

# Cerebral oxygenation and haemodynamic effects induced by nimodipine in healthy subjects

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## Summary

The cerebrovascular effects of nimodipine are still poorly understood even in the healthy condition; in particular, its effects on tissue oxygenation have never been investigated.

The aim of the present study was to investigate changes in cerebral oxygenation and blood volume upon oral administration of nimodipine (90 mg) in the healthy condition.

In eight subjects, changes in cerebral tissue oxygenation and blood volume were determined simultaneously with changes in blood velocity of the middle cerebral artery ( $V_{MCA}$ ) by using, respectively, near infrared spectroscopy (NIRS) and transcranial Doppler ultrasonography (TCD). The subjects also underwent non-invasive assessment of arterial blood pressure (ABP) and end-tidal  $CO_2$ . TCD and NIRS  $CO_2$  reactivity indices were also extracted.

Nimodipine significantly reduced ABP ( $11 \pm 13\%$ ) and increased heart rate, as well as NIRS oxygenation ( $6.0 \pm 4.8\%$ ) and blood volume indices ( $9.4 \pm 10.1\%$ ), while  $V_{MCA}$  was not significantly decreased ( $2.0 \pm 3.5\%$ ). Nimodipine slightly but significantly reduced the  $V_{MCA}$  response to changes in  $pCO_2$  whereas the  $CO_2$  reactivity of NIRS parameters was improved.

The observed changes in cerebral tissue oxygenation and blood volume indicate nimodipine-induced cerebrovascular dilation and increased perfusion, while the effect on  $V_{MCA}$  possibly results from dilation of the innominate artery. The present results cast doubt on the putative nimodipine-induced impairment of  $CO_2$  reactivity.

**KEY WORDS:** cerebral blood flow, hyperventilation, near infrared spectroscopy, nimodipine, rebreathing

## Introduction

Nimodipine is a 1,4-dihydropyridine mainly acting as an antagonist of L-type voltage sensitive calcium channels (L-VSCCs), hence its ability to dilate blood vessels. Unlike other L-VSCC antagonists, such as verapamil and nifedipine, which penetrate the blood-brain barrier poorly and are, therefore, unlikely to reach significant concentrations within the central nervous system (1), nimodipine is highly lipophilic, readily crosses the blood-brain barrier and fully diffuses into the brain and cerebrovascular fluid (2,3); thus, it demonstrates a marked specificity for the cerebrovasculature. Its vasodilatory action on cerebral vessels is considered to be preferentially exerted on arterioles with a diameter of 70-100  $\mu m$ , according to both *in vitro* and *in vivo* studies (4,5).

The use of nimodipine in patients is recommended mainly in clinical conditions in which cerebral perfusion is impaired. Preclinical studies of the influence of nimodipine in various animal models of cerebral ischaemia further support its main indication as a drug with anti-ischaemic activity (6,7).

Nimodipine is used to prevent cerebral ischaemia and post-ischaemic brain damage in a range of cerebrovascular disorders, such as subarachnoid haemorrhage (SAH), acute ischaemic stroke, cerebral ischaemia without stroke, vascular dementia and migraine; however, its beneficial effects in some of the above conditions are still under discussion (6,8). Clinical investigations have shown that it is effective in preventing symptomatic vasospasm and delayed ischaemic neurological deficits following aneurysmal SAH (6,9,10), whereas the clinical efficacy of nimodipine in the treatment of acute ischaemic stroke is much more controversial and needs to be further investigated (6,11,12).

In the field of vascular cognitive impairment, the role of voltage-dependent  $Ca^{2+}$  channel blockade in preventing ischaemic brain tissue death is highly debated (13,14). The short-term benefits of nimodipine demonstrated in some clinical trials do not justify its use as a long-term anti-dementia drug (15) and results obtained in elderly patients affected by subcortical vascular dementia need to be confirmed by other groups and in larger scale trials (16).

In order to better define the possible mechanisms of nimodipine in cerebral disorders and, thus, its therapeutic potential, the authors of this study felt there was a need to reinvestigate its action in healthy individuals, to establish whether nimodipine can be effective in increasing cerebral perfusion in spite of its potential hypotensive effect.

While several animal studies rather consistently reported increased cerebral perfusion by nimodipine (4, ref.s in 17), results are more controversial in the few relevant human studies, which report either increases (18,19) or no change (1,20) in cerebral blood flow (CBF). Also controversial is the modulation of cerebrovascular  $CO_2$  re-

activity, which has been found to range from totally preserved to severely impaired (see below). In addition, it is not known whether nimodipine-induced cerebrovascular changes can affect tissue oxygenation.

