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Regional Cerebral Blood Flow and Verbal Memory after Chronic Exposure to Organic Solvents

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Regional cerebral blood flow (rCBF; ^{133}Xe-inhalation method) was investigated in 32 industrial workers (age: 51 ± 9 years) who had been exposed to organic solvents during an average of 24.5 years. The measurements were made at rest and during learning of associated word pairs. The resting flow level was 17% lower than expected for normal subjects of similar age and the activation-induced changes of rCBF during the test lacked the frontal activation normally seen. Significant correlations between age, length of exposure, and rCBF level were found. In order to control for the age factor, results were also calculated from two subgroups of similar age but with very different levels of exposure (13 and 31 years of average exposure). The two groups differed only slightly in resting rCBF. A marked difference was, however, seen during activation, with significant post-central flow increases recorded in the lower-exposed group only. The results indicate the potential of the rCBF method for elucidating functional cortical changes related to neurotoxic effects of organic solvents.

Long-term exposure to organic solvents has been associated with CNS dysfunction and occasionally even permanent brain damage (Arlien-Søborg, Bruhn, & Melgaard, 1978; Cohr & Stockholm 1979; Knox &

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Nelson, 1966; Mikkelsen, Gregersen, Klausen, Døssing, & Nielsen, 1978; Prockop, 1977). It has been shown to seriously affect memory and cognitive functions as well as psychomotor abilities and emotional factors (Cohr & Stockholm, 1979; Hane, Axelsson, Blum, Hogstedt, Sundell, & Ydreborg, 1977; Hänninen, Eskelinen, Husman, & Nurminen, 1976; Sahroe & Olsen, 1979). A relationship between years of exposure and occurrence of an organic brain syndrome characterized by diminished intellectual functions, fatigue, and reduced memory has been found in occupationally exposed workers (Müncheninger, 1963). Pneumoencephalographic measurements and computerized tomography (CT) have yielded only tentative indications of pathological changes in the brain morphology of exposed workers (Gregersen, Mikkelsen, Klausen, Døssing, Nielsen, & Thygsen, 1978; Juntunen, Eistola, Hupli, & Hernberg, 1979; Elofsson & co-workers, 1979). EEG studies have shown conflicting results varying from an increment in slow waves to a higher occurrence of beta activity (Härkonen, Lindström, Seppäläinen, Sisko, & Hernberg, 1978; Rosen, Haeger-Aronsen, Rehnström, & Welinder, 1978).

The neurophysiological methods used so far have thus not succeeded in showing consistent and conclusive evidence of brain pathology. Consequently there is a great need for new and more sensitive methods for studying brain dysfunction in chronically exposed subjects. The present report is the first in a series aimed at evaluating the noninvasive ^{133}Xe-inhalation method for measurement of regional cerebral blood flow (rCBF) for such studies. Mapping of rCBF offers unique information about neuronal functional levels in the cortex (Raichle, Grubb, Gado, Eichling, & Ter-Pogossian, 1976) and has been successfully used in several studies of the functional organization of the cortex during mental processes in normal man (Maximilian, Prohovnik, Risberg, & Hakansson, 1978; Maximilian, Prohovnik, & Risberg, 1980; Risberg & Ingvar, 1973; Risberg, Maximilian, & Prohovnik, 1977). The clinical usefulness of the method for the differentiation of organic dementia of different etiologies from pseudodementia due to effective disorders or confusion has been demonstrated in several previous investigations (Gustafson, Brun, & Ingvar, 1977; Gustafson and Risberg, 1974; Johanson, Risberg, Silfverskiöld, & Gustafson, 1979; Nilsson, Risberg, Johanson, & Gustafson, 1977). The rCBF method has also given important information about the influence on brain function of other toxic agents such as alcohol (Berglund & Risberg, 1977).

The main purpose of the present study was to elucidate possible cortical functional correlates of impaired memory in a group of occupationally exposed subjects. We wanted to investigate whether rCBF determinations made during the activation of a deficient mental function such as memory would provide relevant information about the neurotoxic effects of industrial solvents.

MATERIAL AND METHODS

Subjects. The study was performed on 32 right-handed male workers (painters, floor layers, dry cleaners, etc.) with a mean age of 51 ± 9 years who sought medical aid for a variety of symptoms such as tiredness, memory disturbances, dizziness, and headache. After a thorough medical examination it was concluded that these symptoms were related to exposure to organic solvents and no other disorder. The subjects had been exposed to a mixture of organic solvents (aromatic hydrocarbons, ketones, ethers, alcohols, etc.) during their work for an average duration of 24.5 years. The measure of exposure throughout the paper refers to duration of occupational exposure in years.

