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CORRELATION BETWEEN CEREBRAL OXYGEN METABOLISM AND CEREBRAL BLOOD FLOW SIMULTANEOUSLY MEASURED BEFORE AND AFTER ACETAZOLAMIDE ADMINISTRATION

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ABSTRACT

The cerebral circulation and metabolism of ten preoperative cardiac surgery patients were assessed. Alterations in regional cerebral blood flow (rCBF), measured by ^{123}I-N-isopropyl-*p*-iodo-amphetamine single-photon emission computed tomography, and in cerebral oxygen metabolism, simultaneously detected by near-infrared spectroscopy (NIRS) before and after acetazolamide administration, were investigated. The rCBF (ml/min/100 g) increased significantly from 40.21±7.65 to 56.24±13.69 ($p<0.001$), and a significant increase in oxyhemoglobin (Oxy-Hb) of 13.9% ($p=0.0022$) and total hemoglobin (Total-Hb) of 5.7% (0.0047) along with a significant decrease in deoxyhemoglobin (Deoxy-Hb) of 8.9% ($p=0.0414$) were observed concomitantly. Thus, the Oxy-Hb/Total-Hb ratio (%Oxy-Hb) rose significantly from 67.26±9.82% to 72.98 ±8.09% ($p=0.0022$). Examination of the relationships between individual parameters showed that the percentage changes in rCBF and Oxy-Hb were significantly correlated ($r=0.758$, $p=0.011$). The percentage changes in rCBF and %Oxy-Hb were also correlated significantly ($r=0.740$, $p=0.014$). In conclusion, this evidence suggested that NIRS is able to detect relative changes in cerebral hemodynamics and reflect luxury perfusion induced by acetazolamide. [S1083-3668(99)00904-1]

Keywords near-infrared spectroscopy; cerebral oxygen metabolism; regional cerebral blood flow; ^{123}I-IMP SPECT; acetazolamide.

1 INTRODUCTION

The main purpose of this study was to clarify the relationship between the parameters of near-infrared spectroscopy (NIRS) and regional cerebral blood flow (rCBF) determined by single-photon emission computed tomography (SPECT) in preoperative cardiac surgery patients, because the incidence of cerebrovascular complications after cardiac surgery has been rising even though operative mortality has decreased.[1] These results have made cardiac surgeons careful to determine preoperative risk factors in relation to neurological sequelae as a means reducing postoperative complications. NIRS is a noninvasive, portable method of monitoring brain oxygen saturation and has been used for monitoring during cardiac surgery with cardiopulmonary bypass.[2–4] Quantitative assessment of absolute NIRS values, however, remains to be elucidated, and the relationship between its values and rCBF has not been adequately determined.

Measuring alterations in rCBF in response to stimulation with CO_2 or acetazolamide is the prevalent method of assessing cerebrovascular reactivity.[5,6] We have also used this method in some patients before cardiac surgery as one means of exploring preoperative cerebral hemodynamics. In the present study, we investigated how NIRS might reflect changes in cerebral hemodynamics in response to stimulation with acetazolamide.

2 SUBJECTS AND METHOD

Data on ten patients were prospectively collected before cardiac surgery. The mean age of the patients was 63.3±12.4 years (43–74 years). The ^{123}I-N-isopropyl-*p*-iodo-amphetamine (IMP) intravenous injection technique was used in this study to measure rCBF. The patients underwent SPECT