Continuous and bedside monitoring of cerebral blood oxygenation and cerebral blood volume is non-invasively performed using near infrared spectroscopy (NIRS), a technique that is not yet employed in routine clinical practice, mainly due to the difficulty in interpreting the many different signals provided (21), as recently highlighted in the assessment of cerebrovascular responses to neurovegetative tests (22). For this reason, interpretation of NIRS monitoring in pathological conditions could be facilitated by a reference study in healthy subjects.

The aim of the present study was to investigate in healthy subjects the effects of nimodipine administration on cerebral haemodynamics and oxygenation through the simultaneous use of transcranial Doppler ultrasonography (TCD) and NIRS. The possibility of detecting changes in cerebrovascular CO<sub>2</sub> reactivity based on NIRS parameters was also investigated and the results compared with standard vascular reactivity based on changes in cerebral blood velocity.

## Materials and methods

### Subjects

Eight healthy volunteers, with a median age of 27 years (2 men and 6 women), were studied. All the subjects were fully informed about the procedure and signed a consent form. The study, which had local ethics committee approval, was conducted at the C. Mondino National Institute of Neurology Foundation in Pavia, Italy.

### Protocol

The study sessions were performed in a quiet room at constant environmental conditions, with subjects lying in a comfortable supine position, without any visual or auditory disturbances. The subjects were not allowed to speak during the experiment and were asked to keep their eyes closed and to relax.

As depicted in figure 1, after a 20-min resting period, necessary to reach stable haemodynamic levels, the subjects performed the CO<sub>2</sub> reactivity tests, i.e., hyperventilation (HV) and rebreathing (RB), separated by a 6-min interval. After 10 min, nimodipine (Nimotop 4% solution, Bayer Health Care Pharmaceuticals Inc., Wayne, NJ, USA) 90 mg was orally administered (subjects received a dose ranging between 1.06 and 1.64 mg/kg). HV and RB were then repeated, once the haemodynamic effects of nimodipine had fully developed (15-20 min after administration).

### Hyperventilation

The subjects were asked to hyperventilate to achieve and maintain for 1 min an end-tidal CO<sub>2</sub> pressure (P<sub>ET</sub>CO<sub>2</sub>) of 20 mmHg. To this end, they were provided with visual feedback from the display of the capnograph (OxiCap 4700, Ohmeda, USA), which was continuously

monitoring P<sub>ET</sub>CO<sub>2</sub> from the expiratory flow collected by a nasal cannula.

### Rebreathing

The subjects breathed, maintaining a spontaneous breathing frequency, through an anaesthesiology mask connected to a 5-L rebreathing bag until a stable P<sub>ET</sub>CO<sub>2</sub> was achieved and maintained for at least 20 s. The mask was also connected with a sampling line to the capnograph (see above) to allow continuous recording of the expiratory flow (P<sub>ET</sub>CO<sub>2</sub>).

Half an hour before the beginning of the recordings, the subjects received instruction and training to ensure that they were able to perform the respiratory manoeuvres correctly.

### Monitoring equipment and measurements

Blood velocity was measured bilaterally in the middle cerebral artery (V<sub>MCA</sub>) using 2 MHz TCD (Multi-Dop X, DWL, Singen, Germany).

Cerebral tissue oxygenation and blood volume were locally detected by NIRS (NIRO 300, Hamamatsu Photonics K.K., Japan), which simultaneously provided Beer-Lambert (BL) conventional spectroscopy and spatially resolved spectroscopy (SRS) parameters. SRS measures of tissue oxygenation and blood volume are provided, respectively, by the tissue oxygenation index (TOI), expressed in %, and the tissue haemoglobin index (THI), expressed in arbitrary units, whereas the BL measures of tissue oxygenation and blood volume are provided, respectively, by concentration changes in oxyhaemoglobin (O<sub>2</sub>Hb) and total haemoglobin (tHb), expressed in μmol/L.

The NIRS probe was placed high on the left side of the forehead as described in a previous paper (22).

Arterial blood pressure (ABP) was measured using a non-invasive pressure monitor (Finapres 2300, Ohmeda, USA).

### Data acquisition and processing

The NIRS signals TOI, THI, O<sub>2</sub>Hb, and tHb were continuously acquired and digitally transferred to a PC by a proprietary software system (Hamamatsu Photonics), (sampling frequency = 2Hz) throughout the whole session. These data were subsequently exported in text files for off-line analysis in Microsoft Excel.

