



Neurological Research A Journal of Progress in Neurosurgery, Neurology and Neurosciences

ISSN: 0161-6412 (Print) 1743-1328 (Online) Journal homepage: http://www.tandfonline.com/loi/yner20

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To cite this article: Aminadav Mendelowitsch, Laligam Sekhar, Rogerio Clemente & Ashfaq Shuaib (1997) EC-IC bypass improves chronic ischemia in a patient with moyamoya disease secondary to sickle cell disease: An in vivo microdialysis study, Neurological Research, 19:1, 66-70, DOI: 10.1080/01616412.1997.11740774

To link to this article: https://doi.org/10.1080/01616412.1997.11740774



Published online: 20 Jul 2016.

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EC-IC bypass improves chronic ischemia in a patient with moyamoya disease secondary to sickle cell disease: An *in vivo* microdialysis study

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Patients with sickle cell disease may develop intracranial vascular disease, with the occlusion or obstruction of the large or small arteries, which may lead to the secondary development of moyamoya disease. In this report, we describe the neurochemical changes in the brain before, during, and after an extracranial–intracranial bypass procedure on a patient with sickle cell disease and a moyamoya disease like pattern on angiography. We used the in vivo microdialysis technique to measure the on-line pH, lactate and amino acid concentrations in the extracellular fluid. There were relatively high resting glutamate levels and a lower-than-normal pH in the extracellular fluid prior to the bypass, associated with chronic ischemia. During the bypass there was a short-lived increase in the glutamate levels. After revascularization, there was a rapid decrease in the glutamate levels and an increase in the pH value. The patient's preoperative neurological deficit improved post-operatively, corresponding to the biochemical changes towards normal values. These changes after revascularization suggest that chronic biochemical abnormalities due to brain ischemia may improve after cerebral revascularization. [Neurol Res 1997; **19**: 66–70]

Keywords: Moyamoya; chronic ischemia; microdialysis; glutamate; lactate; on-line pH

INTRODUCTION

Sickle cell disease (SCD) is due to the inheritance of a gene for a structurally abnormal sub-unit (β 2) of hemaglobin. Patients with this gene have a molecular substitution of valine for glutaminic acid at position number six of the β chain, which leads to hypoxia and deoxyhemaglobin S polymerization. The abnormal intracellular HbS polymer changes the red blood cells from biconcave disks to 'sickle shaped' cells. The sickled cells sludge inside blood vessels, leading to organ damage (due to chronic ischemia), chronic hemolytic anemia, acute vaso-occlusive crises, and the resulting clinical manifestations of the disease¹.

The most serious consequences of SCD are the deleterious effects on the central nervous system caused by cerebral infarction (about 80%) or intracranial hemorrhage. The principal clinical presentation in patients with the disease is hemiparesis². Abnormalities in both the large and small vessels and their territories may also occur. Physicians diagnose the central nervous system manifestations of sickle cell anemia based on the

clinical picture and either computed tomography (CT) or magnetic resonance imaging (MRI). In addition, cerebral angiography shows abnormalities in approximately 30% of these patients. The angiographic appearance of SCD is similar to that of moyamoya disease; namely, spontaneous occlusion in the arteries of the circle of Willis and the subsequent development of a collateral circulation involving the lenticulostriate perforating vessels, presumably due to chronic ischemia^{2–4}. Several procedures can be performed to improve the cerebral circulation of patients with compromised blood flow^{5–9}. One such procedure is an extracranial–intracranial (EC– IC) bypass¹⁰.

In this article, we report on a young patient with sickle cell disease who underwent an EC-IC graft bypass to improve the blood supply to the brain. Before, during, and after the bypass, we used microdialysis to measure the extracellular cerebral amino acids, lactate and online pH. This is the first report of the effects of chronic brain ischemia on cerebral amino acid and lactate levels, as well as the first study of the response of these chemicals to revascularization.

