Acta Neurochirurgica Printed in Austria

# Clinical Article Cerebral blood oxygenation changes induced by bypass blood flow in moyamoya disease and non-moyamoya cerebral ischaemic disease

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Received June 26, 2005; accepted December 6, 2005; published online February 9, 2006 © Springer-Verlag 2006

## Summary

*Background.* Superficial temporal artery–middle cerebral artery (STA–MCA) anastomosis has been used to prevent stroke in patients with moyamoya disease (MD) and non-moyamoya ischaemic disease (non-MD). However, little is yet known regarding the difference between these groups of patients in the extent to which the bypass contributes to maintaining adequate cerebral blood oxygenation (CBO), or the temporal changes after surgery. In the present study, we evaluated the CBO changes induced by bypass blood flow in patients with MD and non-MD during the peri-operative periods employing optical spectroscopy.

Methods. We investigated 13 patients who underwent STA-MCA anastomosis, including 5 MD and 8 non-MD patients. We evaluated the effects of STA blood flow on the CBO in the MCA territory on the anastomosis side, employing visual light spectroscopy during surgery and near infrared spectroscopy (NIRS) at one week after surgery.

Findings. In 4 MD patients and one non-MD patient, the STA blood flow increased the oxyhaemoglobin and cortical oxygen saturation (CoSO<sub>2</sub>), indicating that the bypass supplied blood flow to the ischaemic brain; the CBO changes were observed more frequently in MD than in non-MD patients (p < 0.02). The pre-anastomosis CoSO<sub>2</sub> (65.4 ± 5.4%) in MD was significantly lower than that (72.8 ± 7.6%) in non-MD (p < 0.05). Postoperative NIRS demonstrated that the bypass began to supply blood flow to the brain in 5 non-MD patients whose bypass did not supply blood flow during surgery.

*Conclusions.* Although MD has vessels of small diameter as compared to non-MD, the bypass begins to supply blood flow to the ischaemic brain earlier in MD than in non-MD after anastomosis. The fact that the  $CoSO_2$  in MD was lower than that in non-MD suggested that the perfusion pressure in MD was lower than that in non-MD, and this might account for the difference in the bypass blood supply after anastomosis between MD and non-MD. Our data suggest that, even if the bypass does not supply blood to the brain during surgery in non-MD, the bypass blood flow gradually increases after surgery.

*Keywords:* EC–IC bypass; cerebral ischaemia; moyamoya disease; near infrared spectroscopy; visible light spectroscopy.

# Introduction

Moyamoya disease is a rare occlusive cerebrovascular disease characterized by progressive stenosis of the terminal portions of the internal carotid arteries on both sides (ICAs), which is followed by the development of abnormal vascular networks in the basal ganglia and other cerebral regions. [26] EC-IC (extracranial-intracranial) bypass such as superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis has become a standard surgical therapeutic option in moyamoya disease to prevent recurrent ischaemic events [14, 20, 24]. In addition, EC-IC bypass surgery has been performed to prevent stroke in patients with transient ischaemic attacks (TIA) caused by haemodynamic compromise [2, 8, 23, 27]. Indeed, neuroradiological studies have demonstrated beneficial effects of bypass surgery on cerebral haemodynamic status in both moyamoya disease [14, 20] and non-moyamoya ischaemic diseases [2, 8, 23, 27]. However, little is yet known regarding the difference in bypass function and its temporal changes after surgery between these patients.

Near infrared spectroscopy (NIRS), an optical technique, allows non-invasive monitoring of the cerebral blood oxygenation (CBO) changes caused by haemodynamic alterations [1, 11, 13, 17, 21]; NIRS measures concentration changes of oxyhaemoglobin ( $O_2Hb$ ), deoxyhaemoglobin (HHb) and total haemoglobin ( $=O_2Hb +$ HHb; tHb) in the cerebral vessels by means of the absorption spectra of haemoglobin in the near infrared range [13]. Employing NIRS, we have evaluated postoperative bypass function in patients with non-moyamoya ischaemic disease by measuring the CBO changes in the MCA territory caused by compression of the anastomosed STA; when decreases in O<sub>2</sub>Hb and tHb were observed, the bypass was considered to function because decreases in O<sub>2</sub>Hb and tHb indicate cerebral ischaemic changes [17, 21]. We have shown that the bypass came to function gradually within one year in many patients. However, the bypass function during the peri-operative periods as well as the differences between moyamoya disease and non-moyamoya ischaemic disease remain to be elucidated; there may be differences in bypass function between these patients because the brain in moyamoya disease suffers from ischaemia over a long period and has smaller cortical branches as compared to those of nonmoyamoya ischaemic disease [16].

