Surgical Revascularization Reverses Cerebral Cortical Thinning in Patients With Severe Cerebrovascular Steno-Occlusive Disease

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Background and Purpose—Chronic deficiencies in regional blood flow lead to cerebral cortical thinning without evidence of gross tissue loss at the same time as potentially negatively impacting on neurological and cognitive performance. This is most pronounced in patients with severe occlusive cerebrovascular disease in whom affected brain areas exhibit “steal physiology,” a paradoxical reduction of cerebral blood flow in response to a global vasodilatory stimulus intended to increase blood flow. We tested whether surgical brain revascularization that eliminates steal physiology can reverse cortical thinning.

Methods—We identified 29 patients from our database who had undergone brain revascularization with pre- and postoperative studies of cerebrovascular reactivity using blood oxygen(ation) level-dependent MRI and whose preoperative study exhibited steal physiology without MRI-evident structural abnormalities. Cortical thickness in regions corresponding to steal physiology, and where applicable corresponding areas in the normal hemisphere, were measured using Freesurfer software.

Results—At an average of 11 months after surgery, cortical thickness increased in every successfully revascularized hemisphere (n=30). Mean cortical thickness in the revascularized regions increased by 5.1% (from 2.40±0.03 to 2.53±0.03; P<0.0001).

Conclusions—Successful regional revascularization and reversal of steal physiology is followed by restoration of cortical thickness. (Stroke. 2011;42:1631-1637.)

Key Words: brain imaging ▪ cerebrovascular reactivity ▪ dementia ▪ reperfusion ▪ steal phenomenon

Chronic deficiencies in regional cerebral blood flow lead to thinning of the cerebral cortex even without evidence of gross tissue loss on conventional MRI. In such instances, perfusion of brain tissue may be just sufficient to prevent gross ischemia but fails to respond adequately to increases in demand such as those normally occurring during neuronal activation. The integrity of this flow response system can be assessed by measures of cerebrovascular reactivity (CVR), a measure of the change in cerebral blood flow in response to a vasodilatory stimulus. Reductions in CVR can range from a blunted increase in blood flow in response to a stimulus in mild cases, to “paradoxical” reduction in regional blood flow indicating steal physiology, in severe cases.

Patients, in whom neuronal activity is no longer met with a commensurate augmentation of cerebral blood flow, are believed to be at a higher risk of an acute ischemic stroke, even in the absence of acute ischemia. Experimental animal models simulating a state of nonischemic chronic hypoperfusion demonstrate a decline in neuronal structure and viability. In humans, vascular cognitive impairment is associated with the loss of cortical gray matter whereas steno-occlusive disease without stroke has been associated with neurocognitive decline. Looking at it from another perspective, neurodegenerative disorders such as Alzheimer disease and Huntington disease are associated with reduced vascular function. These studies indicate that there may well be a pathophysiological association among vascular impairment, structural changes in the brain, and neurocognitive dysfunction.

Our aim was to study the association between vascular dysfunction in the form of steal phenomenon and cerebral cortical thinning. We hypothesized that the reduction of vascular reserve was etiologically connected to the cortical thinning. We therefore investigated whether restoring CVR by surgical revascularization could arrest or reverse cortical thinning.
Patient CVR database (n=262)

- Surgical revascularization procedure?
  - Yes (n=84)
    - No (n=31)
    - Steal physiology on pre-operative CVR map?
      - Yes (n=53)
        - Normal appearing brain tissue on structural MRI?
          - Yes (n=30)
            - Availability of post-operative CVR map?
              - Yes (n=29)
                - Included (n=29)
              - No (n=1)
                - Excluded (n=233)

Figure 1. Flow chart with selection criteria. CVR indicates cerebrovascular reactivity.

Methods

Subjects
The study was approved by the research ethics board of the University Health Network (REB, UHN). Subjects were identified from a prospectively maintained database of patients who underwent CVR blood oxygenation level-dependent (BOLD) MRI as part of a series of REB-approved studies at the Toronto Western Hospital (n=262). All subjects provided signed informed consent for the CVR study. Selection criteria for this study were (1) patients who had undergone a surgical revascularization procedure (extracranial–intracranial bypass or carotid endarterectomy) performed for reducing stroke risk in the affected hemisphere; (2) the presence of “steal physiology” on the prevascularization CVR map; (3) with normal-appearing brain tissue on structural MRI pre- and postoperatively (small hyperintense T2 foci in the white matter were considered acceptable); (4) availability of postoperative CVR MRI maps. The selection process is described in Figure 1.

