Heterogeneity in Infarct Patterns and Clinical Outcomes Following Internal Carotid Artery Occlusion

Thanh G. Phan, FRACP, PhD; Geoffrey A. Donnan, FRACP, MD; Velandai Srikanth, FRACP, PhD; Jian Chen, ME; David C. Reutens, FRACP, MD

Objective: To investigate whether the extent of infarction and clinical outcomes after internal carotid artery (ICA) occlusion depends on the additional occlusion of the middle cerebral artery (MCA).

Design: Using statistical parametric mapping, we compared infarct patterns in stroke patients.

Setting: A tertiary care hospital.

Patients: Patients with coexistent ICA and MCA occlusion (n=25), isolated ICA occlusion (n=20), and isolated MCA occlusion (n=40).

Main Outcome Measure: Modified Rankin scale score.

The independent effect of infarct type on clinical outcome was estimated using logistic regression, adjusting for age and sex.

Results: The mean age was 62.6 years (standard deviation [SD], 15.5 years) in patients with ICA and MCA occlusion, 64.3 years (SD, 12.9 years) in patients with isolated ICA occlusion, and 67.4 years (SD, 14.2 years) in patients with isolated MCA occlusion. Infarct patterns, volume (P = .13), and the proportion of patients with poor outcomes (P = .3) were similar between those with ICA and MCA occlusions and those with isolated MCA occlusion. Compared with the other 2 groups, those with isolated ICA occlusion were less likely to have infarction of the insula (P < .001) and superior temporal lobe (P < .001) and had smaller infarct volume and lower modified Rankin scale scores (all P < .05). Compared with those with isolated ICA occlusion, the risk of poor clinical outcome was greater in those with coexistent ICA and MCA occlusion (P = .02) and those with isolated MCA occlusion (P = .06) independent of age and sex.

Comments: Patients with ICA occlusion but without coexistent MCA occlusion have different infarct patterns, less extensive infarcts, and better clinical outcomes than those with coexistent MCA occlusion or MCA occlusion alone. It may not be warranted to exclude such patients from acute stroke trials.

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INFARCT EXTENT AND TOPOGRAPHY provide important clues to the site of arterial occlusion and are relevant for clinical decision-making. For example, a large hemispheric infarct pattern may suggest a poor prognosis1 and/or development of malignant hemispheric syndrome.2 Patients with internal carotid artery (ICA) occlusion are currently excluded from some thrombolytic trials3 on the basis of potentially extensive infarction and lack of response to thrombolytic therapy.4-5 However, it is unknown if all patients with ICA occlusion uniformly have extensive and homogenous infarcts and, if this is not the case, what modifies the extent and pattern of infarction. Researchers have examined the primary and ophthalmic collateral systems without success in explaining the difference in infarct extent.6-9 It is possible that coexistent middle cerebral artery (MCA) occlusion modifies the clinical outcome and infarct patterns of patients with ICA occlusion. This has not been well characterized previously. We hypothesized that the pattern of infarction and clinical outcome following ICA occlusion varied according to coexistent MCA occlusion.

METHODS

PATIENT SELECTION

We studied stroke patients at Austin Health and Monash Medical Centre (January 1999-June 2007) who underwent magnetic resonance angiography and selected patients with 3 different patterns of arterial occlusion: (1) ICA occlusion together with MCA trunk or branch occlusion; (2) ICA occlusion alone; and (3) MCA occlusion alone. Demographic data and 3-month clinical outcomes (modified Rankin
Infarcts were segmented and registered to a standard brain template (details can be found in a previous publication\textsuperscript{10}). Similar to our previous development of cerebral infarct digital atlases,\textsuperscript{10,11} infarcts arising from ICA and MCA trunk or branch occlusion were manually segmented on T2-weighted images. The images from subjects with infarcts in the right hemisphere were turned along the y-axis so that all infarcts lay on the left side of the image according to the radiological convention.

**REGISTRATION**

In the preanalysis stage, the images were spatially smoothed with a Gaussian kernel of 12 mm. These images were normalized to standard stereotactic coordinates for the voxel analysis. A spatial mask of the left hemisphere was applied so that the voxel analysis was constrained to the left hemisphere.

**t STATISTICS**

A parametric voxel-based analysis (SPM; Wellcome Trust Centre for Neuroimaging, London, England) was used to produce statistical parametric maps. Images were spatially smoothed with a Gaussian kernel of 12 mm full-width at half-maximum. This analysis used the unpaired t test in SPM5 to compare the distribution of the means in 2 groups regarding the infarction risk at a voxel level. This test was chosen to examine the difference in the probabilities of infarction within the regions of interest for different occlusion types. The spatially smoothed images were compared using a t test in SPM5 to compare the distribution of the means in 2 groups regarding the infarction risk at a voxel level. This test was chosen to examine the difference in the probabilities of infarction within the regions of interest for different occlusion types.