V<sub>MCA</sub>, ABP, P<sub>ET</sub>CO<sub>2</sub>, tHb, THI, and TOI were continuously and simultaneously displayed and digitized on a PC (sampling frequency = 200Hz) using the PowerLab 8/SP

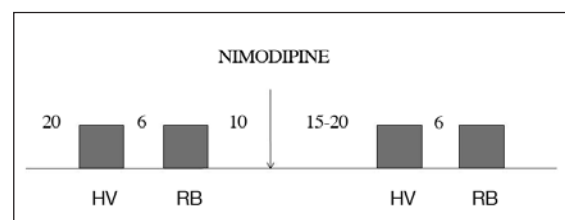


Figure 1- Schematic representation of the experimental protocol. HV=hyperventilation, RB=rebreathing. Time intervals are expressed in minutes. Nimodipine oral administration is indicated by the arrow.

data acquisition system and Chart 5.0 software (ML 785, ADInstruments).

The same software was used to extract mean values and relative changes in the different signals throughout the different tests. It also allowed for off-line calculation of heart rate (HR), end-diastolic  $V_{MCA}$  ( $V_{MCA\text{dia}}$ ) and peak systolic  $V_{MCA}$  ( $V_{MCA\text{sys}}$ ), as well as cerebrovascular resistance and  $\text{CO}_2$  reactivity indices.

The *pulsatility index* (PI) was calculated by subtracting the  $V_{MCA\text{dia}}$  from the  $V_{MCA\text{sys}}$ , and then dividing by the mean  $V_{MCA}$ . The *cerebrovascular resistance index* (CVR) was calculated as  $\text{CVR} = \text{ABP} / V_{MCA}$ .

$\text{CO}_2$  reactivity values both for TCD and NIRS variables were computed. For  $V_{MCA}$  and THI, the  $\text{CO}_2$  vascular reactivity value was calculated as the percentage change in the variable divided by the absolute change in  $P_{\text{ET}}\text{CO}_2$ , according to the following formula:

$$\text{CO}_2 \text{ reactivity}_{\text{Var}} = [\text{Var}_{\text{test}} - \text{Var}_{\text{Baseline}}] / \text{Var}_{\text{Baseline}} \times 100 / \Delta P_{\text{ET}}\text{CO}_2$$

For TOI, tHb and  $\text{O}_2\text{Hb}$ , we calculated  $\text{CO}_2$  vascular reactivity as the absolute change in the variable divided by the absolute change in  $P_{\text{ET}}\text{CO}_2$ , according to the following formula:

$$\text{CO}_2 \text{ reactivity}_{\text{Var}} = [\text{Var}_{\text{test}} - \text{Var}_{\text{Baseline}}] / \Delta P_{\text{ET}}\text{CO}_2$$

where  $\text{Var}_{\text{test}}$  is the value of the variable averaged over the last 20-s period of the respiratory manoeuvre (HV or RB) and  $\text{Var}_{\text{Baseline}}$  is the value of the variable averaged over the 60-s period preceding the start of the manoeuvre (23-25).

Systemic and cerebrovascular effects of nimodipine were evaluated by assessing changes exhibited by the different variables at 15-20 min after oral administration (post-) with respect to the control (pre-administration) value. Both values were averaged in reference to a 1 min interval.

The effects of the drug on cerebrovascular reactivity to altered  $P_{\text{ET}}\text{CO}_2$  were also evaluated by comparing  $\text{CO}_2$  reactivity before with  $\text{CO}_2$  reactivity after drug administration.

**Statistical analysis**

Statistical analysis was performed using SAS version 9.1 for Windows® software (SAS Institute Inc., Cary, North Carolina).

Statistical comparisons between pre- and post-nimodipine measurements were performed using a Student's paired sample t-test, for normally distributed data, or the Wilcoxon signed-rank test, for non-normally distributed data. The normality of within-pair difference was assessed by means of the Shapiro-Wilk test.

P values less than 0.05 were considered statistically significant.

Data are expressed as mean±SD in the tables and text and as mean±SEM in the graphs.

**Results**

**The effects of nimodipine on systemic and cerebrovascular variables**

No adverse reaction to the drug was reported and the examination was well tolerated by all the subjects.

The changes induced by nimodipine in  $V_{MCA}$ , ABP,  $P_{\text{ET}}\text{CO}_2$ , tHb, THI and TOI in a representative subject are shown in figure 2. The maximum haemodynamic effect of the drug is generally observed between 15 and 20 min after administration.

