Status of the Circle of Willis and Intolerance to Carotid Cross-clamping During Carotid Endarterectomy

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WHAT THIS PAPER ADDS?

Identification of a non-invasive system that may reasonably predict the intolerance to cross-clamping during carotid endarterectomy is important in order to plan the correct therapeutical approach. Results of our analysis demonstrate that MRA may identify patients at risk for intolerance and that two, or more, interruptions of the Circle of Willis are associated with high risk of intolerance to cross-clamping.

Purpose: During carotid endarterectomy (CEA), an intolerance to the cross-clamping (CC) can occur. The purpose of this study was to evaluate whether preoperative magnetic resonance angiography (MRA) can predict CC intolerance.

Material and methods: Seventy-one patients (57 males, 14 females, mean age 71.8 years, age range 46—86 years) underwent 71 CEA procedures under local anaesthesia. Before CEA, patients underwent an MRA of the Circle of Willis (CoW) and were then classified into three groups: group A consisted of patients with a complete CoW, group B included patients with one agenesis/obstruction in the CoW and group C comprised patients with two or more agenesiae/obstructions in the CoW. The association between the number of anatomical variants in the CoW, corrected for the status of the contralateral carotid artery, and the onset of CC intolerance was evaluated.

Results: The prevalence of intolerance to CC was 15.5% (11/71). The Fisher test and logistic regression analysis showed a statistically significant association between the intolerance to CC and two or more agenesiae/obstructions in the CoW (p value < 0.00001 and p < 0.001, respectively). No neurological complications were observed.

Conclusion: The results of our study showed that two or more agenesiae/obstructions of the CoW identified by MRA were associated with a high risk of intolerance to CC during CEA.

Carotid endarterectomy (CEA) is considered a safe and effective method to prevent stroke in the short- and long-term period in patients with severe internal carotid stenosis.1–3 During CEA, carotid cross-clamping (CC) is performed to allow for artery incision and the removal of plaque. However, the role of the CEA is mainly related to its ‘safety’ (low incidence of post/peri-procedural complications). Carotid CC causes blood flow reduction to the Circle of Willis (CoW), and some patients show intolerance to CC; in these cases, it is necessary to use a temporary shunt. The incidence of intolerance to carotid CC varies between 7% and 30% according to different studies.4–6 Differences in the incidence mainly depend on the use of different methods for detecting neurological deficits or for cerebral perfusion analysis, such as the trans-cranial Doppler (TCD).

Because of the risk of cerebral ischaemia during carotid CC, it is mandatory to adopt methods of cerebral monitoring that can rapidly and effectively reveal any sign of intolerance and indicate the need for the intra-operative use of a shunt. Monitoring of cerebral functions can be achieved through both clinical and instrumental means. In the clinical case, local anaesthesia allows for continuous and direct monitoring of cerebral functions when the patient is invited to answer the surgeon or to perform some movements with the contralateral upper limb (i.e., squeeze a rattle). Monitoring of neurological status can also be performed in cases of general anaesthesia by using short-action drugs (i.e., remifentanil); immediately before carotid clamping, infusion of the drug is suspended, the patient regains consciousness and is asked to squeeze a toy in his or her contralateral hand.7,8 Many centres opt for instrumental monitoring with electroencephalography (EEG), or somatosensory evoked

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http://dx.doi.org/10.1016/j.ejvs.2012.11.012
potentials (SSEPs) or TCD, which can detect a sudden alteration of the cerebral function or a deficit in the intracranial flow. However, these surveys are complex, expensive and require expert operators. Some authors eschew the use of any cerebral monitoring devices and propose the routine use of the shunt; however, this practice carries a significant risk of complications (mainly distal dissection of the internal carotid artery) due to shunt placement. Therefore, the selective use of the shunt for cases of CC intolerance is the first choice of most operative groups.9–11

Local anaesthesia is largely used for CEA.12 The onset of intolerance to the CC during CEA under local anaesthesia can produce difficulties in the management of the patient because of a loss of consciousness, convulsions, respiratory problems and haemodynamic instability.

The purpose of this study was to evaluate whether preoperative magnetic resonance angiography (MRA) evaluation of the CoW can predict CC intolerance.

**MATERIAL AND METHODS**

**Patient population**

Between October 2010 and December 2011, 71 patients (57 males and 14 females) in the age range of 46–86 years (mean age 71.8 years) underwent 71 carotid endarterectomies under local anaesthesia. Each patient signed an informed consent and was informed about the potential risks related to the general co-morbidities, occlusion or severe stenosis of the contra-lateral carotid or reduction of the intracranial collateral circulation.