Method. The rCBF measurements were made by the atraumatic ^{133}Xe-inhalation technique (Mallet & Veall, 1965) using a standard bilateral 32 detector system (NOVO Diagnostic Systems, Hadsund). The reader is referred to Obrist, Thompson, Wang, and Wilkinson (1975); Risberg, Ali, Wilson, Wills, and Halsey (1975); and Risberg (1980) for a detailed description of the analytic model and technical details. During the measurements the subjects breathed the inert and freely diffusible tracer ^{133}Xe mixed with air (2.5 mCi/liter) for 1 min through a face mask. The 1-min ^{133}Xe inhalation was followed by 10 min of normal air breathing during which the washout of the isotope was recorded by 32 scintillation detectors placed in parallel at a right angle to the lateral surfaces of both hemispheres (Fig. 1). The total radiation dose to the lungs was 0.7 mGy per measurement. A separate detector continuously recorded the ^{133}Xe concentration in a sample of expired air to correct for recirculation of the isotope. The rate of isotope washout from the brain is the basis for the flow calculations. The data were analyzed with a HP 9825 desk-top computer using programs based on principles developed by Obrist et al. (1975) and Risberg et al. (1975). In this paper rCBF will be described by the initial slope index (ISI), a flow

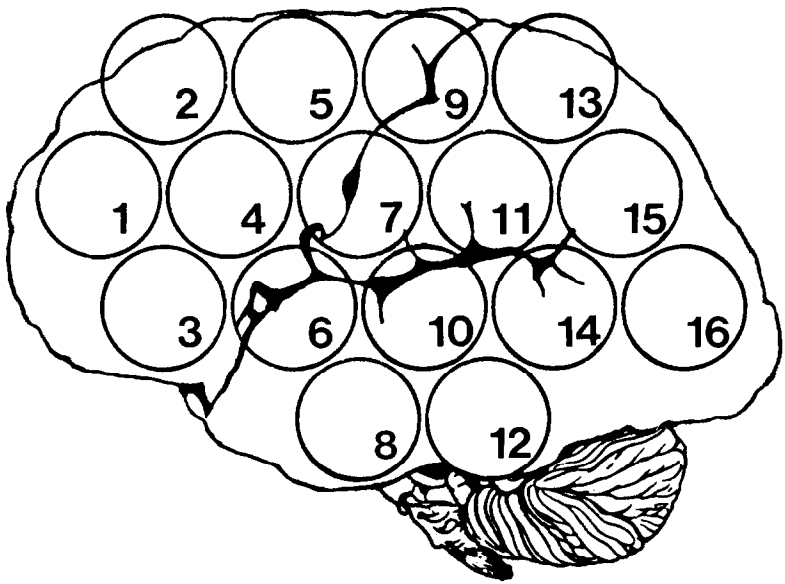

FIG. 1. Average detector localization over homologous regions of both hemispheres.

parameter dominated by gray matter flow, which due to its high stability and reliability is preferable in clinical studies such as the present one (Risberg et al., 1975). Arterial pCO_2 was estimated from recordings of end-tidal CO_2 (Beckman LB2 analyzer) and blood pressure was measured by auscultation.

Experimental design. The rCBF of each patient was measured twice, during a resting session with closed eyes and during a verbal memory activation task. During the testing session the subjects were required to learn 60 associated word pairs presented visually on six slides. Each slide was shown for 1 min on a screen suspended upon the subject's head. Recall of the learned material was tested immediately after the end of the rCBF activation measurement. All subjects were instructed in detail about the measurement procedure and were given training items of the test.

RESULTS

Total Material (N = 32): rCBF during Rest

In healthy subjects 20–30 years old the rCBF distribution in the cerebral cortex during rest is characterized by flows about 5–10% above hemispheric mean in the frontal regions, at the mean level centrally, and 5–15% lower in posterior and temporal areas (Maximilian et al., 1980; Risberg et al., 1977). As can be seen in Fig. 2, the average regional distribution of the present group did not deviate from this pattern. The mean hemispheric flows were 43.5 (± 5) in both hemispheres, compared to 55 (±6) in a group of younger subjects (Maximilian et al., 1980).