Figure 3 shows the average changes in the different variables induced by the drug while table I (over) shows the respective values before and after nimodipine administration. A slight but significant decrease in ABP was observed ( $11\pm13\%$ ) together with a concomitant increase in HR ( $32\pm21\%$ ).  $V_{MCA\text{dia}}$  was lowered (by

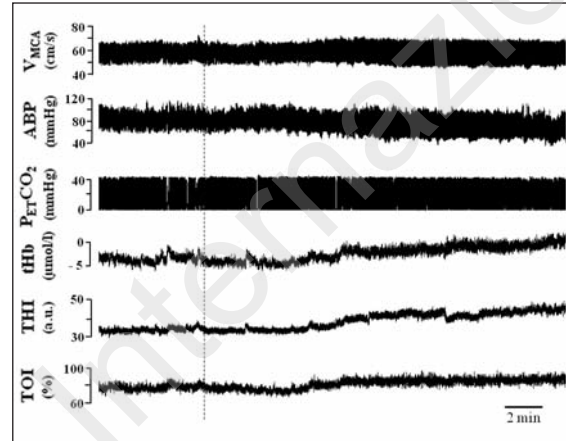


Figure 2 - Response to nimodipine in a representative subject. From top to bottom:  $V_{MCA}$ =cerebral blood velocity; ABP=arterial blood pressure;  $P_{\text{ET}}\text{CO}_2$ =end-tidal  $\text{CO}_2$ ; tHb=total haemoglobin concentration; THI=tissue haemoglobin index; TOI=tissue oxygenation index. Nimodipine oral administration is indicated by the dashed line.

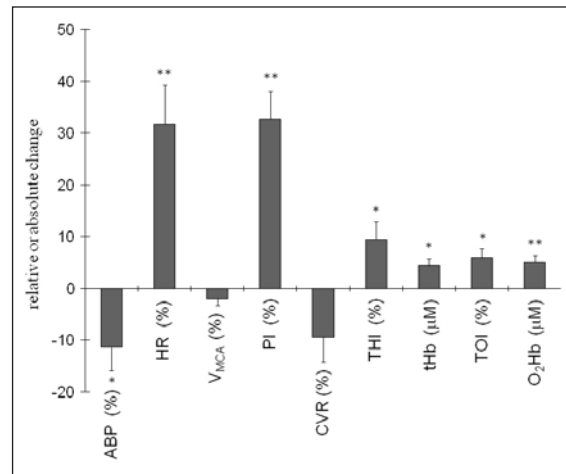


Figure 3 - Average changes in the different variables induced by nimodipine. ABP=arterial blood pressure; HR=heart rate;  $V_{MCA}$ =cerebral blood velocity; PI=pulsatility index; CVR=cerebrovascular resistance index; THI=tissue haemoglobin index; tHb=total haemoglobin concentration; TOI=tissue oxygenation index;  $\text{O}_2\text{Hb}$ =oxyhaemoglobin concentration.

Changes are expressed in relative terms (%) for ABP, HR,  $V_{MCA}$ , PI, CVR, THI and TOI; changes are expressed in absolute terms (original units) for tHb and  $\text{O}_2\text{Hb}$ . Statistical significance is derived from table I and indicated by \* ( $p<0.05$ ) and \*\* ( $p<0.01$ ).

3.8±2.7%), whereas  $V_{MCA_{Asys}}$  increased non-significantly (by 3.9±5.3%). As a consequence, mean  $V_{MCA}$  only slightly decreased (by 2.0±3.5%). The cerebrovascular resistance indices showed an opposite trend, i.e. CVR was reduced in 6 out of 8 subjects (overall reduction: 9.4±13.7%) while PI was sharply increased (by 33±15%). Nevertheless, a significant correlation was found between the two indices ( $r = -0.72, p < 0.05$ ).

Table I - Systemic and cerebral haemodynamic variables before and after nimodipine administration

Variable	before nimodipine	after nimodipine
ABP (mmHg)	80±9	71±12 <sup>†</sup>
HR (bpm)	72±7	93±11 <sup>††</sup>
$V_{MCA}$ (cm/s)	54±2.6	53±3
$V_{MCA_{dia}}$ (cm/s)	48±2	47±2 <sup>††</sup>
$V_{MCA_{sys}}$ (cm/s)	63±3	65±3.7
PI (a.u.)	0.26±0.02	0.35±0.05 <sup>††</sup>
CVR (mmHg*s/cm)	1.5±0.2	1.3±0.3
THI (a.u.)	46±13	50±11 <sup>†</sup>
tHb (µM)	0.4±7	4.8±11 <sup>†</sup>
TOI (%)	74±5	78±5.7 <sup>†</sup>
$O_2Hb$ (µM)	0.4±5	5.6±8.5 <sup>††</sup>

Abbreviations: ABP=arterial blood pressure; HR=heart rate;  $V_{MCA}$ =cerebral blood velocity;  $V_{MCA_{dia}}$  = diastolic  $V_{MCA}$ ;  $V_{MCA_{sys}}$  = systolic  $V_{MCA}$ ; PI=pulsatility index; CVR=cerebrovascular resistance index; THI=tissue haemoglobin index; tHb=Beer-Lambert total haemoglobin concentration; TOI=tissue oxygenation index;  $O_2Hb$ =Beer-Lambert oxyhaemoglobin concentration; a.u.=arbitrary units. Values are expressed as mean±SD. Statistical significance between before and after nimodipine mean values is indicated by <sup>†</sup> ( $p < 0.05$ ) and <sup>††</sup> ( $p < 0.01$ ).