PATIENTS AND METHODS Patient history and clinical course

A 21 year old black man (KS) with sickle cell disease and a history of stroke at age three presented with a second

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Figure 1 A: Preoperative magnetic resonance angiography in patient KS showing the characteristic development of collateral circulation involving small perforating vessels in moyamoya disease ('puff of smoke') on both sides. B: Post-operative magnetic resonance angiography shows a patent bypass graft (arrow) and less 'puff of smoke' on the left operated side

stroke one month prior to coming to our hospital. His initial presentation consisted of bilateral leg and arm weakness followed by a right hemiparesis. His sickle cell disease had been very mild for a number of years, with no neurological symptoms, and he was making a gradual recovery from the second stroke at the time of our evaluation. Preoperative MRI revealed a capsular stroke in the left hemisphere and severe dilatation of the lenticulostriate vessels, a pattern suggestive of moyamoya disease (Figure 1a). Angiography confirmed that he had bilateral internal carotid artery (ICA) occlusion in the supraclinoid segment as well as the reconstitution of middle cerebral artery (MCA) branches via dilated lenticulostriate vessels. He had spontaneous collateral circulation on the right side through the external carotid circulation, but very poor collateral circulation on the left side. This may explain the occurrence of stroke preferentially in the left hemisphere.

We decided to perform an EC-IC graft bypass to provide additional blood supply to the brain. His right hemiparesis was stable before we proceeded with the operation. The procedure consisted of a left frontotemporal craiotomy with a radial artery graft from the cervical internal carotid artery to the M2 segment of the middle cerebral artery. Three M2 branches of the MCA were observed at its trifurcation. The middle one was selected to receive the radial artery graft because the other two were dilated and thin-walled due to the collateral channels. During temporary occlusion of the MCA, the patient's systolic blood pressure was elevated to 140/150 mmHg and he was placed in barbiturateinduced burst suppression for neuroprotection. The distal anastomosis was performed first, a temporary clip was placed on the radial artery graft, and the MCA flow was resumed. The graft was led through a retroauricular tunnel, and then corrected proximally to the cervical ICA. The duration of temporary occlusion was 51 min for the M2 segment and 41 min for the cervical ICA. The total period of burst suppression was

2 h. Intraoperative angiography revealed excellent graft flow. Follow-up magnetic resonance angiography (MRA) performed 1.5 months later showed a patent graft (*Figure 1b*), with the disappearance of the moyamoya pattern on the left side. Neurological examination revealed a significant improvement in his right hemiparesis.

Microdialysis

The protocol of intraoperative microdialysis monitoring in cerebrovascular surgery was approved by the George Washington University's Office of Human Research. Prior to the operation, informed consent was obtained for the microdialysis.

Immediately after the craniotomy, a microdialysis probe (CMA-20, 4 mm membrane, 0.5 mm diameter, CMA, Stockholm, Sweden; presterilized at 60°C with ethylene dioxide) was inserted into the anterior portion of the middle temporal gyrus. The probe was perfused with sterile 0.9% saline at 4 μ l min⁻¹ until closing of the dura mater. During surgery, the on-line pH of the dialysate was recorded. Fractions of 40 microliters were collected. After the operation, the *in-vitro* relative recoveries of all parameters were measured at room temperature using the same probe, flow rate and perfusion medium used intraoperatively.

Amino acid and lactate analysis

The microdialysate was stored at -70° C until measurements were performed. Glutamate, glycine and GABA concentrations in the perfusate were analyzed by high-performance liquid chromatography (HPLC) with electrochemical detection using a modification of the method of Donzanti and Yamamoto¹¹, which has been described in detail previously^{12,13}. Briefly, pre-column (Nopak C18; 3.9×150 mm, Waters, Toronto, Canada) derivatization of amino acids with ophthaldialdehyde (OPA)/betamercaptoethanol (BME)

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was performed prior to electrochemical detection with a 715 Ultra Wisp Sample Processor (Waters, Toronto, Canada). Due to the inherently unstable nature of the amino acids, we used a fully automated system for the derivation procedure. The Ultra Wisp dispensed the reagent into the microdialysis perfusate and mixed it thoroughly in a 200 μ l loop. The injection was made precisely two minutes after the reaction time. With a baseline chromatography work station, the amino acid concentrations can be measured accurately and stored for analysis. The mobile phase consisted of 0.10 M disodium hydrogen orthosphate, 0.13 M ethlenediamine tetraacidic acid-sodium salt and 20% methanol. External standards of 0.625, 1.25, 2.5, 25, 100, 300 and 1300 pmol 10 μ l⁻¹ were used for all samples. Lactate was measured by an enzymatic fluorimetric method using 15 μ l of dialysate¹⁴. Baseline lactate values were recorded 30 min after the insertion of the probe.

