmol/l, ratio total-to-HDL serum cholesterol of > 5, or history of lipid lowering therapy; 5) signs of atherosclerosis at ultrasound studies defined as intima-media thickness (IMT) in the common carotid artery (CCA) of >1 mm and/or >30% local stenosis of the CCA, external carotid artery (ECA), or ICA at the origin (8); 6) serious illness (e.g., hepatic, cardiac, or renal failure) or a complex disease that may prevent the performance of the study; 7) contraindication to undergo MRI (e.g., pacemaker, claustrophobia); 8) women known to be pregnant, lactating, or having a positive or indeterminate pregnancy test.

Laboratory assays. Venous blood sampling included the determination of glucose, cholesterol, LDL and HDL cholesterol, and the ratio of total-to-HDL cholesterol. Premenopausal women underwent a pregnancy test in the urine.

Ultrasound study of the cerebral arteries. An ultrasound examination of the IMT of both CCA and the cerebral arteries was performed by an experienced medical doctor using a color duplex scanner (Acuson Sequoia, Mountain View, CA) with the patients and control subjects in a supine position. IMT was determined on the distal wall of both CCAs at 2 cm below the carotid bifurcation. Values of ≥1.0 mm were considered to be abnormal (12, 13). Extra- and transcranial CDS was done as reported before (4, 8). In brief, the CCA, the origin of the ICA and the ECA, and the subclavian and vertebral arteries were examined with 4–8-MHz linear probes. For insonation of the cervical ICA and for transorbital and transcranial CDS studies, 2–3.5-MHz sector probes were employed. Transorbital CDS was used to assess the carotid siphon, and transtemporal CDS was used to investigate the terminal (C1) ICA and the middle, anterior, precommunicating and postcommunicating posterior cerebral arteries. The intracranial vertebral artery and the basilar artery were imaged in the foramen magnum. Published criteria were used for assessing cerebral artery stenosis and occlusion (5, 7, 46). Patients with insufficient ultrasound windows were also investigated with the echocoustic agent SonoVue.

Complete recanalization of a dissected ICA was diagnosed when peak systolic velocity was ≤90 cm/s in women or ≤80 cm/s in men and when the peak systolic velocity quotient sICAD/contralesional cervical ICA was ≤1.12 (32).

Acquisition of anatomical data with MRA and MRI. Included patients and controls underwent cervical MRA and MRI on a 3T whole body scanner (Achieva, Philips Healthcare, Best, The Netherlands). Anatomical data of the right carotid arteries were acquired by two-dimensional time-of-flight gradient echo sequence MRA at the neutral position of the head (Fig. 1, A and B, left) after maximal rotation to the left (Fig. 1A, right), after 45° rotation to the left followed by hypextension of the neck (Fig. 1B, right), as well as at intermediate positions of the head movements (not shown) (11). Full MRA and MRI details are provided in the study of Callaghan et al. (11). MRI in-plane acquisition resolution was 0.8 × 0.8 mm², and reconstructed resolution following zero-filled interpolation was 0.4 × 0.4 mm² with slice spacing of 2 mm. Vessel wall thickness was measured by T1-weighted turbo field-echo MRI in the neutral head position in the CCA (10–20 mm proximal to the bifurcation), carotid bifurcation (midway between the CCA bifurcation junction and the bifurcation apex), and ICA (10–20 mm distal to the bifurcation). Acquired in-plane resolution was 0.35 × 0.35 mm² at a slice spacing of 2 mm.
The artery walls were modeled in the form proposed by Gasser et al. (20), considering the histological structure of arteries including an elastin matrix and embedded, preferentially orientated, collagen fibers:

\[ \psi = C(I_1 - 3) + \frac{k_1}{2k_2} \sum_{i=1}^{2} \left[ e^{k_i E_i} - 1 \right] \]

with

\[ E_i = \kappa I_1 - 3 + (1 - 3\kappa) \left( I_{4i(\text{num})} - 1 \right) \]

where \( \psi \) is the strain energy per unit reference volume; \( I_1 \) is the first invariant of the modified right Cauchy-Green tensor; and \( C, k_1, k_2 \) are material properties. The parameter \( C \) is the coefficient of the linear contribution of the elastin, whereas \( k_1 \) and \( k_2 \) are coefficients of the nonlinear anisotropic contribution of collagen fibers. \( E_i \) characterizes the deformation of the two families of collagen fibers symmetrically aligned by \( \gamma_i \) about the mean direction \( \vec{\Gamma} \) with a dispersion factor \( \kappa \) (see Table 1). \( I_{4i(\text{num})} \) are thus pseudoinvariants of the modified right Cauchy-Green tensor and the mean direction of fiber alignment \( \vec{\Gamma} \pm \gamma_i \).