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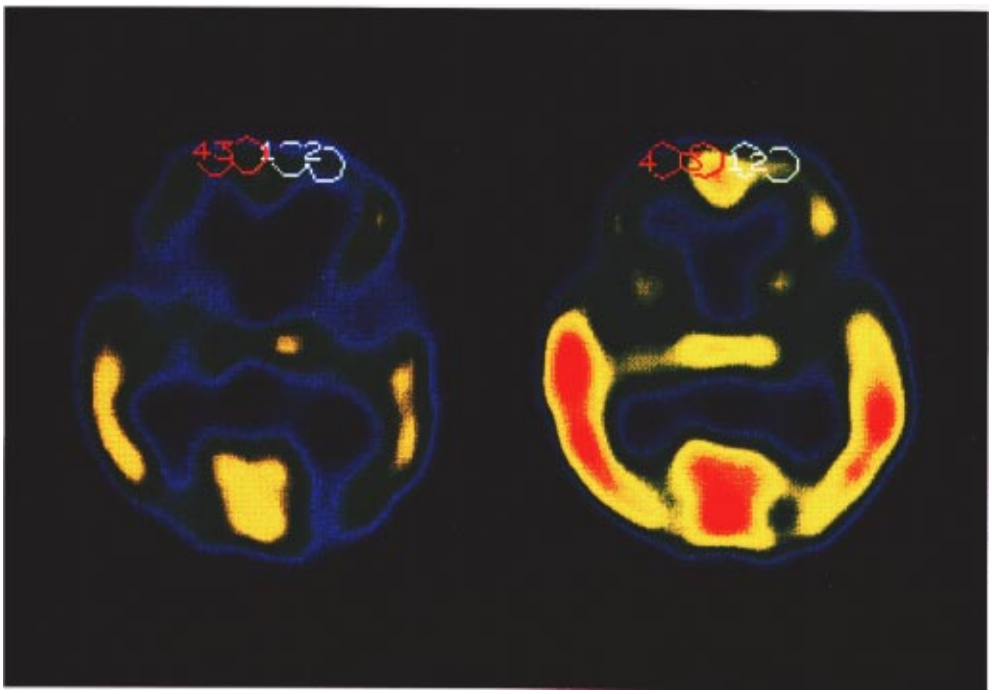

Fig. 1 Measurement of rCBF by ^{123}I-IMP SPECT. These are axial sections of the SPECT images that include the frontal cortex and striatum in the same patient. The section on the left shows the resting state, and the section on the right shows the state after acetazolamide administration. The small round ROIs show the areas analyzed for quantitative measurement of rCBF. rCBF: regional cerebral blood flow, ^{123}I-IMP: ^{123}I-*N*-isopropyl-*p*-iodoamphetamine, SPECT: single-photon emission computed tomography.

with one-point arterial blood sampling from the femoral artery (10 min post-IMP administration). The rCBF images were calculated according to the IMP autoradiographic (ARG) method. This IMP ARG method with single arterial sample was performed by the method described by Iida and colleagues.[7] They evaluated the accuracy of this method by comparing it with an independent technique using positron emission tomography (PET). They demonstrated reasonable agreement between the rCBF images calculated by the IMP ARG method and those obtained by the ^{15}O water PET method. They also showed a significant correlation between the rCBF values obtained by these two methods. In our measurements ROIs were drawn on the SPECT images covering 4–6 regions of the frontal cortex, and the average rCBF in these regions was regarded as the rCBF counterpart of the near-infrared light path (Figure 1). No ischemic change was detected by preceding computed tomography or magnetic resonance imaging in these regions. The resting study, and a second study 10 min after intravenous injection of 1000 mg of acetazolamide, were performed on separate days.

The fiberoptic probe of the NIRS (OM-200, SHIMADZU, Japan) was attached on the forehead, and cerebral oxygenation was measured simultaneously during both procedures. Quantitation of NIRS data is normally not possible due to uncertainties over the optical path length in the tissues. The OM-200, however, has two separate light detectors and determines the optical absorption of tissues *in vivo* based on spatially resolved spectroscopy[8] instead of calculations by using equations derived from the Lambert–Beer's law. This made it possible to calculate the concentrations of hemoglobin, assuming tissue homogeneity and an average scattering coefficient. In this study, oxyhemoglobin (Oxy-Hb), deoxyhemoglobin (Deoxy-Hb), total hemoglobin (Total-Hb: Oxy-Hb+Deoxy-Hb), and the Oxy-Hb/Total-Hb ratio (%Oxy-Hb) provided by the OM-200 were compared as NIRS parameters before and after injection of acetazolamide. We also evaluated the relationships between these parameters and rCBF.