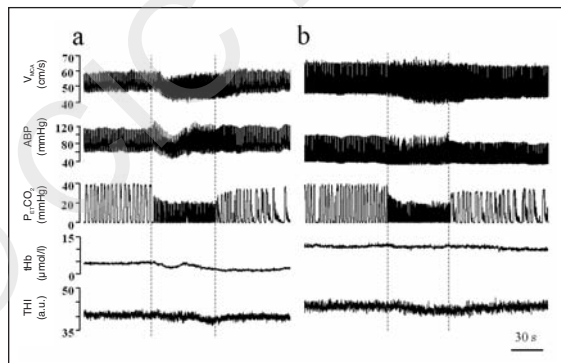


Figure 4 - The response to hyperventilation in a representative subject, before (a) and after (b) nimodipine administration. From top to bottom:  $V_{MCA}$ =cerebral blood velocity; ABP=arterial blood pressure;  $P_{ET}CO_2$ =end-tidal  $CO_2$ ; tHb=total haemoglobin concentration; THI=tissue haemoglobin index. Hyperventilation start-end points are marked by dashed lines.

The two NIRS blood volume indices, THI and tHb, concordantly increased (THI by 9.4±10.1%; tHb by 4.4±3.9 µM), as did the two NIRS oxygenation indices, TOI and  $O_2Hb$  (TOI by 6.0±4.8%;  $O_2Hb$  by 5.1±3.7 µM).

### Effects of nimodipine on cerebrovascular reactivity

The typical effect induced by nimodipine on cerebral  $CO_2$  vascular reactivity is shown in figures 4 and 5. It can be observed that the response of the NIRS parameters to the  $CO_2$  challenge was quantitatively smaller than that exhibited by  $V_{MCA}$  and that the  $V_{MCA}$  response was clearly reduced by nimodipine administration.

The  $CO_2$  reactivities of TCD and NIRS parameters and their levels of significance from baseline values, before and after nimodipine administration, are shown in tables II and III and graphically represented in figures 6 and 7. Hyperventilation led to a significant decrease in  $V_{MCA}$  in the control condition; this response was only slightly but significantly reduced by drug administration. None of the NIRS parameters was significantly affected by  $CO_2$  in the control condition, while significant changes were apparent after nimodipine.

Rebreathing produced a significant increase in  $V_{MCA}$  in the control condition, and  $V_{MCA}$  reactivity was decreased by nimodipine, albeit not significantly. The NIRS parameters exhibited little responsiveness to RB in the control condition, significant changes being observed only in tHb. Nimodipine increased  $CO_2$  reactivity in blood volume indicators but not in oxygenation indices, TOI and  $O_2Hb$ .

### Discussion

In the present work we analysed the response to oral nimodipine administration (effects on cerebral haemodynamics and oxygenation) by integrating Doppler velocimetry with NIRS. As regards the general action of the drug, we observed a slight but significant hypotensive effect, partially counteracted by a compensatory increase in HR with no significant effects on  $V_{MCA}$ . An increase in cerebral blood volume was detected by NIRS parameters, along with an increase in cerebral oxygena-

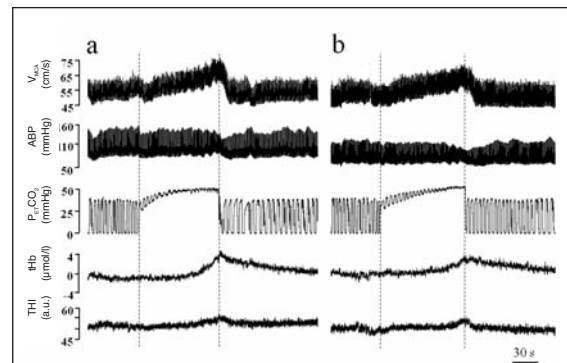


Figure 5 - The response to rebreathing in a representative subject, before (a) and after (b) nimodipine administration. From top to bottom:  $V_{MCA}$ =cerebral blood velocity; ABP=arterial blood pressure;  $P_{ET}CO_2$ =end-tidal  $CO_2$ ; tHb=total haemoglobin concentration; THI=tissue haemoglobin index. Rebreathing start-end points are marked by dashed lines.