According to Lavy, Melamed, Cooper, Bentin, and Rinot (1979) normal brain CBF (ISI) = 62.46 − .2239 × age of subject. Using this age regression equation the mean flows of the exposed workers were 17% lower than expected in normal subjects of similar age. Mean pCO_2 was 38 (± 4) mm Hg and mean arterial blood pressure (MABP) was 102 (± 10) mm Hg.

rCBF Changes during Memory Activation

Activation-related increases of rCBF were seen in posterior areas only, while healthy subjects undergoing an identical testing procedure had in addition significant flow increases in the frontal cortex (Maximilian et al., 1978). Recall performance was 33% lower in the exposed workers as compared to the normal group (30 vs. 50 recalled word pairs).

Correlations between CBF, age, and exposure. Significant negative correlations were obtained between age and CBF ($r = -.55$ left hemisphere, and $-.54$ right hemisphere; $p < .01$ and .05, respectively). Recall performance was significantly correlated with length of exposure ($r = -.49$; $p < .01$) but not with age ($r = -.21$).

Age-matched subgroups. To control for the effect of aging per se we have selected two age-matched subgroups out of the total 32 subjects.

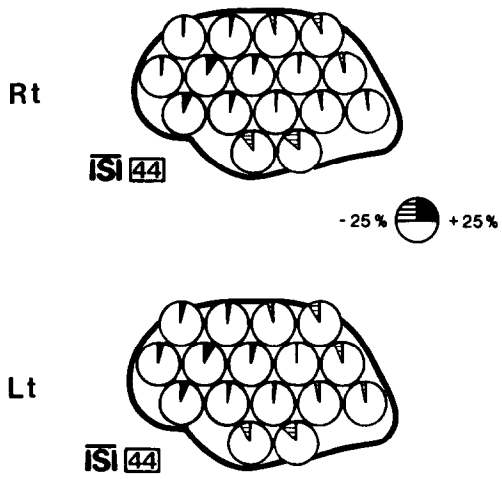

FIG. 2. Regional cerebral blood flow distribution during rest (N = 32). Mean hemispheric flows are shown in boxes; regional values are expressed as deviations from those means. Darkened sections denote a value above the mean and striped sections denote a value below the mean (90° = 25%).

The short-exposure group (SE) included 10 subjects with a mean age of 50 (± 8.2) years who were exposed for 13 (± 5) years. The long-exposure group (LE) included 10 subjects with a mean age of 49 (± 9.5) years and 31 (+ 10.6) years of occupational exposure.

rCBF during Rest and Activation

The resting rCBF distribution patterns of both groups were normal, with mean hemispheric flows of 45 and 44 in the SE and LE groups, respectively (Fig. 3). This small difference was accentuated during the mental activation session. Nine out of the ten SE subjects increased their flow during verbal learning (3% in the right hemisphere and 5% in the left hemisphere), while in the LE group four subjects increased, two decreased, and the remaining four showed no change in flow from resting to testing (average bihemispheric group increases of 1%).

The hemodynamic response to verbal memorization for both groups is depicted in Fig. 4. The SE subjects had significant posterior flow increases in the inferior parietal and superior temporal regions of the left hemisphere which were twice as high as those in the respective regions of the LE group. None of the groups showed frontal increases during testing.

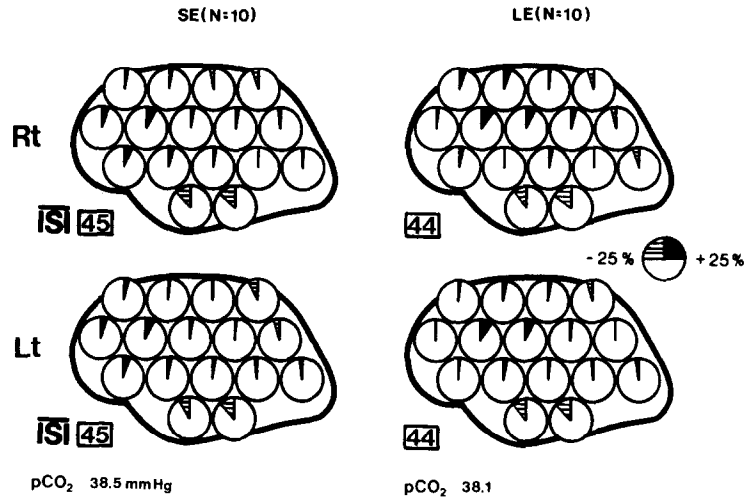

FIG. 3. Regional cerebral blood flow distribution during rest. Resting landscape of age-matched subgroups. Note the similar hemispheric means and the hyperfrontal pattern of both groups.

