Cerebral Hemodynamic Response to Mental Activation in Normo- and Hypercapnia

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SUMMARY Changes of regional cerebral blood flow from rest to mental activation by a visually presented spatial reasoning test were measured during normo- and hypercapnia in 10 healthy subjects. Hypercapnia, elicited by inhalation of 6% CO₂, resulted in similar flow increases in all 32 cortical regions measured. Increases of flow during testing were seen in post-central regions of the brain whether the resting level was augmented by hypercapnia or not. The results show that an elevated local functional level in the cortex causes an automatic local vasodilatory response which is totally independent of the basal level of perfusion and availability of metabolic substrates.

MATERIAL WORK leads to regional cerebral blood flow (rCBF) increases in specific cortical areas considered to be functionally active during performance of the task. These changes in flow are directly coupled to variations of regional cerebral metabolic rate of oxygen (CMRO₂) indicating a local level of neuronal activity. Although cerebral circulation increases as a result of a higher CMRO₂, this relationship is not reciprocal. While CBF is globally increased during hypercapnia, and hypoxia, CMRO₂ remains constant within PaO₂ levels of 15-80 mm Hg.

By superimposing local metabolic activation, by means of a mental task, upon a globally increased cerebral circulation due to hypercapnia, the relationship between these 2 regulatory mechanisms was investigated in the present study. Two possible outcomes were considered: 1) An rCBF increase as a result of mental activation added to the hyperperfusion caused by hypercapnia, or 2) no further increase due to the already high CBF, the tissue being sufficiently supplied.

Another aim of the investigation was to define the lateralizing properties of visual-spatial problem solving (Raven's Matrices) and to test the reliability and reproducibility of the regional activation response.

Material and Methods

Measurements of rCBF were made in 10 righthanded healthy male volunteers (mean age 26 ± 4 years) by the 18Xe inhalation technique as modified by Obrist. Our 18Xe inhalation system (Meditronic-Novo Diagnostic Systems, Denmark) enables simultaneous measurements of 16 homologous regions of both hemispheres by 32 scintillation detectors (1/2 X 1/2 NaI (T1) crystals; lead collimators 20 mm deep and 22.5 mm wide) placed in parallel at a right angle to the lateral surfaces of the head. 18Xe mixed with air (2.5 mCi/l) was inhaled by the subjects through a tight-fitting mask and a rebreathing spirometer system for one min followed by 10 min of breathing air.

The first measurement in each subject was preceded by a 30 sec background registration, with a 5 min recording of remaining activity preceding each subsequent measurement (fig. 1). A separate detector continuously recorded radiation in a sample of expired air (via a catheter in the face mask). End tidal values were later used to correct for recirculation. An additional scintillation detector continuously monitored possible leakage of 18Xe from the face mask. A window setting of the pulse-height analyzers was 65-95 KeV. Fourteen bit binary integrators integrated counts during 5 sec epochs for the head detectors and during 0.3125 sec periods for the air curve detector. Peak count rates of approximately 500 cps were recorded for the head curves while 1500 cps were obtained for the end-tidal values of the air curve. Using computer programs developed by Obrist and Risberg, the paper tape punched data (Facit, Sweden) were later analyzed by an HP 9825-A desk top computer system, solving, among other variables, for f, the flow of rapidly perfused grey matter compartment, and ISI (Initial Slope Index). The arterial PCO₂ was estimated from recordings of end-tidal CO₂ concentrations (Beckman LB2 analyzer) and blood pressure was measured by auscultation. (For a more detailed description of the 18Xe inhalation technique, see Obrist et al. and Risberg.)

Experimental Design

Each subject had 4 consecutive measurements consisting of counterbalanced rest and problem solving activation during both normal breathing and inhalation of 6% CO₂ mixed with air. The CO₂-air mixture was administered for one min prior to the 18Xe inhalation, discontinued for technical reasons during the one min isotope intake, and recommenced for an additional 8 min (fig. 1).

Before the experiment, each subject was informed in detail about the measurement procedure and the possible discomfort of CO₂ breathing. Each was instructed on the activation test and given at least 3 training items to exercise problem-solving strategy. Subjects were allowed to become accustomed to the experimental situation (breathing in a face mask, supine position with head immobilized by the detec-
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Xenon Inhalation measurement procedure, combined with testing and CO₂ inhalation.