The material properties of the media (Table 1) were applied from the experimental data obtained by Delfino et al. (15) as defined by Hariton et al. (25). Adventitia properties were defined by calculating the experimental data obtained by Delfino et al. (15) as defined by Hariton et al. (25). Adventitia properties were defined by calculating the mean media-to-adventitia ratios from experimental testings of arterial material models by Gasser et al. (24). This approach assumes the fiber alignment with a dispersion factor \( \kappa \) (see Table 1). \( I_{4i(\text{num})} \) are thus pseudoinvariants of the modified right Cauchy-Green tensor and the mean direction of fiber alignment \( \vec{\Gamma} \pm \gamma_i \).

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As the MRA data provide lumen anatomy in a preloaded state, i.e., a residually stressed state at diastolic pressure, it was necessary to compute the stress-free state of the artery and add residual and diastolic loads before artery deformation because of head and neck movements. We assumed, based on the observations of Delfino (14), that a stress-free state corresponds to a reduction in vessel diameter of 14% from its diastolic form. For all models, a constant diastolic plus residual pressure equal to 11.3 kPa (85 mmHg) was applied to the lumen surface to introduce a basal stress state, accounting for stresses residual pressure equal to 11.3 kPa (85 mmHg) was applied to the lumen surface to introduce a basal stress state, accounting for stresses residual pressure equal to 11.3 kPa (85 mmHg) was applied to the lumen surface to introduce a basal stress state, accounting for stresses residual pressure equal to 11.3 kPa (85 mmHg) was applied to the lumen surface to introduce a basal stress state, accounting for stresses residual pressure equal to 11.3 kPa (85 mmHg) was applied to the lumen surface to introduce a basal stress state, accounting for stresses residual pressure equal to 11.3 kPa (85 mmHg) was applied to the lumen surface to introduce a basal stress state, accounting for stresses residual pressure equal to 11.3 kPa (85 mmHg) was applied to the lumen surface to introduce a basal stress state, accounting for stresses residual pressure equal to 11.3 kPa (85 mmHg) was applied to the lumen surface to introduce a basal stress state, accounting for stresses residual pressure equal to 11.3 kPa (85 mmHg) was applied to the lumen surface to introduce a basal stress state, accounting for stresses.

The arterial material model was verified for a global pressure to domain of the model but rather coupled to structural nodes to drive the displacement of the vessel during the specified head movements. Statistics. Normally distributed data were compared using paired \( t \)-test and nonnormally distributed data using Mann-Whitney \( U \)-test. Significance was declared at \( P < 0.05 \). Data were analyzed without patient identification using MATLAB (Mathworks, Natick, MA).

### Table 1. Arterial wall material properties

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Media Layer</th>
<th>Adventitia Layer</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, kPa</td>
<td>35.7</td>
<td>242.7</td>
</tr>
<tr>
<td>( k_1 ), kPa</td>
<td>13.9</td>
<td>27.8</td>
</tr>
<tr>
<td>( k_2 )</td>
<td>13.2</td>
<td>189.6</td>
</tr>
<tr>
<td>( \kappa )</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>( \gamma_i )</td>
<td>39</td>
<td>39</td>
</tr>
</tbody>
</table>

*See Eqs. 1 and 2.