Because the t statistic is applied to many voxels within the images, correction for multiple-hypothesis testing is required. Bonferroni correction for multiple-hypothesis testing at each voxel is not appropriate for image analysis, since a large number of truly active voxels could still be rejected with this conservative method. Instead of controlling for the chance of any false-positive results (as with the Bonferroni method), we used a false discovery rate (FDR), which controls the expected proportion of false-positives among the voxels that have exceeded a certain threshold on the raw t statistics map.\textsuperscript{12} In this analysis, the FDR is set at 0.05 so that, among the significant voxels above the t threshold, 5% are false-positive. The FDR is more sensitive than a traditional Bonferroni correction.\textsuperscript{13} If no voxels are above the t threshold, then using the FDR will not result in any significant voxels.

**INFARCT PATTERNS**

The segmented infarcts were averaged to create a map of the probability of involvement by infarction at each voxel for the 3 groups. Anatomical interpretation was facilitated through the use of an existing database that matches Talairach coordinates to anatomical structures.\textsuperscript{13}

### INFARCT VOLUME AND CLINICAL OUTCOME

Mean infarct volumes were compared using a t test. Clinical outcomes were dichotomized as good (modified Rankin scale score \(\leq 2\)) or poor (modified Rankin scale score > 2), and a Fisher exact test was used to compare the proportion of people with poor outcomes between groups. Logistic regression was used to estimate the effect of infarct type (either ICA/MCA occlusion or isolated MCA occlusion) on clinical outcome, with isolated ICA occlusion as the reference category, adjusting for age and sex. Version 17.0 of SPSS was used for this analysis.

### RESULTS

#### DEMOGRAPHICS

There were 26 patients (16 men) in the ICA/MCA-occlusion group (mean age, 62.6 years; standard deviation [SD], 15.5 years), 20 patients (13 men) in the ICA-occlusion group (64.3 years; SD, 12.9 years), and 40 patients (21 men) in the MCA-occlusion group (mean age, 67.4 years; SD, 14.2 years). The stroke risk factors were presented in Table 1. Large artery disease was the stroke mechanism in all patients with ICA infarcts. Details on the time of magnetic resonance imaging, stroke mechanisms, and sites of arterial occlusion for MCA infarcts have been published previously.\textsuperscript{10}

#### INFARCT TOPOGRAPHY

The probabilities of infarction within the regions of interest are displayed in Table 2. The infarct topography is displayed in the Figure. The t statistic maps showed that infarct topography was similar in the ICA/MCA occlusion and MCA occlusion–only groups. The ICA occlusion–only group had a significantly lower probability of infarction in the insula and superior temporal lobe (Table 2) than both the MCA occlusion and MCA/ICA–occlusion groups.

#### INFARCT VOLUME

The mean infarct volumes were 112.5 mL (SD, 113.4 mL) in the ICA–occlusion group, 21.1 mL (SD, 24.1 mL) in the ICA/MCA–occlusion group, and 68.0 mL (SD, 66.1 mL) in the MCA–occlusion group. Mean
farct volume was significantly different between the ICA-occlusion and the ICA/MCA–occlusion groups ($P = .003$) and between the ICA-occlusion and MCA-occlusion groups ($P = .002$), but not between the ICA/MCA–occlusion and MCA-occlusion groups ($P = .13$).

**CLINICAL OUTCOME**

The mean modified Rankin scale scores were 1.05 (SD, 1.08) in the ICA/MCA–occlusion group; 2.62 (SD, 1.68) in the ICA-occlusion group, and 2.45 (SD, 1.60) in the MCA-occlusion group. There were significantly higher proportions of patients with poor outcome in the ICA/MCA–occlusion (n = 14 [56.0%], $P = .01$) and MCA-occlusion (n = 17 [42.5%], $P = .04$) groups than in the ICA-occlusion group (n = 3 [15.0%]). The proportion of patients with poor outcomes was similar between the ICA/MCA–occlusion and MCA-occlusion groups ($P = .5$). After adjusting for age and sex, there was a significantly greater risk of poor outcomes in those with coexistent ICA and MCA occlusions ($P = .02$) compared with patients with only an ICA occlusion. There was also a strong trend for an increased risk of poor outcomes in those with only an MCA occlusion ($P = .06$) compared with those with only ICA occlusions.