The degree of carotid stenosis was assessed according to the European Carotid Surgery Trial criteria by using preoperative Duplex scans and computed tomography (CT) angiography of the epiaortic vessels. The decision for surgical treatment was based on SPREAD guidelines.13 Nineteen patients had significant bilateral carotid artery stenosis (>70%), and the contralateral carotid artery was obstructed in six additional patients. All patients underwent an MRA study of the CoW. The patients were classified into three groups: group A included patients with a complete CoW, group B consisted of patients with one agenesis/obstruction in the CoW and group C included patients with two or more agenesis/obstructions in the CoW.

All CEAs were performed under local anaesthesia. During the procedure, the patient was invited, before, during and after the CC, to answer some questions and to squeeze a toy (rattle) in the contralateral hand to check for intolerance to the carotid CC. In cases of CC intolerance, a silicone T-Tube (Pruitt-Inahara shunt), Le Maitre Vascular, Burlington, MA, USA) was inserted through the same arteriotomy used for the CEA.

**MR technique**

All examinations were performed with a Gyroscan 1.5-T superconducting magnet (Philips, Best, The Netherlands). In all patients, a three-dimensional (3D) time of flight (TOF) MRA of the CoW was performed. 3D multislab TOF MR angiograms were obtained from the petrous portion of the internal carotid artery to the level of the genu portion of the corpus callosum by using the following imaging parameters: 25-35/3-7/1 (TR/TE/excitation), a flip angle of 20°, five slabs, an effective section thickness of 0.8 mm, a field of view of 200 mm and a matrix of 256 × 256 pixels. The angiographic images were reconstructed with a maximum intensity projection (MIP) and volume-rendering (VR) algorithms.

**Identification of variants in the CoW**

The presence of anomalies in the CoW on preoperative 3D TOF MR angiograms (Fig. 1) was evaluated. The following arteries were evaluated: the anterior communicating artery (AcoA), the A1 segments, the P1 segments, and the left and right posterior communicating arteries (PcoAs). As previously described by Hoksbergen et al.14 we used a forced-choice method (absent or present) in the decision analysis and those arteries that could not be visualised were defined as absent, while those that could be visualised were defined as present. We dedicated special care to differentiating the PcoAs from the anterior choroidal arteries by scrolling through the sections and sequentially determining the course of the arteries. The communication of the PcoA with the posterior cerebral artery had to be visualised for defining the PcoA.

Because the purpose of this work was to explore the association between agenesis/obstructions in the CoW and intolerance to carotid CC, in the case of fusion of the anterior cerebral arteries (absence of AcoA) the anterior collateral pathway was defined as functional and therefore not absent.

After review of 3D TOF MR angiograms, CoW morphology was classified as an optimal communicator when no anatomical variations were detected, sufficient communicator when one variation was detected and poor communicator when two or more variations were identified.

Two experienced vascular radiologists with 6 and 4 years of experience in MRA imaging evaluated the CoW independently, and the inter-observer concordance was tested. In the case of disagreement between the observers, a consensus was reached by consulting a third senior radiologist with 9 years of experience in MRA imaging.

**Statistical analysis**

The prevalence of CC intolerance was expressed as cases per 100, and 95% confidence intervals (CIs) were calculated according to the Poisson distribution.

The association between agenesis/obstruction in the CoW and age was analysed with the Kruskal–Wallis test. The association between agenesis/obstruction in the CoW and gender, smoking habit, hypertension, diabetes, hypercholesterolaemia, CC intolerance and contralateral ICA stenosis was analysed with the Fisher chi square test.

The potential confounding effect of contralateral ICA stenosis on the association between CC intolerance and the agenesis/obstruction in the CoW was explored through a multivariate logistic regression. CC intolerance was the
dependent variable, while interruption in the Cow and contralateral ICA stenosis were the independent variables. The logistic regression was calculated according to a backward stepwise procedure, which deleted non-associated variables from the model.

The MRA validity in predicting the CC intolerance was evaluated through sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV) analyses.

Agreement between observers in the CoW categorisation was calculated using a Cohen kappa test.

Statistical Package for the Social Sciences (SSPS) 18.0 (SSPS INC, Chicago, IL, USA) software was used to perform the statistical analysis.

RESULTS

The Cohen test between radiologists showed an extremely high kappa value (kappa = 0.93) by demonstrating an optimal inter-observer concordance.

In Table 1, the demographic characteristics and risk factors were categorised according to the group (A, B or C) of the cohort and with the associated comparative analysis that showed that there were no differences between the cardiovascular risk factors among the three groups.