To address these issues, we evaluated the CBO changes induced by bypass blood flow during the perioperative periods of STA-MCA anastomosis employing optical spectroscopy. We used NIRS to evaluate the postoperative bypass function. It is difficult, however, to monitor CBO changes continuously during craniotomy by NIRS, because NIR light from the surgical microscope migrates into the NIRS detector through the brain tissue leading to interference with its measurements. In contrast, visible light spectroscopy (VLS), which measures CBO changes by means of the absorption spectra of haemoglobin in the visible light range [6, 15], is more suitable for intra-operative monitoring than is NIRS, because visible light can easily be shaded during surgery. We therefore employed VLS for intraoperative monitoring of the CBO changes induced by the bypass blood flow. These CBO changes were compared in patients with moyamoya disease and non-moyamoya ischaemic disease.

## Patients and methods

### Patients

We investigated 13 patients undergoing craniotomy for STA-MCA anastomosis during the period from June 2003 to November 2004. The subjects included 5 patients with moyamoya disease (mean age [mean  $\pm$  SD], 21.8  $\pm$  8.6 years) and 8 with non-moyamoya ischaemic disease (58.1  $\pm$  11.7 years) including 4 patients with occlusion of the ICA and 4 patients with occlusion of the MCA. The mean age of the moyamoya disease patients was significantly lower than that of the non-moyamoya disease patients (p < 0.001). In the moyamoya disease patients, cerebral angiography revealed stage 3 in 2 patients, stage 4 in 2 patients and stage 5 in one patient according to the angiographical staging of moyamoya disease [26]. All moyamoya disease patients had suffered multiple episodes of TIA's, while MRI did not demonstrate cerebral infarction in these patients. There were no significant differences in the physiological parameters during surgery between patients with moyamoya disease and non-moyamoya ischaemic disease (p>0.05). Table 1 summarizes the patient profiles and physiological parameters during surgery. MR angiography performed one week after surgery revealed patency of the anastomosed STA in all subjects studied. The present study was approved by the Committee for Clinical Trials and Research on Humans. The ethical committee of our university hospital approved the protocol of the study.

In all patients, employing SPECT (PRISM 2000XP, Shimadzu Co., Japan), we measured the regional cerebral blood flow (rCBF) at rest and at 10 min after intravenous injection of acetazolamide (1.0 g). To evaluate the regional haemodynamics, regions of interest were designated in the cortical territory of the MCA. SPECT demonstrated a reduced rCBF at rest ( $\leq$ 30 ml/100 g/min) and reactivity to acetazolamide (%CVR  $\leq$ 10%) before surgery in all of the moyamoya disease and non-moyamoya ischaemic disease patients.

## VLS system

We employed the intra-operative VLS monitoring system which we developed recently. The system was as described by us in a previous

	Case no.	Age (y)/ sex	Clinical type of stroke	Cause of stroke	BP (mmHg)	BT (°C)	HR (bpm)	PaO <sub>2</sub> /PaCO <sub>2</sub> (mmHg)	Hb (g/dl)/ Ht (%)	SO <sub>2</sub> (%)
MD	1	35/m	TIA	MD	148/92	34.4	58	216.3/35.8	14.2/41.7	100
	2	23/m	TIA	MD	148/62	34.3	65	241.6/38.7	13.0/39.4	100
	3	14/f	TIA	MD	125/70	34.5	73	213.5/41.9	13.2/38.4	100
	4	14/f	TIA	MD	120/65	35.1	58	293.0/38.0	12.4/36.4	100
	5	23/f	TIA	MD	145/80	35.5	65	250.6/40.9	13.2/38.5	100
Non-MD	1	45/m	Other	ICA-O	135/84	34.4	63	314.0/42.0	14.1/41.4	100
	2	71/m	AE	ICA-O	143/80	35.0	65	170.5/38.0	13.5/40.5	100
	3	74/m	AE	ICA-O	150/65	34.5	75	182.9/42.2	13.4/39.1	100
	4	48/m	TIA	ICA-O	130/65	35.7	85	134.6/37.6	12.8/37.6	100
	5	49/f	BI	MCA-O	130/75	35.7	69	213.1/36.0	10.7/31.8	100
	6	61/m	AE	MCA-O	165/80	35.0	58	244.2/37.0	13.4/39.4	100
	7	49/f	TIA	MCA-O	130/80	35.0	75	125.2/42.6	12.6/37.6	100
	8	68/m	Other	ICA-O	130/60	36.0	55	151.4/40.1	10.4/32.2	100