**INFARCT VOLUME AND CLINICAL OUTCOME**

This study showed heterogeneity in infarct volume and clinical outcomes following ICA occlusion. This important finding is consistent with some observation studies on this topic.\(^5\)\(^,\)\(^7\) Currently, patients with ICA occlusion are excluded from acute stroke trials\(^3\) on the premise of potentially extensive infarction and lack of response to therapy. The premise for this exclusion criterion was based on studies by Linfante and colleagues,\(^5\) who compared differences in outcomes in patients with ICA plus MCA occlusion vs isolated MCA occlusion and found a higher rate of recanalization in the MCA-occlusion group. However, this group did not examine patients with ICA occlusion without MCA occlusion. Similarly, other investigators found that proximal ICA thrombosis conferred an odds ratio of 3.3 for a poorer outcome but also cautioned that only 30% of the patients had a good response to thrombolytic therapy.\(^4\) It is possible that the patients with ICA occlusion who responded to thrombolytic therapy had recanalization of the MCA but that the therapy had no effect on recanalization of the ICA because of the larger thrombus burden.\(^16\)

**INFARCTION PATTERNS AND VASCULAR ANATOMY**

**Primary Collateral System**

Similarities and differences between the ICA and MCA infarct territory can be understood from a brief review of the vascular anatomy. From the intradural ICA stem the ophthalmic artery, posterior communicating artery, anterior choroidal artery,\(^12\) MCA, and anterior cerebral artery (ACA). The anterior communicating artery connects to the contralateral ICA and MCA via the A1 segment of the ACA. In the setting of ICA occlusion (below the carotid T junction where the A1 segment and MCA stem from the ICA) but preserved anterior communicat-

### Table 2. Regional Risk of Infarction in the ICA- and MCA-Occlusion Groups

<table>
<thead>
<tr>
<th>Location</th>
<th>Voxel Coordinate</th>
<th>ICA Only</th>
<th>ICA and MCA</th>
<th>MCA Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corona radiata</td>
<td></td>
<td>0.45</td>
<td>0.43</td>
<td>0.54</td>
</tr>
<tr>
<td>Lentiform</td>
<td></td>
<td>0.05</td>
<td>0.32</td>
<td>0.60</td>
</tr>
<tr>
<td>Gaudate</td>
<td></td>
<td>0.10</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>Insula</td>
<td></td>
<td>0.05</td>
<td>0.65</td>
<td>0.49</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>–61, –19, and 9</td>
<td>0.05</td>
<td>0.35</td>
<td>0.24</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>–46, –48, and 30</td>
<td>0.10</td>
<td>0.26</td>
<td>0.27</td>
</tr>
<tr>
<td>Angular gyrus</td>
<td>–44, –71, and 31</td>
<td>0.05</td>
<td>0.17</td>
<td>0.16</td>
</tr>
<tr>
<td>Posterior limb of internal capsule</td>
<td></td>
<td>0.05</td>
<td>0.44</td>
<td>0.27</td>
</tr>
<tr>
<td>Optic radiation</td>
<td></td>
<td>0.00</td>
<td>0.20</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Abbreviations: ICA, internal carotid artery; MCA, middle cerebral artery.  
\(^a\) Statistically different at voxel level between the MCA-occlusion and coexistent ICA/MCA–occlusion groups.
ing artery, the cross-flow from the nonoccluded side to the occluded ICA can provide blood to the MCA territory.8,18 This is not possible if the ICA occlusion occurs at the carotid T junction. Additionally, blood flowing from the posterior cerebral artery (PCA) via the posterior communicating artery can act as another source for the occluded ICA (if the ICA occlusion is below the origin of the posterior communicating artery).8,19,20 When there is occlusion of both the ICA and MCA, there is no rescue from the primary collateral system via the anterior or posterior communicating arteries to the MCA territory, and combined ICA and MCA occlusion results in infarcts resembling MCA infarcts. The ophthalmic artery has been proposed previously to be a secondary collateral system, but in clinical studies its presence has not been shown to modify outcome or infarct pattern.6,7,21