### Table 2. Right carotid sinus length and diameter after maximal head rotation to the left and maximal head rotation to the left followed by hyperextension of the neck

<table>
<thead>
<tr>
<th>Head Position*</th>
<th>Patients</th>
<th>Controls</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>17.5 (2.7)</td>
<td>18.3 (5.6)</td>
<td>17.8 (4.2)</td>
</tr>
<tr>
<td>45° Rotation</td>
<td>1.06 (0.05)</td>
<td>1.09 (0.05)</td>
<td>1.07 (0.05)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.06</td>
<td>0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>Max. Rotation</td>
<td>1.10 (0.07)</td>
<td>1.10 (0.04)</td>
<td>1.10 (0.05)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.02</td>
<td>0.003</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hyperextension</td>
<td>1.08 (0.02)</td>
<td>1.18 (0.10)</td>
<td>1.14 (0.09)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.01</td>
<td>0.008</td>
<td>0.002</td>
</tr>
<tr>
<td>Diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral</td>
<td>7.0 (0.7)</td>
<td>7.2 (0.8)</td>
<td>7.1 (0.7)</td>
</tr>
<tr>
<td>45° Rotation</td>
<td>0.98 (0.07)</td>
<td>0.99 (0.04)</td>
<td>0.98 (0.06)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Maximal rotation</td>
<td>0.94 (0.08)</td>
<td>0.98 (0.04)</td>
<td>0.96 (0.07)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.1</td>
<td>0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Hyperextension</td>
<td>0.97 (0.08)</td>
<td>0.95 (0.04)</td>
<td>0.96 (0.06)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>0.3</td>
<td>0.03</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Neutral head position: absolute values shown as means (SD). Values at other head positions are relative to the corresponding neutral dimension. \( P \) values are paired Student’s \( t \)-test results against the corresponding neutral head position. No differences between patient and control values were significant.
RESULTS

Recruitment of sICAD patients and controls. One hundred and two patients with unilateral left sICAD were admitted to the Department of Neurology of the University Hospital Zurich between October 1992 and August 2009. Of the 102 sICAD patients, 25 had no vascular risk factor including one patient who died from malignant middle cerebral artery infarction. Of the remaining 24 survivors without vascular risk factor, 18 (75%) showed a complete recanalization of the dissected vessel at 6 mo follow-up. Five of the 18 patients with complete recanalization who were diagnosed most recently and had also a straight cervical ICA on both sides at the usual MRA follow-up were asked to participate in the study, and all consented. Five controls who met no exclusion criterion were selected from volunteers among staff at the University Hospital Zurich and underwent MRA. All had bilateral straight cervical ICA and were included.

Head movements and deformation of carotid sinus anatomy. The extent of maximal head rotation to the left was 60–90°. The extent of hyperextension of the neck following 45° head rotation to the left was 25–40° relative to the transverse plane. Both head movements showed no difference between patients and controls \((P > 0.48)\). Carotid sinus length increased and carotid sinus diameter decreased in patients and controls during the two head movements (Table 2). During the first 45° of head rotation, 60% of maximal sinus elongation occurred in patients and 90% of maximal sinus elongation in controls. The value of relative sinus length increase at 45° was not significantly greater in controls compared with patients \((P = 0.45)\). Following the maximal extent of the two head movements, carotid sinus length had increased significantly in patients, controls, and both groups combined (Table 2). Carotid sinus diameter decreased significantly in both groups combined and showed a nonsignificant trend to decrease in patients and controls separately (Table 2). Variation of sinus length and diameter is likely to influence the vessel wall stress development during head movements.

Stress on the media and the adventitia of the cervical ICA. Media wall stress increase from the basal level (stress at diastolic blood pressure and no head rotation) above the 80th and the 90th percentile after the two head movements consistently covered an area from 7.4 mm below to 10 mm above the cranial edge of the carotid sinus (Fig. 3). Inspection of the stress tensors at this location reveals the vessel wall under axial tension. Subject \(G\) and, to a lesser extent, subject \(I\) showed changes in curvature of the ICA in addition to deformation of the carotid sinus, which resulted in a wider stress distribution. Additionally, 9 of the 10 subjects (5 controls) showed a stress increase above the 90th percentile at the distal end of the cervical ICA. Stress distribution in the adventitia

Fig. 3. Time-of-flight magnetic resonance angiography (anteroposterior view) and superimposed the increase of the media wall stress outside of the 80th percentile (yellow) and the 90th percentile (red) in the right cervical ICA of 5 patients with spontaneous dissection of the left cervical ICA (A–E) and 5 matched controls (F–J) after maximal head rotation to the left (α panels, right) and after 45° head rotation to the left followed by hyperextension of the neck (β panels, right) compared with the neutral position of the head (left image of each panel). The anteroposterior views are displayed with transparency to show stresses on the reverse side of the artery.
(not shown) showed a similar pattern to that found in the media. Stress distribution was analyzed by three independent observers blinded to subject group. All concluded that stress distribution showed no difference between patients and controls for both head movements. No data were obtained at neck hyperextension from subjects D and E because they developed claustrophobia in the MRI.