In all 71 cases, the surgical procedure was completed, and removal of the plaque and restoration of blood flow to the brain hemisphere was achieved. Among the 71 CEA procedures, 11 patients showed CC intolerance (prevalence of 15.5%). In 10 patients, motor weakness (an inability to move the contralateral hand) along with mental confusion or loss of consciousness occurred, and convulsions and respiratory distress occurred in one patient. In the patients with CC intolerance, a Pruitt–Inahara shunt was placed, resulting in prompt (within 1 min) restoration of consciousness and neurological functions in 10 patients and a slower restoration (within 2 min) in one patient.

Table 2 shows the association of CC intolerance with the presence of 0, 1, 2 or more agenesiae/obstructions in the CoW, as previously identified with MR. The statistical analysis demonstrated that the presence of two or more agenesiae/obstructions in the CoW is statistically associated with the risk of developing CC intolerance, whereas the other factors (ipsilateral, contralateral carotid stenosis and preoperative symptoms) are not significantly associated.

The sensitivity, specificity, PPV and NPV were calculated and the following results were found: sensitivity 82% (probability of having two agenesiae/obstructions in the CoW in patients with CC intolerance), specificity 90% (probability of having zero or one agenesia/obstruction in patients without CC intolerance), PPV 60% (probability of a patient having CC intolerance when the CoW has two agenesiae/obstructions), NPV 96% (probability of a patient not having CC intolerance when the CoW has zero or one agenesia/obstruction).

Logistic regression analysis was also performed by using a backward stepwise procedure to evaluate the association between CC intolerance and complete CoW, one agenesis/
interruption in the CoW, two or more agenesiae/interruptions in the CoW and contralateral ICA stenosis. In the stepwise procedure, contralateral ICA stenosis was not significantly associated and did not show confounding effects; therefore, it was deleted from the model. The logistic regression model indicated that the presence of two agenesiae/obstructions versus complete CoW had a statistically significant risk to develop CC intolerance with a $p$ value $< 0.001$ (odds ratio (OR) 51; 95% CI from 5.4 to 479.5) while there was not a statistically significant difference in the risk to develop CC intolerance between the presence of one agenesia/obstruction in the CoW versus complete CoW ($p$ value $= 0.71$; OR 1.7; 95% CI from 0.1 to 28.7).

At the end of the CEA, the patients underwent neurological evaluations and no complications were observed. The patients who tolerated CC were discharged on postoperative day 2, while the patients who had shown CC intolerance were discharged on postoperative day 3.

**DISCUSSION**

During CEA, most vascular surgical teams use a shunt only in patients who show neurological signs of intolerance to CC.$^{9-11}$ Therefore, a method that reliably predicts CC intolerance is useful to alert the surgical/anaesthesiological team about the potential need for a vascular shunt and for more complex anaesthesiological management.

MRA is a non-invasive method that does not require the injection of contrast material and is widely used for the assessment of the CoW morphology. This technique has some advantages compared to the TCD because of the higher reproducibility and compared to the arteriography because of the absence of procedural risks.$^4$ The previous observation that the MRA of the CoW is useful for predicting cerebral ischaemia$^4$ represents an important issue.

In our study we found that the absence of collateral cerebral blood flow evaluated by MRA is strictly related to the risk of cerebral ischaemia during carotid CC. Furthermore, we observed a statistically significant association between two or more agenesiae/obstructions in the CoW versus complete CoW ($p$ value $= 0.0001$). These results are concordant with a previous study by Bagan et al.$^4$ where the authors described the presence of intolerance to CC in the CoW with a configuration type 5 type 14 and type 15 according to the Lazorthes’ configuration.$^{15}$ Our study differs from that of Bagan et al.$^4$ because to the best of our knowledge, it is the first study to demonstrate that the number of agenesiae/obstructions in the CoW are significantly associated with the intolerance to CC, independent of the CoW configuration ($p$ value $= 0.0001$).

In the past, TCD has also been proposed as predictive method for the evaluation of carotid CC intolerance, assuming that the carotid compression test exactly reproduces the haemodynamic variations induced by carotid CC.
The elements that can determine this process are as follows: (1) the structure of the vascular system (in particular the CoW); (2) the presence of critical extra- and intra-cranial stenosis, contralateral carotid occlusion or stenosis/occlusion of the vertebral and/or basilar arteries and (3) the arterial blood pressure. These elements, variously combined, can influence a cerebral perfusion deficit. In particular, our experience seems to demonstrate that when two or more agenesiae/obstructions in the CoW are present, a cerebral perfusion deficit is highly probable. The presence of only one agenesia/obstruction in the CoW, not associated to contralateral carotid occlusion or low blood pressure, appears to be insufficient to determine intolerance during carotid clamping. The presence of two or more agenesiae/obstructions in the CoW is an infrequent, but not rare, event. The location of the anomalies of the CoW can influence the extent of the hypo-perfused cerebral area and consequent clinical signs.