XENON INHALATION

FIGURE 1. The measurement procedure differences between first and subsequent sessions (e.g. measurement 2) during rest and mental activation (testing). CO₂ was identically administered during rest and test measurements. The smooth, dotted line represents an extracranially recorded head curve while the sharply oscillating line shows a typical air curve, highest during the one minute 133Xe inhalation. End tidal points, used for estimating arterial concentration of 133Xe are on the trough during inhalation and on the peak afterwards.

tors, etc.) for 5 min preceding the first measurement in an attempt to eliminate any anxiety. Each measurement was made only when the subject showed normal breathing as monitored by the capnograph. During the resting measurements (normal air breathing: R; and CO₂ inhalation: RCO₂), the subjects were asked to relax with eyes closed and covered. The mental activation (subsequently labelled A and ACO₂) consisted of parallel versions of Ravens' Advanced Progressive Matrices which were presented via a slide projector on a screen suspended on the ceiling over the subject's head. This particular test was chosen because previous experience showing a well-defined posterior activation of cerebral blood flow during the activation session. The testing began 30 sec after the start of 133Xe inhalation (fig. 1) and was continued for the duration of the measurement. An answer (a number between 1-8) given orally via a microphone mounted in the face mask was immediately followed by a new slide which was projected for as long as the subject required.

Statistical Analysis

The main statistical methods were one-way analysis of variance, Pearson correlations and t-tests for related samples, constructed and programmed by one of the authors (I.P.) for a Hewlett-Packard 9825-A. All analyses were run for each variable (detector or hemispheric mean) across R, RCO₂, A and ACO₂ measurements with a simple mixed effects model.

Results

A summary of the data for each of the 32 detectors, hemispheric mean (fₘ and ISI) and average PCO₂ level for the 4 measurements is given in the table. Detector localization is depicted in figure 2.

Resting Measurements

The resting flow landscape characterized by higher frontal and lower postcentral flows was evident during both R and RCO₂ (fig. 3). Mean PCO₂ increased significantly by 25%, mean hemispheric flow by 34%, and ISI by 14% (table; F = 6.743, p < 0.001).

The only significant difference in flow distribution between normo- and hypercapnia was located in a midrolandic region of both hemispheres (area 7; F = 2.867, p < 0.05). Inhalation of 6% CO₂ resulted

FIGURE 2. Average localization of homologous detectors over the cerebral hemisphere. Detectors are referred to by number.
in significant flow increases in all cortical regions (F = 6.743, p < 0.001). Flow values as a function of Pco₂ are shown in figure 4. The CBF increases during hypercapnia were uniform among the subjects. Average breathing rate per min was 11.8 (± 2.44) and 12.5 (± 3.37) during normo- and hypercapnia respectively.

Mental Activation Measurements

Differences in rCBF between resting and problem solving consisted of significant posterior flow increases in the right hemisphere in areas 12 (F = 4.377, p < 0.01), 14, 16 (F = 6.743, p < 0.001) and in the left hemisphere in areas 14 (F = 6.743, p < 0.001), 15 (F = 2.867, p < 0.05) and 16 (F = 6.743, p < 0.001). As can be seen in figure 5 there is no marked right-left asymmetry in response to mental activation. Hypercapnia did not change the posterior cerebral blood flow increases during problem solving. These are in the right hemisphere in areas 13 (F = 4.377, p < 0.01), 14 (F = 2.867, p < 0.05), 15, 16 (F = 6.743, p < 0.001), and in the left hemisphere in 14 (F = 4.377, p < 0.01) and 15, 16 (F = 6.743, p < 0.001). Mean hemispheric increases were approximately 7% and 4% in A and ACO₂ respectively. Test performance (number of correct items divided by the total number of items presented) was 64% during A and 52% during ACO₂.
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Discussion

The activation response to problem solving, consisting of significant posterior cerebral blood flow increases, has been replicated. No significant frontal increases were observed during activation or activation and O₂, confirming earlier observations about the lack of specific frontal involvement in visual-spatial problem solving. The results suggest that Raven's Matrices may be clinically useful for determination of post central cerebral dysfunction.

The hemodynamic response to activation showed no hemispheric asymmetry (fig. 5). Task components known to be lateralized are visual-spatial relationships (right hemisphere) and analytical (verbal) solutions of problems (left hemisphere). It is thus likely that both hemispheres are involved to an equal extent in this complex task. The magnitude of activation response in flow units was shown to be fairly constant among highly variable resting flow levels: testing increased mean flows (f₁) by 4.8 and 4.0 ml/100g/min in normo- and hypercapnia. This additive effect of hypercapnic vasodilation and mental activation indicates that the activation response within an individual — and probably also among individuals — can be compared with different resting flow levels. The validity of this reasoning holds as long as the flow differences are mainly caused by arterial Pcao differences or other predominantly vasoactive agents, and not because of differences in metabolic rates. In an earlier publication we suggested that task performance in healthy brain tissue is associated with a typical flow level, and, consequently, CBF increases during testing will be inversely related to resting flow levels when they reflect different metabolic states. The present results show that the magnitude of flow increases (in absolute units) is constant across different resting levels when these differences are vascular in origin. The CBF reactivity to arterial Pcao changes showed, as expected, no significant regional differences. A Pcao increase of 10.55 mm Hg caused an f₁ increase of 34% (25 ml/100g/min) during rest, i.e. a correction factor of 3.2% or 2.3 ml/mm Hg, which compared with what has been reported by other groups. During activation the correction factors were slightly lower: 2.9% and 2.3 ml/mm Hg. The corresponding corrections for ISI were considerably lower: 1.4% or 0.75 ml during rest and 1.3% or 0.75 during activation, demonstrating the limited sensitivity of this flow parameter in hyperemic situations.