Table II - Cerebral CO<sub>2</sub> reactivities of TCD and NIRS parameters in response to hyperventilation, before and after nimodipine administration

	before nimodipine	after nimodipine
V <sub>MCA</sub> (%/mmHg)	0.65±0.25 *	0.54±0.21 * †
THI (%/mmHg)	0.13±0.42	0.20±0.20 *
TOI (%/mmHg)	0.12±0.14	0.16±0.11 *
tHb (µM/mmHg)	0.017±0.12	0.033±0.035 *
O <sub>2</sub> Hb (µM/mmHg)	0.028±0.10	0.039±0.046 *

Abbreviations: V<sub>MCA</sub>=cerebral blood velocity; THI=tissue haemoglobin index; TOI=tissue oxygenation index; tHb=Beer-Lambert total haemoglobin concentration; O<sub>2</sub>Hb= Beer-Lambert oxyhaemoglobin concentration. \*=significantly different from 0 (p<0.05); †=significantly different from before nimodipine (p<0.05).

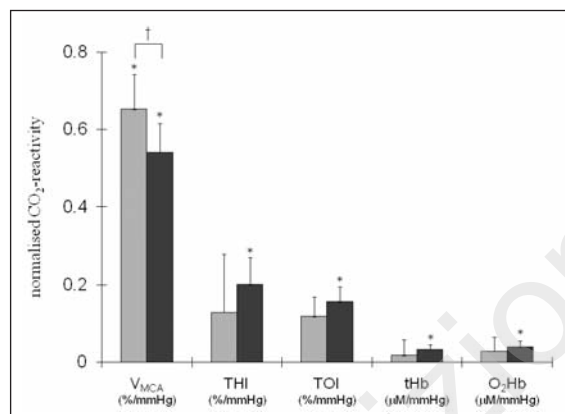


Figure 6 - Effect of nimodipine on cerebrovascular CO<sub>2</sub> reactivity of TCD and NIRS parameters during hyperventilation. Grey bars=CO<sub>2</sub> reactivity before nimodipine; black bars=CO<sub>2</sub> reactivity after nimodipine. V<sub>MCA</sub>=cerebral blood velocity; THI=tissue haemoglobin index; TOI=tissue oxygenation index; tHb=total haemoglobin concentration; O<sub>2</sub>Hb=oxygenated haemoglobin concentration. \*=significantly different from 0 (p<0.05); †=significantly different from before nimodipine (p<0.05).

tion. Nimodipine appeared to reduce CO<sub>2</sub> reactivity of V<sub>MCA</sub> while producing an opposite trend in CO<sub>2</sub> reactivity of NIRS variables.

#### Nimodipine effect on cerebral blood flow

The literature contains controversial data on CBF response to nimodipine administration.

In numerous *in vitro* studies, nimodipine was found to inhibit contractions of cerebral arteries both in animals and in humans (ref.s in 4, 26-28). Furthermore, dilation of cerebral arterioles has been demonstrated *in situ* in a number of animal studies and in a few studies in humans. The technique widely used to study cerebrovascular reactivity *in situ* is direct observation of pial vessels through a cranial window, following intravenous or topi-

Table III - Cerebral CO<sub>2</sub> reactivities of TCD and NIRS parameters in response to rebreathing, before and after nimodipine administration.

Variable	before nimodipine	after nimodipine
V <sub>MCA</sub> (%/mmHg)	1.7±0.5 *	1.4±0.8 *
THI (%/mmHg)	0.59±0.67	0.77±0.48 *
TOI (%/mmHg)	-0.012±0.21	-0.024±0.21
tHb (µM/mmHg)	0.21±0.12 *	0.36±0.36 *
O <sub>2</sub> Hb (µM/mmHg)	0.071±0.10	0.17±0.22

Abbreviations: V<sub>MCA</sub>=cerebral blood velocity; THI=tissue haemoglobin index; TOI=tissue oxygenation index; tHb=Beer-Lambert total haemoglobin concentration; O<sub>2</sub>Hb= Beer-Lambert oxyhaemoglobin concentration. \*=significantly different from 0 (p<0.05); †=significantly different from before nimodipine (p<0.05).