 Table 1. Individual patient profiles and intra-operative physiological parameters

*MD* Moyamoya disease; *Non-MD* non-moyamoya ischaemic disease; *TIA* transient ischaemic attack; *AE* artery to artery embolism; *BI* border zone infarct; *Other* lacunar infarct or branched atheromatous disease; *ICA-O* internal carotid artery occlusion; *MCA-O* middle cerebral artery occlusion.





report [12]. Figure 1a gives a block diagram of the system. Briefly, the VLS measures the changes of O<sub>2</sub>Hb and HHb concentration in the cerebral vessels by means of the characteristic absorption spectra of haemoglobin in the visible light range. White light from the LED was directed at the tissue through a fiber optic bundle, and the reflected light was transmitted to a cooled charge-coupled device spectrometer. The relative concentration changes in O<sub>2</sub>Hb and HHb were calculated by least square error curve-fitting based on the differential spectrum; the analysed wavelength range was 520-580 nm. The ratio of O<sub>2</sub>Hb/[O<sub>2</sub>Hb + HHb] indicates the cortical oxygen saturation (CoSO<sub>2</sub>). The sampling rate was 0.5 sec. A strong correlation was noted between the SO<sub>2</sub> values measured with the VLS system and a blood gas analyser (Fig. 1b).

## Intra-operative monitoring of CBO changes by VLS

The parietal branch of the STA was anastomosed end-to-side to the  $M_4$  portion of the MCA. In moyamoya disease patients, encephalo-myosynangiosis was performed after the STA–MCA anastomosis. The physiological parameters during surgery were within the normal ranges in all patients; there were no significant differences in physiological parameters between the moyamoya disease and non-moyamoya disease groups (Table 1). In order to measure the CBO changes in the MCA territory on the side of anastomosis, the recording probe (outer diameter, 7 mm; distance between the emitter and receiver fiber bundles, 1.5 mm) was placed under the subdural space, 15 to 20 mm distal to the part of the  $M_4$  portion where the STA was anastomosed (Fig. 1c). We then repeated clamping and declamping of the STA to evaluate the effects of STA blood flow on the CBO; the MCA was declamped during this test.

Fig. 1. (a) Block diagram of the VLS system. *C-CCD* Cooled charge-coupled device. (b) Relation between oxygen saturation measured with the VLS system (ordinate) and with a blood gas analyser (abscissa). (c) Recording setting during surgery. The probe was placed under the subdural space, at a position 15 to 20 mm distal to the part of the  $M_4$  portion where the STA was astomosed

#### Postoperative evaluation of bypass function by NIRS

In 6 of the non-moyamoya disease patients, employing NIRS, we evaluated the bypass function at one week after surgery. The method of NIRS measurement was as described by us previously [17, 21]. To evaluate the bypass function, digital compression was applied to the STA at the pre-auricular region for 30-100 sec during the NIRS measurement. When decreases of O<sub>2</sub>Hb and tHb were observed, the bypass was considered to supply blood flow to the MCA territory because decreases in O<sub>2</sub>Hb and tHb indicate cerebral ischaemic changes. None of the patients revealed damage to the STA or neurological symptoms during and after the STA compression.

#### Data analysis

In order to evaluate the effects of the STA blood flow on the MCA territory on the lesion side, we compared the VLS parameters during a 5-sec control period with those observed during declamping of the STA for a 5-sec period. For evaluation of the bypass function, we compared the NIRS parameters during a 5-sec period before STA compression with those during STA compression for a 5-sec period in which maximum changes were observed. When a difference was detected at p < 0.01 by the paired t-test, the changes occurring in these parameters were considered to be significant. In addition, we compared the VLS parameters, pre-operative rCBF and STA blood flow between the moyamoya disease and non-moyamoya disease groups employing the Mann Whitney U-test. Differences in the frequency of CBO changes induced by the STA blood flow between the moyamoya disease groups were analysed by Fisher's exact test.