The present findings raise the question of what causes the local hemodynamic response to mental
work. In addition to producing hyperemia, hypercapnia also increases the arterial Po2 level.14 It is thus highly unlikely that activation-induced flow increases during hypercapnia are caused by any chemical changes related to lack of metabolic substrates. Animal studies have demonstrated a poor coupling between CBF and tissue pH where it was shown that during bicuculline-induced seizures, net tissue acidosis did not occur until after maximal vasodilatation万个.

This would suggest that the local effects of elevated H+ concentrations are not the immediate precursor of augmented CBF. The rise of cerebral perfusion through local vasodilatation seems to occur automatically and obligatorily in parallel with increased neural metabolism and is mediated by yet unknown chemical agents and/or neurogenic control.

Acknowledgment

This work was supported by grants from the Swedish Council for Social Science Research, from the Swedish Medical Research Council (project no. 14X-04969) and Konsul Thure Karlsson Foundation. The authors are indebted to Professors G. Smith and B. Siesjö, Drs. L. Gustafson and B. Hagberg for valuable discussion and criticism of the manuscript. We are greatly grateful to Ms. Barbro Hjorth Jönsson for typing the manuscript and to Helena Fernö for preparations of illustrations.

References

Deleterious Effect of Glucose Pretreatment on Recovery from Diffuse Cerebral Ischemia in the Cat

I. Local Cerebral Blood Flow and Glucose Utilization

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AND WILLIAM W. BUDD, B.S.

SUMMARY Diffuse cerebral ischemia was created in pentobarbital-anesthetized cats by basilar and bilateral carotid artery occlusions and hypotension. Local cerebral blood flow (LCBF) was assessed autoradiographically with **C-antipyrine, and local cerebral glucose utilization with **C-2-deoxyglucose. In animals without glucose pretreatment, 15 min of ischemia led to a homogeneous reduction of post-ischemic cerebral perfusion to 31% of control; ischemia of 30 min produced post-ischemic perfusion heterogeneities in the cerebral cortex and deep gray structures. In animals pretreated with dextrose, 1.5 gm/kg intravenously, heterogeneous cerebral perfusion was observed following only 15 min of ischemia, and a severe global impairment of cerebral reperfusion occurred after the 30 min insult. Deoxyglucose autoradiograms in the latter animals were remarkable for a complete suppression of tracer uptake in the cerebral cortex and a paradoxically increased tracer concentration in the cerebral white matter. Mean plasma glucose in the treated animals exceeded 1000 mg/100 ml. Large glucose loads prior to ischemia dramatically impair post-ischemic cerebral perfusion.

OUR UNDERSTANDING of the factors which prevent the brain from recovering from episodes of ischemia remains incomplete. Myers and coworkers have provided evidence that the fed or fasted condition of an animal may dramatically affect its response to cerebral ischemia: Food-deprived juvenile rhesus monkeys subjected to 14-min periods of cardiac arrest characteristically showed good neurological recovery and preserved ability to perform visual discrimination tasks; at neuropathological examination, their brains were either intact or exhibited injury restricted to brain stem nuclei, Purkinje cells, and hippocampus. By contrast, 2 animals which had received glucose infusions immediately prior to cardiac arrest developed fasciculations, myoclonic activity, decerebrate rigidity and fixed, dilated pupils; their brains showed cerebellar tonsillar herniation and microscopic evidence of widespread necrosis involving cerebral cortex and basal ganglia. These findings were subsequently confirmed in a larger series. In a similar study, Siemkowicz and Hansen examined the effect of varying blood glucose levels on clinical survival in rats exposed to 10 min of complete brain ischemia by compression of neck vessels with a pneumatic cuff. Normoglycemic animals survived chronically with minor neurologic deficits, whereas hyperglycemic rats remained comatose and died within 24 h. Because of the potentially important implications of these observations, we were prompted to investigate this phenomenon in a standardized experimental model of global cerebral ischemia developed in our laboratory, in which the hemodynamic, metabolic, and neuropathological consequences of graded cerebral ischemia have already been extensively documented. Preliminary findings have been reported in abstract form.
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*Stroke*. 1980;11:342-347
doi: 10.1161/01.STR.11.4.342

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/11/4/342

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