2.1 STATISTICAL ANALYSIS

All values are expressed as means±standard deviation. The Wilcoxon signed-rank test was performed to compare differences between before and after acetazolamide administration. A simple regression analysis was used to evaluate the correlation between rCBF and NIRS parameters. A probability value less than 0.05 was considered significant.

3 RESULTS

Procedures and measurements were completed without any systemic hemodynamic changes or adverse effects during the examination in all of the patients. No neurological sequelae occurred following the subsequent cardiac surgery.

3.1 CHANGES IN rCBF AND NIRS PARAMETERS AFTER ADMINISTRATION OF ACETAZOLAMIDE

The rCBF (ml/min/100 g) increased significantly from 40.21±7.65 at rest to 56.24±13.69 after injection of acetazolamide (see Table 1). The percentage change was +39.7%. On the other hand, we observed a significant increase in Oxy-Hb of 13.9% and Total-Hb of 5.7%, and a significant decrease in Deoxy-Hb of 8.9%. Thus, %Oxy-Hb rose significantly from 67.26±9.82% to 72.98±8.09%, and the percentage change was +8.5%. Serial changes in each parameter during the procedure are shown in Figure 2. Ten minutes after stimulation with acetazolamide significant increases in Oxy-Hb, Total-Hb, and %Oxy-Hb and a significant decrease in the Deoxy-Hb were found, with no subsequent changes.

3.2 SIMPLE REGRESSION ANALYSIS OF CORRELATIONS BETWEEN rCBF AND NIRS PARAMETERS

There were no significant correlations between the absolute rCBF values and those of the Oxy-Hb, Deoxy-Hb, Total-Hb and %Oxy-Hb, whether acetazolamide was administered or not. However, the percentage changes in rCBF were found to be significantly correlated with the changes in Oxy-Hb ($r=0.758$, $p=0.011$) and in %Oxy-Hb ($r=0.740$, $p=0.014$) (Figure 3).

4 DISCUSSION

In this study, we demonstrated a significant increase in Oxy-Hb, Total-Hb, and %Oxy-Hb, and a significant decrease in Deoxy-Hb measured by NIRS after administration of acetazolamide, as well as positive correlations between the changes in rCBF and those in Oxy-Hb and %Oxy-Hb, respectively. There have been previous studies investigating cerebrovascular reactivity tested by CO_2 or acetazolamide administration on the basis of the relationships between the reactivities and the Oxy-Hb measured by NIRS. Smielewski et al.[9] demonstrated a linear correlation between Oxy-Hb and the reactivity of cerebral blood flow velocity in response to CO_2 challenge. In a study using the NIRS and the 133Xe CBF method, Kaminogo et al.[10] showed that an increase in Oxy-Hb was always induced when rCBF was increased after acetazolamide administration, and that a relationship existed between them such that the greater the percentage change in rCBF, the larger the percentage change in Oxy-Hb. More recently, Holzschuh et al.[11] also reported that changes in CBF could be detected by NIRS in a similarly designed clinical study. They

Table 1 Changes in rCBF and NIRS parameters after administration of 1000 mg of acetazolamide. Oxy-Hb: oxyhemoglobin, Deoxy-Hb: deoxyhemoglobin, Total-Hb: total hemoglobin, %Oxy-Hb: oxyhemoglobin/total hemoglobin, rCBF: regional cerebral blood flow.