Imaging Protocol and Analysis
A customized gas blender with a sequential rebreathing mask (RespirAct; Thornhill Research Inc, Toronto, Canada) was used to apply a precise, repeatable series of vasodilatory stimuli consisting of iso-oxic pseudosquare wave changes in end-tidal CO₂ (PetCO₂) from 40 mm Hg up to 50 mm Hg. The precise repeatability of the target PetCO₂ sequence and consistent MR sequence enabled the direct comparisons of the CVR in a subject over time and the comparison of CVR between subjects. CVR maps were obtained with MRI consisting of BOLD acquisitions with echoplanar imaging gradient echo (TR 2000, TE 30 ms, 3.75×3.75×5 mm voxels). The acquired MRI and PetCO₂ data were analyzed using AFNI software. BOLD images were volume-registered and slice-time corrected and coregistered to an axial 3-dimensional T1-weighted inversion-recovery prepared fast spoiled gradient-echo volume (voxel size 0.86×0.86×1.0 mm) that was acquired at the same time. The acquired PetCO₂ data were time-shifted to the point of maximum correlation with the whole brain average BOLD signal. Next, a linear least-squares fit of the BOLD signal data series to the PetCO₂ data series was performed voxel by voxel. CVR is calculated as the percent change in BOLD signal per mm Hg change in PetCO₂. The correlation was color-coded and superimposed on the corresponding voxel of the anatomic volume to generate a color-coded CVR map. Previous work describes this quantitative technique in more detail.

Cortical Thickness Analysis
Cortical thickness measurements were derived from the acquired anatomic volume data using Freesurfer software (http://surfer.nmr.mgh.harvard.edu/), a method for automated surface reconstruction and accurate cortical thickness measurement. In brief, the software reconstruction of the brain creates an inflated 3-dimensional brain surface image, which facilitates interpretation of functional MRI data across the entire cortical surface after accounting for cortical folding. The generated cortical thickness maps are not restricted to the voxel resolution of the original data, therefore allowing detection of submillimeter differences between examinations. The region of interest (ROI) comprised of cortical regions exhibiting “steal physiology” was indicated by the CVR map overlaid on the inflated preoperative cortical surface (a paradoxically negative BOLD response to hypercapnia depicted in blue on CVR maps in Figures 2A and 2C). All cortical thickness measurements were confined to these ROIs, and the results were automatically generated by the software. To enable comparisons of pre- and postoperative cortical thickness, the ROI was automatically copied onto the postrevascularization cortical surface (Figures 2B and 2D). In cases in which steal physiology was not bilateral, additional cortical thickness comparisons were performed with the nonrevascularized contralateral hemisphere (n=20 hemispheres) by reflecting the ROI encompassing the brain area with “steal physiology” onto the healthy contralateral hemisphere on both the pre- and postrevascularization CVR maps (Figure 2B).

Cortical thickness was measured in each ROI (Tables 1 and 2). An independent sample t-test was used to evaluate significant differences in cortical thickness before and after surgical revascularization. Fisher exact test was used to determine whether the thickness changes were directly related to the successful revascularization or over time. A probability value <0.05 was considered significant.

Results

Patient Demographics
Of the 29 patients (15 female) included in this study, 21 had Moyamoya disease and 8 had other carotid or large intracranial vessel occlusive disease (Table 3). Mean age was 41 years (range, 13 to 66 years). Four of the 29 subjects exhibited continuing “steal physiology” on the postoperative CVR study, indicating that the surgical revascularization was unsuccessful. These 4 patients (2 of whom had bilateral procedures and therefore provided 6 hemispheres) were therefore counted as “sham-operated” controls. Of the 25 patients who showed normalization of CVR (ie, successful
revascularization), 5 patients had bilaterally affected hemispheres and underwent bilateral surgeries for a total of 30 hemispheres with successful revascularization.