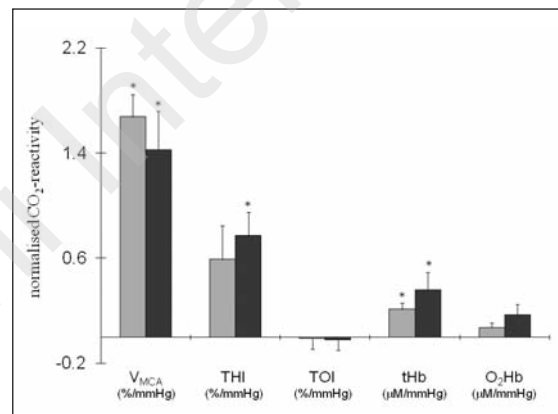


Figure 7 - Effect of nimodipine on cerebrovascular CO<sub>2</sub> reactivity of TCD and NIRS parameters during rebreathing. Grey bars=CO<sub>2</sub> reactivity before nimodipine; black bars=CO<sub>2</sub> reactivity after nimodipine. V<sub>MCA</sub>=cerebral blood velocity; THI=tissue haemoglobin index; TOI=tissue oxygenation index; tHb=total haemoglobin concentration; O<sub>2</sub>Hb=oxygenated haemoglobin concentration. \*=significantly different from 0 (p<0.05).

cal nimodipine administration; in humans this is possible in patients undergoing cranial surgery (4,5).

Despite the above evidence, *in vivo* studies evaluating the effect on CBF changes have produced quite heterogeneous results.

With a few exceptions (29-31), nimodipine has been shown to increase CBF in the majority of animal studies (ref.s in 4,17); however, the few available studies in healthy humans provide non-homogeneous results.

Studies performed by combining SPECT of inhaled <sup>133</sup>Xenon with the arteriovenous oxygen difference method showed that ~ 2 mg of nimodipine (i.v.) induced either an increase (8%) or no change in CBF, while similar decreases in ABP were observed (18,20). Furthermore, a study performed in patients undergoing cardiopulmonary bypass and administered nimodipine (i.v.)

at a dose of  $0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  failed to find significant differences in CBF (32).

More recently, effects on CBF were inferred from changes in  $V_{\text{MCA}}$ , as measured using TCD, although possible changes in MCA diameter may complicate the interpretation. Buggy et al. (1) reported no change in CBF on the basis of unchanged  $V_{\text{MCA}}$  in response to 60 mg of orally-administered nimodipine. In another study a decrease in  $V_{\text{MCA}}$  in response to the same dosage was instead interpreted as a "CBF increase inadequate to fully offset a concurrent increase in the MCA calibre" (19). In a previous study by Kraaier et al. (33),  $V_{\text{MCA}}$  was also slightly lowered (by 4.7%) by nimodipine, administered orally in two different doses of 30 mg and 60 mg t.i.d. for four days. The non-significant effect on  $V_{\text{MCA}}$  observed in the present study is in agreement with previous reports (1,33). Since constriction of large cerebral vessels has never been reported in the literature, the possibility of a reduction in MCA diameter in response to nimodipine should be excluded *a priori*. Thus, we are left with the possibility that CBF ( $=V_{\text{MCA}} \cdot \text{cross sectional area of MCA}$ ) was either unchanged or increased, depending on whether the vessel diameter was unchanged or increased, respectively.

Other parameters taken into consideration in order to infer changes in cerebrovascular resistance are CVR and PI. Paradoxically, an increase of cerebrovascular resistance in response to nimodipine was reported on the basis of the observation of a PI increase (34). However, the PI is known to be affected by several confounding factors. In particular, the pulsatility of blood flow is known to increase with compliance of the vascular bed, which in turn decreases with increasing blood pressure (35). On this basis, the nimodipine-induced increase in PI probably indicates increased compliance of the vascular bed, which could be secondary to the concomitant decrease in ABP as well as to a direct action of the drug on the myogenic tone of the vessels. For this reason, PI should not be considered a reliable index of cerebrovascular resistance. Conversely, a non-significant 9% decrease in cerebrovascular resistance is provided by CVR; however, a hypothetical dilation of MCA would lead to underestimation of blood flow in the MCA and consequently to underestimation of the decrease in CVR.

### Cerebral oxygenation and blood volume

To our knowledge, there are no previous NIRS-based investigations of the effects of nimodipine. Furthermore, the effect of another dihydropyridine calcium channel blocker, nifedipine, has been investigated, in surgical patients, in only two studies. While Choi et al. (36) did not observe nifedipine-induced changes in regional cerebral oxygen saturation in patients undergoing orthognathic surgery, Morimoto et al. (37) reported significant increases in  $\text{O}_2\text{Hb}$  in patients recovering from gynaecological surgery.