The role of contralateral carotid occlusion or stenosis did not appear to be a determinant in this study. However, this fact could be attributed to the small number of the patients in the cohort with this condition. The relationship between the presence of contralateral occlusion and the onset of CC intolerance has been assessed previously in both symptomatic and asymptomatic patients.

In our experience the correlation between the presence of at least two CoW agenesiae/obstructions and the onset of carotid clamping intolerance was highly statistically significant. In those cases in which there was no intolerance to carotid clamping despite the presence of two CoW agenesiae/obstructions, it is likely that a very small cerebral area or a neurologically insignificant area was hypoperfused. Further studies are necessary to better define the role of CoW anatomy and the site of breaks together with the state of the contralateral artery, the vertebrobasilar circle and haemodynamic status.

As shown in Table 2 the prevalence of CoW variation was 50.7% (36/71) and this result is in agreement with previous anatomic studies.

The Cohen test between radiologists showed an extremely high kappa value (kappa = 0.93), indicating that

<p>| Table 2. CoW characteristics related to carotid clamping intolerance, ipsi- and contra-lateral carotid stenosis and preoperative symptoms. |</p>
<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal communicator (complete CoW)</td>
<td>Sufficient communicator (one agenesia/obstruction in the CoW)</td>
<td>Poor communicator (two or more agenesiae/obstructions in the CoW)</td>
<td></td>
</tr>
<tr>
<td>Endarterectomies</td>
<td>35 (49.3%)</td>
<td>21 (29.6%)</td>
<td>15 (21.1%)</td>
</tr>
<tr>
<td>CC intolerance</td>
<td>1 (2.9%)</td>
<td>1 (4.8%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Ipsilateral carotid stenosis</td>
<td>70—79%</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>80—89%</td>
<td>7</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>90—99%</td>
<td>9</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Contralateral carotid stenosis</td>
<td>0—70%</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>70—99%</td>
<td>12</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Preoperative symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>28</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Single TIA</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Multiple TIA</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

a Fisher-test.

during surgery. However frequently TCD cannot be performed due to the absence of a temporal bone window, and common carotid compression test does not simulate the exact haemodynamic conditions during endarterectomy when the external carotid artery is clamped. Therefore, TCD could underestimate the effective perfusion pressure realised during surgery.

The possibility to predict CC intolerance is a key element in surgical decision making because it provides patients with more information to make an informed decision. Moreover, this information helps the surgical and anaesthesiological teams determine the appropriate type of anaesthesia and the necessary experience level of the operators. Local anaesthesia is a valid method of clinical neurological monitoring that is simple, inexpensive and does not require intra-operative instrumental monitoring. However, the management of a patient under local anaesthesia can become difficult in the case of CC intolerance, especially during the period when shunt placement is necessary to restore neurological functions. This event occurs in a minority of cases, but it makes this surgical phase highly dramatic and potentially dangerous.

The normal anatomy of the CoW protects the patient from ischaemia because it allows the perfusion of all cerebral areas, even when an internal carotid artery is clamped. Even when the contralateral internal carotid artery is occluded, CC often does not induce ischaemia despite the brain being perfused only via the basilar artery. However, in presence of anomalies of the CoW, the perfusion of some cerebral areas can become insufficient and produce clinical neurological deficits. This event occurs when the perfusion pressure in some cerebral areas drops to critical levels. The elements that can determine this drop in perfusion pressure are as follows: (1) the structure of the vascular system (in particular the CoW); (2) the presence of critical extra- and intra-cranial stenosis, contralateral carotid occlusion or stenosis/occlusion of the
the MRA interpretation of the CoW configuration is quite reproducible.

This series presents a potential limit due to the cohort size. In order to have 80% power of detecting the association between CC intolerance and the presence of agene-siae/obstructions in the CoW, each group should include 23 patients. However, the difference among the three groups is highly significant (Fisher p value < 0.00001); this result allows one to achieve the goal to demonstrate a statistical difference in the presence of CC intolerance among patients with 0, 1 or 2 interruptions in the CoW.

Further investigations with a larger sample size are necessary for in-depth analysis of potential influence of other factors such as the status of the extra-cranial arteries.

A precise knowledge of the risk of CC intolerance could influence the therapeutic strategy.

ACKNOWLEDGEMENT

We thank Claudia Sardu for her important contribution for statistical analysis.

CONFLICT OF INTEREST/FUNDING

None.

REFERENCES