	Before	After	% change	*p* value
Oxy-Hb (μmol/L)	19.79±11.06	22.54±10.72	+13.9%	0.0022
Deoxy-Hb (μmol/L)	9.87±3.17	8.99±3.23	–8.9%	0.0414
Total-Hb (μmol/L)	29.01±14.03	30.66±13.35	+5.7%	0.0047
% Oxy-Hb (%)	67.26±9.82	72.98±8.09	+8.5%	0.0022
rCBF (ml/min/100 g)	40.21±7.65	56.24±13.69	+39.7%	<0.001

demonstrated a positive correlation between the changes in CBF and Oxy-Hb, whereas no correlations were found between the absolute value of CBF and Oxy-Hb at rest or after stimulation with acetazolamide. Our findings confirmed these results, because the increase in %Oxy-Hb and the percentage increase in rCBF after the acetazolamide challenge as well as the coefficient of the correlation between the changes in CBF and Oxy-Hb in the present study were almost the same as those in the previous study. In this study, we used the Shimadzu NIRS, which is a new instrument that applies the spatially resolved technique based on diffusion theory, and correlations between NIRS data and rCBF assessed by IMP-SPECT (ARG method), which is also a newly developed technique, have been demonstrated.

Acetazolamide, a selective inhibitor of carbonic anhydrase, has been shown to induce a rapid increase in CBF.[12] It has been suggested that the effect of carbonic anhydrase inhibition in erythrocytes would prevent oxygen unloading in the capillary bed and consequently increase CBF,[13] or that direct local vasodilation of the cerebral arterioles might occur, apart from its specific effects as a carbonic anhydrase inhibitor;[14] however, the actual mecha-

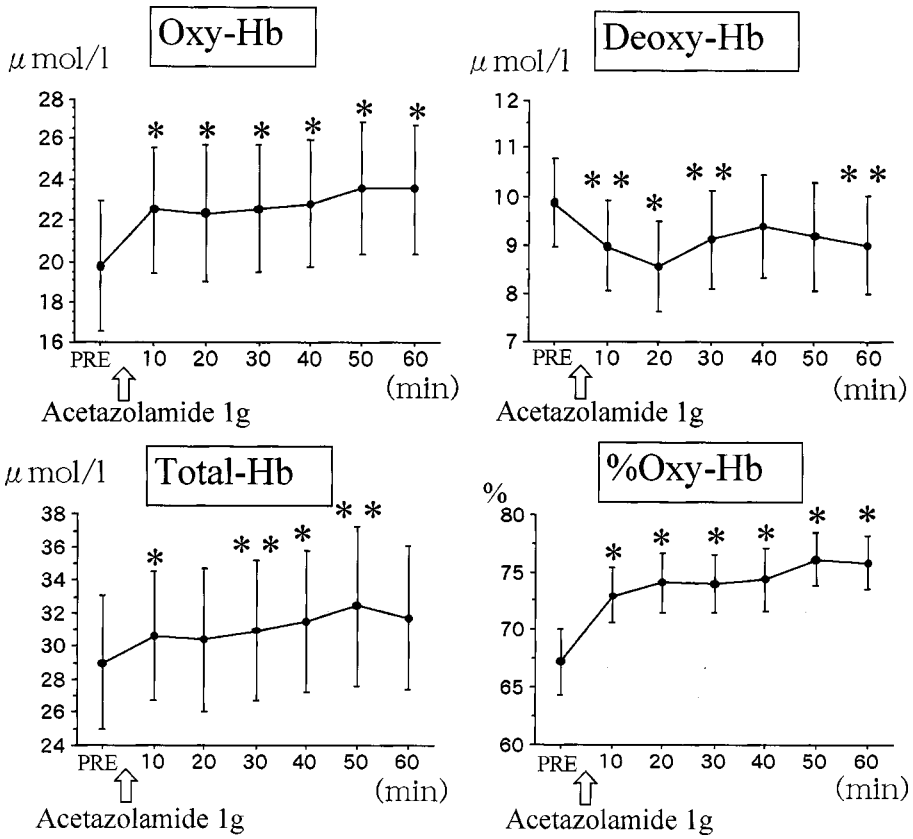

Fig. 2 Serial changes in Oxy-Hb, Deoxy-Hb, Total-Hb and %Oxy-Hb after acetazolamide administration. Oxy-Hb: oxyhemoglobin, Deoxy-Hb: deoxyhemoglobin, Total-Hb: total hemoglobin, %Oxy-Hb: oxyhemoglobin/total hemoglobin. *$p<0.01$, **$p<0.05$.