One important limitation of the NIRS technique in assessing cerebrovascular changes is the potential interference of extracranial circulation. New algorithms have been developed specifically addressing this issue; a recent study showed the higher reliability and specificity of SRS as compared to standard BL parameters (22).

This evidence prompted us to focus on the SRS param-

eters, i.e. THI and TOI, to look for local changes in cerebral blood volume and cerebral oxygenation, respectively.

The significant increase exhibited by THI strongly suggests that nimodipine induced vasodilation in cortical brain tissues, while the observed increase in TOI opens up different possibilities.

If, indeed, brain metabolism is unchanged following nimodipine administration, as reported by a number of studies (20,29,38,39), then the TOI could be considered an indicator of CBF. In fact, increased CBF would result in reduced oxygen extraction by the tissue, thus in increased tissue oxygenation. Therefore, increased TOI strongly supports the possibility of a nimodipine-induced CBF increase, occurring in spite of the concomitant decrease in ABP. This datum would confirm the effect reported in some animal studies (see above) and in a few human studies (18,19). Stiefel et al. (40) measured intraparenchymal tissue oxygen tension in patients affected by subarachnoid haemorrhage and found decreased oxygenation in seven out of 11 patients treated with nimodipine (60 mg), in spite of maintained ABP. We have no explanation for their results, which differ from ours; the pathological condition of their patients, as well as the accompanying treatment, might be responsible for the discrepancy.

### Cerebrovascular reactivity

Several studies have investigated the possible effects of nimodipine on cerebrovascular reactivity to changes in  $\text{pCO}_2$  by monitoring changes in CBF, diameter of pial vessels, or  $V_{\text{MCA}}$  in both animals and humans. The literature presents results ranging from no effect (33,41) to strong impairment of  $\text{CO}_2$  reactivity (20,39).

$V_{\text{MCA}}$  monitoring constitutes a sensitive tool to investigate vasoreactivity that, being non-invasive, is widely used (23).  $V_{\text{MCA}}$  responses to HV and RB in the control (pre-administration) condition are compatible with those reported in other studies (42) and both are slightly reduced by nimodipine, thus supporting previous reports of nimodipine-induced reduction of vasoreactivity (see above).

Near infrared spectroscopy has occasionally been used to assess cerebrovascular responses to  $\text{CO}_2$  challenges (22-25) but not to assess the modulatory action of  $\text{Ca}^{2+}$  channel blockers. NIRS parameters, as compared to  $V_{\text{MCA}}$ , were here found to have lower sensitivity to changes in  $\text{pCO}_2$ , in agreement with previous studies (23,24). For this reason, and also due to the small number of investigated subjects,  $\text{CO}_2$  reactivity of SRS parameters failed to reach statistical significance in the control condition. A particularly low reactivity was exhibited by TOI during RB. In the literature, TOI, as well as THI, is reported to decrease in response to hypocapnia (43) and to increase in response to normoxic hypercapnia (24,25), suggesting cerebral vasoconstriction and vasodilation, respectively. However, RB also includes a hypoxic stimulus which can result in partial arterial haemoglobin desaturation. The combination of these two opposite effects, i.e., vasodilation and haemoglobin desaturation, probably explains the minimal TOI response to RB.

With this exception, it is however interesting to observe that the extent and significance of  $\text{CO}_2$  reactivity increased after nimodipine during both HV and RB, sug-

gesting increased potential to constrict and to vasodilate. This apparent contrast with the indication provided by  $V_{MCA}$  can partly be attributed to the fact that TCD and NIRS monitored different brain areas that may have been differently affected by nimodipine (44).

### Limitations of the study

One limitation of this study is that it was not designed as a randomised, double-blind, placebo-controlled study. In a pilot study, secondary effects, including headache and dizziness, were consistently observed in volunteers following nimodipine administration at these doses. For this reason, we assumed that the subjects taking part in the present study could not really have been kept blind with respect to the given drug.

In addition, the measurements were not repeated after the drug effect wore off. This was because we needed to limit the overall duration of the experimental protocol (already lasting over two hours, including the initial preparation).

### Concluding remarks

In conclusion, the combined measurement of TCD and NIRS parameters provided complementary information in assessing the cerebrovascular effects of nimodipine. The present data showed increased blood volume and oxygenation at cerebral level, supporting the idea of cerebrovascular dilation and increase in CBF, respectively.

Incidentally, this would imply a nimodipine-induced dilation of the middle cerebral artery to account for the observed (non-significant) decrease in  $V_{MCA}$ . Although NIRS parameters exhibited lower sensitivity to  $CO_2$  reactivity tests, they challenge the concept that cerebrovascular reactivity is impaired by nimodipine.

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