## Results

In 4 out of the 5 moyamoya disease patients, declamping of the anastomosed STA caused significant increases of  $O_2Hb$  and  $CoSO_2$  and a decrease of HHb during surgery. Associated with these changes, tHb underwent a significantly increase, but the degree of tHb increase was



Fig. 2. Examples of changes in Hb concentrations (a) and  $CoSO_2$  (b) caused by declamping and clamping of the STA during surgery. The ordinates indicate the concentration changes of O<sub>2</sub>Hb, HHb, and tHb in arbitrary units (a) and the cortical oxygen saturation in % (b). The horizontal thick bars indicate the periods of declamping of the STA. Data are expressed as means  $\pm$  SD for every 5 sec (10 samples). \*p<0.01. Note that the increase of tHb was much smaller than those of O<sub>2</sub>Hb and CoSO<sub>2</sub> during declamping of the STA



Fig. 3. (a) Difference in number of cases showing increases of  $CoSO_2$  by STA blood flow during surgery between the moyamoya disease (*MD*) and non-moyamoya ischaemic disease (*non-MD*) groups. An increased CoBF was observed more frequently in MD than in non-MD (p < 0.02). (b) Comparison of the pre-anastomosis  $CoSO_2$  between MD and non-MD patients. The ordinate represents the cortical oxygen saturation in %. The pre-anastomosis  $CoSO_2$  in the MD patients was significantly lower than that in the non-MD patients (p < 0.05)



Fig. 4. Comparison of CBO changes induced by STA blood flow evaluated by intra-operative VLS and postoperative NIRS in a non-moyamoya ischaemic disease patient. The ordinates indicate the concentration changes of  $O_2$ Hb, HHb, and tHb in arbitrary units (a.u.). The horizontal thick bars indicate the periods of declamping of the STA during surgery (a) and compression of the STA after surgery (b). Data are expressed as means  $\pm$  SD for every 5 sec (10 samples); the SD is not shown in A due to its small value. \*p < 0.01. Note that the intra-operative VLS revealed no changes in CBO during declamping of the STA (a); however, at one week after surgery, NIRS demonstrated ischaemic changes (i.e. decreases of  $O_2$ Hb and tHb) during compression of the STA (b), indicating that the anastomosed STA had begun to supply blood flow to the MCA territory on the lesion side

much smaller than that of the O<sub>2</sub>Hb increase (Fig. 2). In contrast, only one non-moyamoya disease patient exhibited such CBO changes after declamping of the STA; the other 7 non-moyamoya disease patients failed to demonstrate significant changes in CBO after declamping. There was a significant difference in the frequency of CBO changes induced by STA blood flow between the moyamoya disease and non-moyamoya disease groups (p < 0.02) (Fig. 3a).

The CoSO<sub>2</sub> before anastomosis in the moyamoya disease group (65.4  $\pm$  5.4%) was significantly lower than that in the non-moyamoya disease group (72.8  $\pm$  7.6%, p<0.05) (Fig. 3b). However, there were no significant differences in the pre-operative rCBF measured by SPECT, %CVR or STA blood flow between these groups (p>0.05).

At one week after surgery, in 6 out of the 8 nonmoyamoya disease patients, NIRS revealed that transient compression of the anastomosed STA caused decreases of  $O_2Hb$  and tHb in the MCA territory on the side of the STA–MCA anastomosis, indicating that the STA supplied blood flow to the MCA territory. It should be noted that 5 out of these 6 patients did not exhibit increases in  $O_2Hb$  and  $CoSO_2$  after declamping of the STA during surgery (Fig. 4).

## Discussion

Monitoring of the haemodynamic changes during the peri-operative periods of bypass surgery is particularly important because most of the surgical complications such as ischaemia or hyperperfusion occur during surgery or immediately after surgery [7, 9, 10, 18, 28]. In the present study, in order to understand the mechanism of cerebral ischaemia and hyperperfusion during bypass surgery, we evaluated the dynamic changes of the CBO induced by bypass blood flow during the peri-operative periods employing VLS and NIRS. In addition, we compared the CBO changes between patients with moyamoya disease and non-moyamoya cerebral ischaemic disease.

The VLS system demonstrated that STA blood flow increased the  $O_2Hb$  and  $CoSO_2$  in 4 patients with moyamoya disease and one patient with non-moyamoya disease. Concentration changes in  $O_2Hb$  correlate to changes in rCBF under conditions of constant haematocrit [5, 11]. In addition, we have observed significant positive correlations between the  $O_2Hb$  and  $CoSO_2$  measured by VLS and the cortical blood flow (CoBF) measured by laser-Doppler flowmetry in a rat cerebral ischaemia model [12]. Such CBO changes indicate therefore that the STA blood flow increased the CoBF in the MCA territory on the lesion side. These observations are consistent with a previously reported study which employed a thermal diffusion method [4]. It should be noted, however, that the increase in tHb caused by the STA blood flow was much smaller than that in  $O_2$ Hb, suggesting that the STA blood flow increased the CoBF through small dilatation or recruitment of cortical vessels during surgery.