**Intervention and Follow-Up Time**

Surgical revascularization was in the form of an extracranial–intracranial bypass for 34 hemispheres and carotid endarterectomy in 2 hemispheres (Table 3). Surgery was successful in eliminating all evidence of “steal physiology” in 30 hemispheres (Figures 2A and 2C). Mean duration between surgery and postoperative CVR study was 11 months (median, 8 months). There was no correlation between follow-up time and cortical thickness changes ($r^2=0.0004$). The mean time between pre- and postoperative CVR studies was 16 months (Table 1).

**Revascularization Increases Cortical Thickness in Brain Areas Exhibiting Steal Physiology**

Analyses of cortical thickness were conducted using methods that corrected for interference from cortical folding (“Methods”). The ROI comprised cortical regions exhibiting “steal physiology” as indicated by the preoperative CVR map (Figures 2A and 2C). All postoperative measurements were made in the same ROI as the preoperative measurement (Figures 2B and 2D). Compared with preoperative values, cortical thickness increased by 5.1% (mean±SEM) from 2.40±0.03 to 2.53±0.03 ($P<0.0001$; Table 1; Figure 3) in the ROI in successfully revascularized hemispheres.

In contrast, in the 6 hemispheres in which revascularization was unsuccessful, as gauged by persistent steal physiology on the postoperative CVR study, there was progression of cortical thinning (mean±SEM) from 2.48±0.04 to 2.37±0.04, ($P<0.03$; Table 1; Figure 3). Thus, successful revascularization improves cortical thickness.

**Changes in Cortical Thickness in Affected Versus the Contralateral, Nonrevascularized Hemisphere**

We compared the cortical thickness in the ROI within the brain areas with steal physiology to the corresponding area in the contralateral, nonrevascularized hemisphere (Figure 2B) to control for the accuracy of the cortical thickness measurements. Cortical thickness in the 20 subjects with unilateral steal physiology showed a mean cortical thickness increase of 1.9% (mean±SEM) 2.44±0.009 to 2.49±0.002 ($P<0.001$; Table 2; Figure 3) in the ROI in nonrevascularized hemispheres.

Unlike in the revascularized hemispheres, which all showed increases in cortical thickness, not every nonrevascularized hemisphere exhibited a thickness increase (Table 2). This may be due to variations in vascular collateral blood flow (eg, incomplete circle of Willis) between patients. A significant thinner cortex was also found when comparing the preoperative cortical thickness between the revascularized hemisphere exhibiting steal physiology versus the nonrevascularized hemisphere ($P<0.05$; Figure 3). There was no significant difference in cortical thickness between the postoperative revascularized hemisphere and nonrevascularized hemisphere ($P=0.65$; Figure 3).

Furthermore, cortical thickness comparison in the 20 subjects with unilateral steal physiology showed a mean cortical thickness increase of 0.13 mm (±0.05) in the revascularized hemispheres versus 0.05 mm (±0.08) in the nonrevascularized, contralateral hemispheres ($P<0.002$).

**Discussion**

To our knowledge, this is the first report of a surgical therapy resulting in a reversal of cortical thinning in patients with steno-occlusive disease. Each of the successfully revascularized hemispheres showed an increase in cortical thickness postrevascularization with a mean cortical thickness increase of 5.1% ($P<0.0001$; Table 1; Figure 3), whereas the 6
unsuccessfully revascularized hemispheres showed progressive cortical thinning of 4.4% \( (P < 0.01) \). Furthermore, the contralateral nonrevascularized hemispheres also exhibited some increases in thickness (1.9%, \( P < 0.001 \); Table 2; Figure 3), although this was smaller and less consistent.

The mechanism of restoration of cortical thickness requires further investigation. Increased cortical density has been described in patients with bipolar disorder treated with lithium, which is attributed to an increased neuropil.22 Certainly, animal studies after acute ischemia confirm that

<table>
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Values are depicted in millimeters (mean ± SD). Note that hemispheres 31 to 36 are the nonsuccessfully revascularized hemispheres. Pre- and postoperative cortical thickness measurements and volume of the region of interest for the successfully revascularized hemispheres (hemispheres 1 to 30) and unsuccessfully revascularized hemispheres (hemispheres 31 to 36).

ROI indicates region of interest; CVR, cerebrovascular reactivity.

