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LETTER TO THE EDITOR

A comment on "Contralateral cerebral hemodynamic changes after unilateral direct revascularization in patients with moyamoya disease"

Giuseppe Esposito · Jorn Fierstra · Annick Kronenburg · Luca Regli

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Sir

We read with great interest the article by Ma et al. [8] that was recently published in your journal. The authors focus the attention on contralateral hemodynamic changes after unilateral bypass surgery in patients with moyamoya disease (MMD); a feature that has been little analyzed but of particular interest given the complex cerebral hemodynamics resulting from MMD. As the authors' findings contradict with other work done on this topic, we would like to provide some comments on this study and highlight some recent literature.

Ma et al. reported their experience in the hemodynamic evaluation of contralateral (nonoperated and asymptomatic) hemispheres in 15 MMD patients who received one-sided direct bypass revascularization of the symptomatic hemisphere. Pre- and postoperative brain hemodynamic evaluations were performed by acetazolamide-enhanced Xenon-computed tomography. Cerebral revascularization consisted of double superficial temporal artery (STA) to middle cerebral artery bypass surgery (using both the frontal and the parietal branch of the STA). Postoperative digital subtraction angiography was used to confirm bypass patency, and postoperative hemodynamic studies were performed at 1, 3, and 6 months after surgery for evaluation of regional cerebral blood flow (rCBF) and cerebrovascular reserve (CVR). Among the 15 symptomatic (operated) hemispheres, all exhibited preoperatively impaired CVR, 14 hemispheres demonstrated decreased rCBF. Twelve patients presented with minor ischemic symptoms (transient ischemic attacks, TIAs) while 3 patients presented with a stroke. Each of the 15 nonoperated contralateral hemispheres showed good rCBF whereas 6 hemispheres exhibited impaired CVR. The preoperative rCBF and CVR in the operated hemispheres was much lower than the contralateral side (32.8±5.5 ml 100 g^{-1} min^{-1} versus 50.4±8.4 ml 100 g^{-1} min^{-1}; $P<0.001$, and 6.1±13.2% versus 31.7±9.0% respectively; $P<0.001$). Revascularization was successful in all hemispheres, with no new signs of ischemia and significant improvement of rCBF and CVR at 1-month follow-up. However, 3 months postoperatively, CVR of the contralateral hemispheres decreased significantly (25.8±8.1%; $P=0.003$) and at 6-month follow-up, the rCBF in the contralateral hemispheres showed a downward trend (47.4±8.0 ml 100 g^{-1} min^{-1}; $P=0.05$). At this time point, three patients had markedly decreased rCBF and impaired CVR in the non-treated hemisphere. Among them, two became symptomatic (TIAs) but already showed impaired CVR in the non-treated hemisphere preoperatively, while the other with normal CVR of the contralateral side preoperatively did not develop symptoms. Thus, the authors concluded that unilateral direct revascularization of the symptomatic hemisphere for MMD patients could lead to CVR impairment in the primarily asymptomatic contralateral hemisphere.

We believe that this conclusion may not be fully supported by the results. To begin with, the study design appears to be somewhat flawed since follow-up hemodynamic evaluation is reported inconsistently. For example, 1 month after surgery, only rCBF and CVR data from the operated hemispheres are shown. As for the contralateral

G. Esposito · J. Fierstra · A. Kronenburg · L. Regli
Department of Neurosurgery,
Rudolf Magnus Institute of Neuroscience,
University Medical Center Utrecht,
Heidelberglaan 100, Postbus 85500,
3508 GA Utrecht, The Netherlands

G. Esposito (✉)
Institute of Neurosurgery,
Catholic University School of Medicine,
Largo A. Gemelli, 8,
00168 Rome, Italy
e-mail: esposito_giu@libero.it

hemodynamics—the data of interest for this study—only CVR data are reported at 3-month follow-up and only rCBF findings at 6-month follow-up which makes it hard to objectively identify differences in perfusion over time as well as between treated and non-treated hemispheres. Unfortunately, we have to disagree with the authors in their conclusion that progression of MMD cannot explain the postoperative contralateral hemodynamic worsening. The authors stated that progression of MMD in adults occurs slowly. For this they quoted a recent study reporting that MMD progression occurred in nearly 20% of patients during a mean follow-up period of 6 years [7]. Both in our practice and in the literature [4, 10–12], patients can experience disease progression more acutely (months), and generally MMD patients present with bilateral symptoms [2, 11, 12]. The fact that all patients in this case series exhibited unilateral symptoms might be related to sample size or the fact that patient selection was not randomized. Progression of the disease may very well have been responsible for their observations but cannot be confirmed since no angiography-based follow-up was done. Furthermore, both the hemodynamic trend of operated and nonoperated hemispheres should have been reported in order to completely evaluate hemodynamic and clinical progression of the disease. The authors also considered the possibility that after unilateral direct bypass revascularization, the increased blood flow through the anastomosis could have caused hemodynamic stress with subsequent impaired compensation from other collateral circulation (for example from the posterior circulation including the leptomeningeal collaterals from bilateral posterior cerebral arteries that is known to play a role in supplying the ischemic MMD parenchyma). They concluded that after successful bypass surgery, reduced compensation from the posterior circulation could have caused a decrease in collateral blood supply that may have contributed to the compromised hemodynamics of the contralateral side. To underline this, they reported a case that presented with decreased bilateral leptomeningeal collaterals from the posterior circulation 6 months after unilateral direct revascularization. Although the contralateral (nonoperated) hemisphere may provide collateral flow to the hemodynamically compromised hemisphere, it is likely that the preserved autoregulation in this hemisphere (nonoperated) will ensure enough perfusion despite the support to the compromised side. After restoration of blood flow in the compromised hemisphere by bypass surgery, this collateral support may indeed become obsolete but should not lead to a decrease in blood flow supply to the contralateral (nonoperated) hemisphere. In fact, more blood flow to the brain should actually have a beneficial effect on contralateral hemodynamics.