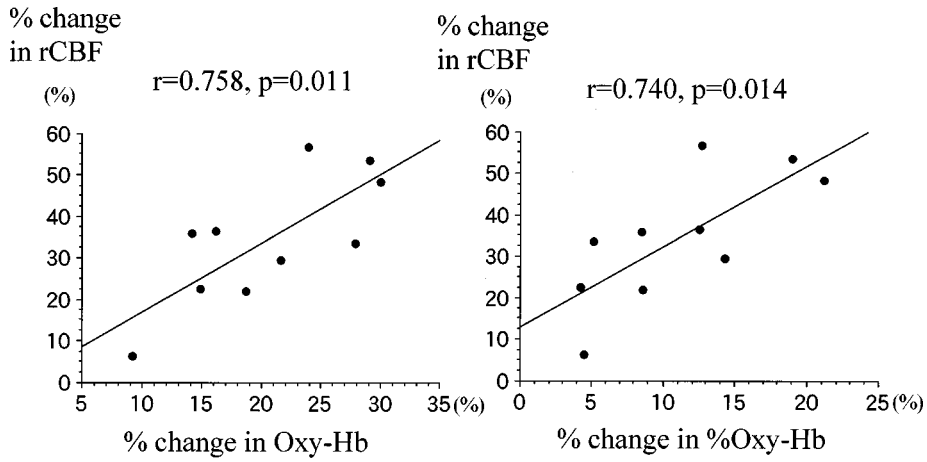

Fig. 3 Correlations between the percentage change in Oxy-Hb (left) and %Oxy-Hb (right) and the percentage changes in rCBF. Oxy-Hb: oxyhemoglobin, %Oxy-Hb: oxyhemoglobin/total hemoglobin, rCBF: regional cerebral blood flow.

nism has not been identified. The change of cerebral metabolic rate for oxygen ($CMRO_2$) after intravenous administration of acetazolamide has also been a subject of controversy. Laux and Raichle[13] observed a decrease in $CMRO_2$ coupled with a significant increase in CBF. Vorstrup et al.,[15] on the other hand, reported a rapid increase in CBF without concomitant changes in $CMRO_2$. An increase in CBF and an unchanged or reduced $CMRO_2$ leads to diminish oxygen extraction, and consequently increase oxygen saturation of venous blood. As the cerebral tissue oxygenation monitored by NIRS predominantly consisted of a venous component,[16] it was considered that the findings in this study directly reflected the increase in $CBF/CMRO_2$ ratio, although the actual $CMRO_2$ was not calculated. In other words, an increase oxygen supply/demand ratio in the brain, so-called cerebral luxury perfusion, was indicated. Although it is currently not possible to compare NIRS parameters in different patients, the significant correlation between the changes in Oxy-Hb and CBF indicated that the responses of these parameters to acetazolamide could be used to compare cerebrovascular reactivity even between different individuals.

Our final goal is precise assessment of perioperative cerebral hemodynamics and oxygen metabolism by NIRS. Actually, there has been an attempt to quantify cerebral flow and volume by NIRS,[4] however, it has not yet come into widespread use as a simple, reliable method. The finding that the change in NIRS parameters correlated with cerebral hemodynamics encourages us to apply it to the evaluation of risk factors for neurological sequelae and cerebrovascular reactivity during preoperative exploration and to the intraoperative assessment of cerebral circulation.

5 CONCLUSIONS

We compared NIRS parameters with rCBF measured by ^{123}I-IMP SPECT in response to stimulation with acetazolamide. After administration of acetazolamide, increases in Oxy-Hb and Total-Hb, and a decrease in Deoxy-Hb were observed by NIRS concomitant with an increase of rCBF. A single NIRS value per se provided little information about rCBF, however, there was a significant correlation between the percentage changes in Oxy-Hb and rCBF. It is suggested that NIRS might reflect luxury perfusion induced by acetazolamide and detect relative changes in cerebral hemodynamics.

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