*Pre indicates cortical thickness prerevascularization; post, cortical thickness postrevascularization.
†No. of voxels in ROI (voxel volume is 1.33 mm³).
‡Follow-up 1 indicates time between pre revascularization CVR MRI study and postrevascularization CVR MRI study (months).
§Follow-up 2 indicates time between surgical revascularization and postrevascularization CVR MRI study (months).
neuropil can be made to increase after stroke by rehabilitation,23 by strategies that enhance neurogenesis using endogenous or exogenous stem cells24–26 or other mechanisms that may lead to enhanced dendritic arborization or synaptogenesis.27 Although in such studies the ischemia produced acute tissue loss, the proposed mechanisms of restoration might be applicable to brain tissue with the chronic ischemia imposed by impaired vascular reserve and steal physiology, in which cortical thinning occurs more slowly.

If the observed changes in cortical thickness are indeed caused by the loss and gain of neuroglial tissue, these structural changes may have direct consequences on brain function, especially in the pathophysiology of vascular cognitive impairment. Mandell et al28 have demonstrated that in young, healthy subjects (age range, 22 to 42 years), the presence of steal physiology in the deep white matter precisely matches with frequency maps of leukoaraiosis.29 Furthermore, Conklin et al30 have shown an increase in apparent diffusion coefficient in normal-appearing white matter underlying the cortex with steal physiology. Like cortical thinning, leukoaraiosis and elevated apparent diffusion coefficient values in white matter tissue have been associated with vascular cognitive impairment.31,32 The distributions of the cortical changes elucidated in the present studies correspond anatomically to those involved in vascular cognitive impairment. Furthermore, a steno-occlusive etiology causing chronic hypoperfusion has been related to a decline in neurocognitive performance in humans.7,8

Other than loss and gain of neuroglial tissue, other changes could have affected the cortical thickness. One possibility is changes in cortical blood volume. A decrease in cerebral blood volume (CBV) in the brain region with steal physiology could potentially account for reduced cortical blood volume. However, studies have shown that although these brain areas are hypoperfused in the presence of steno-occlusive disease in the feeding vessels, CBV is increased33,34 and should normalize when blood flow is restored. In this case, the expected effect on the pattern thickness change is opposite to that observed in this study and to that in our previous publication1 in which we demonstrated cortical thinning in brain areas despite elevated CBV.

It is also possible that hyperperfusion after revascularization could have generated increased CBV, potentially causing cortical thickening. This too seems unlikely because a poten-

Table 2. Cortical Thickness Changes in Nonrevascularized Hemispheres

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<td>2.36 (0.57)</td>
<td>14 071</td>
<td>−0.01</td>
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<tr>
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<tr>
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<td>20</td>
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<td>2.19 (0.77)</td>
<td>33 615</td>
<td>−0.02</td>
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Values are depicted in millimeters (mean±sd). Pre- and postoperative cortical thickness measurements and volume of the region of interest for the nonrevascularized hemispheres.

ROI indicates region of interest.

*Pre indicates cortical thickness prerevascularization; post, cortical thickness postrevascularization.

†No. of voxels in ROI (voxel volume is 1.33 mm3).

Figure 3. Changes in cortical thickness. Statistically significant differences in cortical thickness: *P<0.05; **P<0.001; ***P<0.0001. This figure shows the pre- vs postoperative changes in cortical thickness for the successfully, nonsuccessfully, and nonrevascularized hemispheres. Horizontal line in the box is median, box is interquartile range (25% to 75%), and the whiskers represent the minimum and maximum values.
tial hyperperfusion syndrome, if present, would occur in the acute setting, whereas our postrevascularization CVR MRI studies were conducted months after the surgical intervention (mean, 11±9.4 months), when such changes could be expected to have subsided. CBV measurements were not performed in our cohort because this parameter is difficult to quantify with MRI without the use of intravenous contrast agents. However, a subanalysis of 6 patients from the Japanese Extracranial–Intracranial Bypass Trial, which suggested progressive loss of brain volume in extracranial–intracranial patients despite revascularization suggested a decrease in CBV. However, the reasons for this were not elucidated. Future work, using other imaging modalities such as positron emission tomography, may provide a more definitive answer to this potentially important issue.

Another possible mechanism accounting for cortical volume loss and recovery is changes in extracellular fluid volume. However, dehydration is known to cause a reduction in brain volume. We are not aware of any studies suggestive of reduced cortical extracellular fluid volume in chronic steno-occlusive disease.