RESULTS pH

The pH of the dialysate during the operation was stable (between 6.70 and 6.75) but lower than our previous experience⁶. There were no changes from the baseline during clipping of the MCA or the ICA. In the early reperfusion period and for 10 min after removal of the temporary clip, the pH increased to values between 6.79 and 6.82 (Figure 2).

Lactate

The baseline lactate values were similar to previously described 'normal' lactate values in humans¹⁵. During the temporary clipping of MCA there was a short peak of 420 μ M l⁻¹ which lasted 10 min and then returned to normal. Lactate levels remained stable during the temporary clipping of the ICA and in the early postischemic period (Figure 2).

Amino acids

The dialysate fluid collected during the first 30 min was discarded. Over the next 60 min, monitoring of the amino acids revealed an increase in the levels of glutamate from 157 μ M l⁻¹ to 278 μ M l⁻¹. Previous work in Saskatoon (Canada) and Washington (USA) has consistently shown nonischemic levels to be in the 10-20 μ M l⁻¹ range (*Figure 3*). During the temporary clipping of the ICA there was a 5.5 fold peak of glutamate (851 μ M l⁻¹). The values returned to the baseline within 20 min. In the early reperfusion period (50 min) the glutamate began to fall and then remained stable between $38-58 \ \mu\text{M} \ \text{I}^{-1}$. GABA levels were between 0.6 and 1.7 during most of the surgery. A two-fold increase was also seen in GABA (18 $\mu \breve{M} I^{-1}$) at the time of the arterial occlusion.





Figure 2: Time course of glutamate, lactate and on-line pH during the EC-IC bypass procedure (MCA and ECA) clipping and in the early post ischemic period (see text)

DISCUSSION

It has been shown that there is an increase in the extracellular levels of glutamate with 'simulated ischemia¹⁶ and during seizures¹⁷. An increase in glutamate also occurs in patients with subarachnoid hemor-rhage^{18,19} and brain trauma²⁰. In our patient (KS), the baseline glutamate levels were about 10 times higher than previously recorded nonischemic levels¹⁶. It is possible that sickle cell disease with chronic ischemia may result in chronic neuronal hypoxia and a shift to anerobic metabolism. The patient's relatively low pH value supports this hypothesis²¹.

During the bypass procedure, the glutamate levels increased. We have monitored several other patients during vein and arterial bypass procedures for tumors or giant aneurysms and have never seen such an increase in glutamate levels (Figure 3). In this patient, there was no change in the pH, glycine or lactate associated with the increase in glutamate. The increase in glutamate during the bypass may have been due to the temporary vascular occlusion and further ischemia. However, the patient suffered no apparent ill effects from the temporary vascular occlusion. In addition, Shuaib et

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Α

Figure 3 A: Time course of glutamate during EC-IC bypass procedure in 5 patients. B: The glutamate values in patient KS with the sickle cell and moyamoya disease are much higher than those of the other 4 patients (JH, RW, HL and BE) undergoing EC-IC bypass

al. have previously shown that the extracellular levels of glutamate can change with minor insults if resting levels are high¹⁹. For example, patients with subarachnoid hemorrhage have elevated extracellular glutamate levels post-operatively, and changes in temperature (both hypothermia and hyperthermia) during this period can produce significant fluctuations in their dialysis glutamate levels¹⁸. (Three to five days after surgery, as the glutamate levels return towards the baseline, such fluctuations do not occur¹⁹.) It is possible that the high glutamate peak during the procedure via a similar mechanism.

In patient KS, the glutamate values began to fall rapidly and the pH value began to elevate slightly immediately after revascularization. This suggests to us that the increased cerebral blood flow reversed the chronic neuronal hypoxia, causing the glutamate and pH values to become closer to previously recorded normal values.

Cerebral revascularization procedures carry a high risk of ischemic complications. Currently, intraoperative monitoring using electroencephalography (EEG) and somatosensory evoked potentials (SSEPs) is the most useful means of identifying and preventing complications. On-line microdialysis may prove to be an additional means of monitoring patients at risk for neurological complications during such complex procedures. The advantage of the microdialysis technique is that the probe can be placed near the areas of brain known to be at significant risk due to ischemic complications. Although invasive, the tissue trauma is minimal and we have not observed any adverse effects in patients in over 26 such intraoperative microdialysis procedures performed during the past year in our institution.

ACKNOWLEDGEMENTS

Amal Nadel, MS and Hero Miyashita, BS performed the data analysis and Roy Richardson, RN, MSN constructed the graphs.

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