In this study, we have observed that in the absence of MCA occlusion, patients with ICA occlusion have infarcts centered around the superior deep subcortical region (centrum semiovale) (Figure) but not the deep region, as in the striatocapsular region. The superior deep subcortical region corresponds to the internal borderzone/watershed region.22,23 A possible explanation is that the central semioval region receives its blood from the MCA’s perforating medullary branches, which do not appear to have a significant collateralization with each other or with the lenticulostriate arteries within the deep compartment.22,24,25 The lower frequency of infarction of the striatocapsular region in patients without concomitant MCA occlusion may be due to this region being supplied by the lenticulostriate arteries.26 The lenticulostriate arteries usually originate from the proximal MCA.27 In the case of MCA occlusion after the origin of the lenticulostriate arteries, the striatocapsular region would have been salvaged by collateral flow from the contralateral ICA via the anterior communicating artery to the MCA and then the lenticulostriate arteries.27 Similarly, the lower risk of infarction in the territory of the anterior choroidal artery may be due to the cranial part of the anterior choroidal artery forming anastomoses, with branches of MCA and PCA and the caudal part of the anterior choroidal artery forming anastomoses with branches of the posterior communicating artery and PCA.27 Furthermore, the lower risk of infarction of the insula region from isolated ICA occlusion may be due to this region receiving its arterial supply directly from the M1 segment and branches from superior and inferior divisions of the MCA.28

Figure. Atlases of isolated middle cerebral artery (MCA) (A), coexistent internal carotid artery (ICA) and MCA (B), and isolated ICA (C) infarct territory in stereotaxic coordinate space. The MCA and ICA/MCA infarct territories have similar topographic distribution compared with the ICA-only infarct territory. The highest probability of infarction in patients with combined ICA and MCA occlusion, isolated MCA occlusion, and isolated ICA occlusion is in the deep/subcortical region, whereas combined ICA and MCA occlusion or isolated MCA occlusion is associated with more extensive territorial infarction. The scales show probability of infarction.
In this study, ACA infarcts were rare despite the ACA originating from the ICA. This was observed in the groups with and without MCA occlusion. Cross-flow from the anterior communicating artery can explain the lower risk of infarction of the ACA territory in patients with isolated ICA occlusion. In patients with ICA and MCA occlusion, the lower risk of ACA infarction may be due to salvage by the leptomeningeal anastomoses from the contralateral ACA and ipsilateral PCA. Some previous investigators have observed infarction of the PCA in the setting of ICA steno-occlusive disease, while others have not. In this study, we did not observe such an occurrence.

Leptomeningeal Collateral System

The different patterns of infarction in this study permit indirect observation of the role of the leptomeningeal or pial collateral circulation. These anastomotic arteries are secondary or tertiary branches of the major arteries and form either end-to-end or branched anastomoses. Because these arteries are small (<1 mm), their existence and functionality have been disputed. The presence of anastomoses among superficial cortical arteries were discovered as early as 1874 by Heubner, but interest in the role of leptomeningeal anastomoses in salvaging the superficial cortical compartment agrees with rat, monkey, and baboon models of temporary ischemia. The indirect evidence of the role of the leptomeningeal collateral circulation in salvaging the superficial cortical compartment suggests that this collateral reserve be investigated further as a potential stroke therapy tool.

METHODOLOGICAL LIMITATIONS

In our initial study on MCA occlusion, we included cases of combined ICA and MCA occlusion, raising the possibility that the MCA-occlusion group in this study was different with respect to infarct pattern. However, despite removing these combined cases from the MCA-occlusion group, the regional risk of infarction in the MCA-occlusion group remained the same. There is a potential for bias, because we excluded patients who did not have magnetic resonance imaging studies. Because this may affect the 3 groups by different degrees, it is possible that our results do not reflect all cases of ICA occlusion and may warrant confirmation in relatively unselected data sets. Furthermore, extraction of clinical outcomes from medical records is prone to bias but appeared to be consistent with differences in infarct volume. Lastly, a larger sample size would have probably confirmed an effect of the MCA-occlusion group on clinical outcome.

In the absence of coexistent MCA occlusion, infarcts resulting from ICA occlusion are less extensive and have a predominantly subcortical distribution. These findings should be confirmed in other data sets before patients with isolated ICA occlusion are considered for inclusion in acute stroke trials.

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Correspondence: Thanh G. Phan, FRACP, PhD, Department of Medicine, Monash University, 246 Clayton Rd, Clayton, Australia (thanh.phan@med.monash.edu.au).
Author Contributions: Study concept and design: Phan, Donnan, and Reutens. Acquisition of data: Phan, Donnan, and Reutens. Analysis and interpretation of data: Phan, Srikanth, Chen, and Reutens. Drafting of the manuscript: Phan, Donnan, Srikanth, Chen, and Reutens. Critical revision of the manuscript for important intellectual content: Phan, Donnan, Srikanth, and Reutens. Statistical analysis: Phan, Srikanth, Chen, and Reutens. Obtained funding: Phan, and Reutens. Administrative, technical, and material support: Phan, Srikanth, and Reutens. Study supervision: Phan, Donnan, and Reutens.
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**Announcement**

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