Selective neuronal loss has been observed in the penumbra of acute ischemic stroke. It is plausible that in patients with severe steno-occlusive disorders, a chronic penumbra-like state exists resulting in progressive tissue loss. Whereas reversal of neuronal loss is unlikely, it is conceivable that the “effective volume” of neurons operating in areas of steal physiology shrink in size with decreases in synaptic density and dendritic arborization. Alternatively, there may be a reduction in the numbers or volumes of glial cells. Lastly, the changes in thickness may be due to reversal of myelin loss in the cortex. Our data do not address any of these possibilities.

Conclusions

Our data provide the first evidence that surgical brain revascularization can reverse cerebral cortical thinning. Given the potential for profound implications to neurological and cognitive...
function, these relationships and the mechanisms underlying this phenomenon warrant further study.

Acknowledgments

We thank the Toronto Western Hospital MRI technologists, particularly Eugen Hlasny, David Johnstone, Keith Ta, and Hien Tran, for their contributions to the data acquisition.

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Disclosures

Thornhill Research Inc (TRI) is a for profit spinoff company of the University of Toronto and the University Health Network (UHN) charged with commercializing medical devices developed in these institutions. J.A.F. and D.J.M. participated in the development of the RespirAct and also retain shares in TRI, along with the UHN, according to the intellectual property policies of the institutions.

References

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Abstract 11

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Surgical Revascularization Reverses Cerebral Cortical Thinning in Patients With Severe Cerebrovascular Steno-Occlusive Disease

Jorn Fierstra, MSc; David B. MacLean, BSc; Joseph A. Fisher, MD; Jay S. Han, MSc; Daniel M. Mandell, MD; John Conklin, MSc; Julien Poublanc, MSc; Adrian P. Crawley, PhD; Luca Regli, MD; David J. Mikulis, MD; Michael Tymianski, MD, PhD

(Stroke. 2011;42:1631-1637.)

Key Words: brain imaging ▪ cerebrovascular reactivity ▪ dementia ▪ reperfusion ▪ steal phenomenon

배경과 목적

만성 국소 혈류의 감소는 신경학적 기능 및 인지 기능의 감소를 유도함과 동시에, 전체적인 조직 손상의 증가 없이 대뇌혈관(cerebral cortical) 두께의 감소를 가져올 수 있다. 이것은 중증의 폐쇄성 뇌혈관질환(cerebrovascular disease)을 가진 환자에서 특징적으로 관찰되는데, 이러한 환자들의 뇌에서는 혈류를 증가시키려는 신체의 혈관 확장 신호에 반응하여 뇌혈류가 오히려 감소하는 ‘도료 현상’이 흔히 관찰된다. 저자들은 본 연구에서 도료 현상을 제거하는 수술적 혈관재통방이 대뇌혈관의 감소를 회복시킬 수 있는지에 대하여 연구하였다.

방법

본 연구는 혈관재통방을 받고 재통방 절차로 혈액 상소, 뇌에 기반한 자기공명영상(MRI)을 이용하여 뇌혈관 반응을 측정한 29명의 환자들을 대상으로 하였다. 본 환자들은 저의 구조적 이상 없이 도료 현상이 특징적으로 관찰되었다. 저자들은 도료 현상이 관찰된 영역과 정상 반응의 같은 영역에서 대뇌혈관 두께의 변화를 Freesurfer 소프트웨어를 이용하여 측정하였다.

결과

수술 후 평균 11개월째에 모든 성공적인 혈관재통방 영역에서 대뇌혈관 두께는 증가하였다(n=30). 혈관재통방 영역에서 평균 대뇌혈관 두께는 5.1% (2.40±0.03~2.53±0.03; P<0.0001) 증가하였다.

결론

성공적인 국소 혈관재통방과 도료 현상의 전환은 대뇌혈관 두께의 회복을 유도한다.

Figure 3. Changes in cortical thickness. Statistically significant differences in cortical thickness: ***P<0.05; **P<0.001; ***P<0.0001. This figure shows the pre-versus postoperative changes in cortical thickness for the successfully, nonsuccessfully, and nonrevascularized hemispheres. Horizontal line in the box is median, box is interquartile range (25% to 75%), and the whiskers represent the minimum and maximum values.