Axial slices of the cervical ICA at the region of maximal mediolateral stress showed that in 15 of 18 cases, stress above the 98th percentile was found at the lumen side of the media (Fig. 4).

The ICA was divided into three even portions along its length, corresponding to the proximal, middle, and distal portions of the vessel. The maximum principal stress was averaged circumferentially, radially, and longitudinally within the media and adventitia layers of each axial segment to give a mean stress following each of the two head movements. After the two head movements, mean stress of the media and adventitia increased more in the proximal segment than in the middle and the distal segments of the cervical ICA and showed no difference between patients and controls (Fig. 5). Mean stress values in the cervical ICA after both head movements were six to eight times smaller in the media (Fig. 5A) than in the adventitia (Fig. 5B).

The stress development in the ICA over the range of movement can be viewed in an animation provided as an online supplement to this article.1

DISCUSSION

This case-control study examined wall stress changes of the right cervical carotid artery occurring after maximal head rotation to the left and after 45° head rotation to the left followed by neck hyperextension in five patients with unilateral and recanalized left sICAD and five matched controls. The main findings observed after the two head movements were that wall stresses increased, a stress increase above the 80th and 90th percentile was located at the intimal side of the vessel from 7.4 mm below to 10 mm above the cranial edge of the carotid sinus, and wall stress increases did not differ between patients and controls.

The cervical ICA is fixed at its origin, the carotid bifurcation, and its distal end, the entrance in the osseous carotid canal at the base of the skull. The increase of carotid wall stress observed in every patient and every control indicates that the cervical ICA was stretched during the two head movements. This observation is underscored by the fact that the length of the carotid sinus increased and its diameter decreased during both head movements (Table 2).

Sixty to 90% of maximal sinus length increase occurred during the first 45° of head rotation. These observations are in line with the results of a previous investigation (11) and suggest that the physiological function of the carotid sinus elongation might be the reduction of the wall stress induced by stretching of the cervical ICA during head rotation. In the neutral head position, the ICA wall adopts a longer path axially and circumferentially at the sinus than if the vessel followed the same course, but the sinus was not present. The sinus may be idealized as an ellipsoid with its major axis aligned with the artery centerline and its ends removed to merge with the

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1 Supplemental material for this article is available at the American Journal of Physiology-Heart and Circulatory Physiology web site.
Subsequently, Nedwich et al. (34) postulated that a rupture of the intimal wall leading to hemorrhage into the vessel wall (false lumen) may be related to an intimal tear in patients with sICAD (3, 6). The lack of significance between two groups in the present study (*P* > 0.48) may be related to the low number of the 10 investigated subjects.

When stretched in vitro, carotid arteries initially fail at the intimal tear with a complete rupture occurring following additional strain. The initial failure occurs at lower stresses than required for ultimate failure, and the initial tear is oriented perpendicular to the strain direction (43). These findings agree with our observation of axial stretching of the distal carotid sinus and histological evidence of circumferential tears in sICAD (18). The stress at which initial failure begins as...
detailed by Stemper et al. (43) is much higher (570 kPa) than the peak stresses observed in the media of our model (~60 kPa). This difference can be explained by the fact that our simulations recreate stress patterns from the neutral head position to a maximal head position (rotation or hyperextension) that could be held constant by the subject for approximately 5 min during MRI scanning. As such, the head rotations displayed are not the maximum that can be reached by an individual but rather at a limit of comfort so as to ensure clear MRI results. Another limitation is that we did not include stresses due to systolic pressure since all of our MRI data were held constant by the subject for approximately 5 min.

Our results support the hypothesis that head movements induce wall stress in the distal carotid sinus, which may contribute to the initiation of sICAD. The absence of difference between wall stress values in patients and controls implies that an additional factor such as impaired distensibility also contributes to sICAD.

**GRANTS**

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**REFERENCES**