Interestingly, an increase of CoBF by the STA blood flow was observed more frequently in patients with moyamoya disease than in those with non-moyamoya ischaemic disease. This finding contradicts our expectation that the STA blood supply during surgery may be less in moyamoya disease than in non-moyamoya disease due to the small and fragile cortical branches of the MCA in moyamoya disease [16]. It should be noted, however, that several studies have described the occurrence of hyperperfusion syndrome in patients with moyamoya disease following STA–MCA anastomosis [7, 18, 28]; hyperperfusion syndrome tends to occur after carotid endarterectomy [3, 19] or high flow bypass [25] rather than low flow bypass such as STA–MCA anastomosis.

The detailed physiological mechanisms underlying the differences remain unclear; nevertheless, the following factors should be taken into account. Firstly, the STA blood flow needs to be considered. Intraoperative measurements of the STA blood flow, however, showed no significant difference between the two groups. Secondly, a lower vascular resistance of the recipient vessels could cause a greater STA blood supply. The difference in age between the two groups might influence the vascular resistance; an ultrasound study demonstrated that the flow velocity of the extracranial carotid and vertebral arteries decreased with increasing age [22]. Thirdly, perfusion pressure may play a role in the STA blood supply to the ischaemic lesion. In the present study, VLS revealed a lower  $CoSO_2$  before anastomosis in the moyamoya group than that in the non-moyamoya group, suggesting a lower perfusion pressure and greater pressure gradient between the cortical artery and the STA in the moyamoya group. The greater pressure gradient may result in greater blood supply from the STA to the ischaemic brain. Indeed, it was reported that low rCBF induced hyperperfusion syndrome after surgery [29]. The present findings are consistent with our NIRS study on postoperative bypass function, which indicated that the bypass came to function in cases with a lower rCBF measured by SPECT [17]. In the present study, however, pre-operative SPECT failed to demonstrate significant differences in rCBF between the patients with moyamoya disease and those with non-moyamoya disease in these areas, although the rCBF on the lesion side was low compared with that in the normal hemisphere in both groups. This discrepancy may be related to the differences in sensitivity and measurement volumes between VLS and SPECT. Further studies are needed to clarify the physiological mechanism that underlies the difference in bypass blood supply between moyamoya disease and non-moyamoya ischaemic diseases.

We employed NIRS to evaluate the bypass function following surgery by measuring the CBO changes in the MCA territory on the lesion side during compression of the STA; when ischaemic changes (i.e. decreases of O<sub>2</sub>Hb and tHb) were observed during the STA compression, the bypass was considered to supply blood flow to the ischaemic region [17, 21]. Although NIRS measures CBO changes in both the intracranial and extracranial tissues [1], the changes in NIRS parameters observed during the STA compression reflected mostly changes in CBO, since the STA was removed from the skin and anastomosed to the MCA [17]; the STA thus supplied blood flow to the brain rather the skin. The postoperative NIRS measurements demonstrated ischaemic changes during the STA compression in 6 out of 8 non-moyamoya patients, indicating that the STA supplied blood flow to the MCA territory. Interestingly, 5 out of these 6 patients did not exhibit an increase in CoBF with STA blood flow during surgery. It seems unlikely that the STA was occluded during surgery but became patent shortly after surgery in these cases. We suggest that the STA blood flow was not sufficiently high to increase the CoBF during surgery but there was a gradual increase after surgery in these patients. Our NIRS study on postoperative bypass function demonstrated similar increases of the STA blood flow during one year after surgery [17]. Finally, it should be emphasised that optical spectroscopy provides a useful diagnostic technique for evaluating the function of the EC-IC bypass.

## Acknowledgments

This work was supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Sciences and Technology of Japan (A12307029, A15209047, C15591553, and Industry-University Cooperation Promotion Center Grants 2003) and by Hamamatsu Photonics K.K. (Hamamatsu, Japan).

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## Comments

This is an interesting report about cerebral blood oxygenation CBO changes at the time of EC–IC bypass surgery measured by optical spectrometry and near infrared spectrometry: Blood supply gained by bypass surgery is earlier in Moyamoya disease MD than in non Moyamoya disease non MD. They conclude that this might be due to low perfusion pressure in MD and that these findings might be useful to understand the mechanism of surgical complication of ischaemia or hyperperfusion.

Y. Yonekawa Zurich

The authors should be congratulated in their effort to examine and test the method of optical spectroscopy for testing the efficacy of bypass function during and after surgery. The relevance of this study has to be commended.

> Nadia Khan Zurich

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