Recent literature shows such a contralateral hemodynamic benefit. For example, a review by Bacigaluppi et al. [1] on neurovascular imaging in diagnosis, preoperative assessment, and follow-up of MMD, frequently observed contralateral hemodynamic improvement after unilateral direct bypass revascularization procedures, as shown by improved CVR on quantitative MR imaging postoperatively. More so, another report from the same group, in collaboration with our institution, has shown that successful surgical revascularization can restore cortical thickness in patients with MMD [3]. These structural changes, albeit less consistent, were also observed in the non-treated contralateral hemispheres. Even perfusion studies in MMD patients, not necessarily focusing on contralateral hemodynamics, showed a positive effect in the non-treated hemisphere after unilateral bypass revascularization [5, 6, 9]. A recent study by Ideguchi et al. [5] reporting about the presence of ivy signs on MR imaging to gauge success of revascularization surgery in MMD patients demonstrated improved hemodynamics in the nonoperated contralateral hemisphere as measured with SPECT (Fig. 2 in the paper).

It is evident that after unilateral bypass surgery, postoperative cerebral hemodynamic changes may be expected in both treated and untreated hemisphere. Although Ma et al. did not observe a contralateral hemodynamic benefit from unilateral bypass revascularization, conflicting with recent the literature, we would like to underline the fact that these incongruities may be explained by the complexity of cerebral hemodynamic rearrangement occurring after bypass revascularization in MMD patients and our difficulty in understanding these phenomena.

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Comments

Yan Ma, Meng Li, Li Q Jiao, Hong Q Zhang, Feng Ling, Beijing, China

Moyamoya disease (MMD) is a typical model of chronic cerebral ischemia. Accompanied with the progressive stenosis and occlusion of internal carotid artery (ICA) terminal segment, the formation of collateral networks reveals the specificity of the cranial–cerebral vascular architecture.

In 1986, Matsushima and Inaba [5] described the cerebral collateral systems in detail especially for MMD. They divided the collaterals into six systems. Generally, the "moyamoya vessels" are perforating arteries from the base of the brain (A system) which may anastomose with others from the surface of the brain at the external angle of the lateral ventricle. The cortical leptomeningeal anastomoses (C system) on the surface of brain show extreme individual variations and are correlated with various symptoms in MMD patients. Although the collaterals of the external carotid system including the anastomoses from the dura mater, pericranial muscles, and scalp (C and E system) were believed to have more collateral capacities than in the internal carotid system, the development of the collateral circulation depends on time. Due to the specific anatomic barrier around the brain, intracranial collateral anastomoses are developed firstly. These principles are also the theoretical fundament of direct and indirect surgical treatment for MMD.

Ischemic symptoms are the most common in symptomatic MMD patients either in Asia or in Western countries [1, 6, 9]. But there are almost no articles referring to the lateralization of initial symptoms in MMD patients. By definition, both cerebral hemispheres are involved in MMD. However, the severity can differ between sides [11]. The symptoms and signs can be attributed to change in flow resulting from stenosis and occlusion of ICA [8], which includes the development of collateral circulation and hemodynamic status. In our study, the symptomatic hemisphere was characterized by a more severely compromised reserve capacity, so the unilateral ischemic symptoms were plausible.

Esposito et al. tried to use progression of MMD to explain the postoperative contralateral hemodynamic worsening. But this cannot be confirmed by us because it was only based on their own practice and several case reports. In fact, MMD is more stable in adult than in childhood [10], and the progression is slow and takes several years [7]. Kuroda et al. observed 120 Japanese adult patients and found a progression in 15 of 120 individuals over a 15-year follow-up period [4].

Hemodynamic changes after revascularization for MMD may induce the decrease or disappearance of moyamoya vessels from the posterior circulation. Matsushima and Inaba [5] performed EDAS for MMD patients. Six months later, the moyamoya vessels at the base of the brain began to decrease. Huang et al. [3] observed that progression of the steno-occlusive disease in the posterior cerebral artery occurred in approximately half of the MMD patients that underwent revascularization therapy within a short mean time of 18 months. One explanation for this may be that MMD patients are protected hemodynamically against changes in the anterior circulation by their bypasses, but these remain insufficient to supply the posterior vascular territories in the absence of adequate collateralization from the posterior circulation.

The non-randomized design and the small sample size are the limitations of our study. MMD involving both hemispheres are a clinical entity of unknown etiology. The purpose of our article was to direct the attention toward an asymptomatic hemisphere of MMD. Although many articles are available that reported good results after revascularization for MMD as Esposito et al. mentioned, the surgical treatment is still controversial [7–9]. Randomized controlled multicenter clinical trials will be necessary to evaluate the safety and efficacy of revascularization surgery for MMD patients.

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