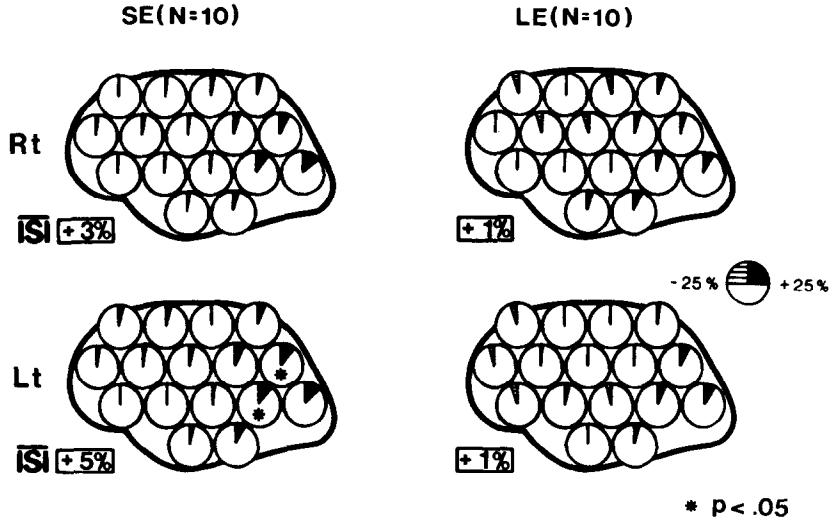

FIG. 4. Regional hemodynamic changes during verbal memory. Mean hemispheric flow increases are shown in boxes; clock symbols denote local flow increases (%) from rest to test. Note the higher mean flow and significant posterior increases in the left hemisphere of SE patients.

Correlations between CBF, exposure, and age. As is shown in Table 1, significant correlations between CBF, age, and exposure were obtained in the LE group only. A high correlation ($r = .96$; $p < .01$) between the age and exposure factors was also found solely in the LE group. Differences between the two subgroups were also found in test performance, the SE subjects recalling 22% more items (34.6 vs. 21.5) than the LE subjects. Independent psychological testing confirmed these group differences showing the SE subjects to be better by 46% in a word pair test and 27% better in the Benton visual retention test. The SE and LE subjects did not differ in their premorbid intellectual endowment as shown by equal performance on a synonyms test.

DISCUSSION

A tendency toward reduced cerebral perfusion was noted in the 32 occupationally exposed workers presently studied. According to the age-corrected normative data of Lavy et al. (1979) the CBF for this particular age group should have been 17% higher. It is also interesting to compare the present subjects with a group of patients (mean age 60) suffering from depression who had a hemispheric blood flow of 47 (Johanson et al., 1979). This level was higher than that of both subsequently selected age-matched subgroups.

While mean cerebral perfusion and bilateral rCBF distribution of the SE and LE subjects were similar, the two groups differed in their hemodynamic response to mental activation. Together with superior recall performance, the SE had a larger and statistically significant increase during testing in task-related regions of the left hemisphere when compared to the LE subjects.

Because the groups were age matched, this difference was most probably due to the different lengths of exposure. Both groups were affected as seen by the relatively low resting flows, but the longer-exposure subjects were apparently more affected.

Due to the small number of subjects within each group, conclusive generalizations of the present material cannot yet be drawn. However,

TABLE 1
PEARSON CORRELATIONS BETWEEN BLOOD FLOW, AGE, AND EXPOSURE (.632 = $p < .05$)

	SE	LE
Age and CBF		
RH	−.07	−.67⁺
LH	−.17	−.66⁺
Age and exposure		
RH	−.39	−.73⁺
LH	−.47	−.71⁺

the low CBF increases during verbal learning accompanied by the low recall performance could be interpreted as a likely physiological correlate to the cerebral dysfunction associated with organic solvent exposure.

The significant negative correlations between age and exposure and CBF were only found in the LE group. These correlations could be partially explained by the slightly larger age variation of the group, but together with the supportive CBF and psychometric results, the difference between SE and LE subjects could indicate what Gregersen et al. (1978) described as a "gradual development of an organic brain syndrome." Our results suggest a combined effect of aging and prolonged toxic exposure leading to cerebral dysfunction. This has already been suggested by Elofson et al. (1979) and agrees well with the accelerated aging process in the brains of chronic alcoholics discussed by Wilkinson and Carlen (1979). A meaningful continuation of this study would be to determine whether mental functions and their neurophysiological correlates improve after termination of exposure, and to provide information about age-factor effects upon the eventual recovery process. The study of reversibility of function would hopefully help elucidate another aspect of the effects of solvents upon the brain, namely, whether these effects are functional or organic. Incidences of damaged myelin have been reported in chronic alcoholics (Tichy, Alling, Deucher, & Svennerholm, 1970). One possibility is that the initial effects of prolonged exposure are linked to impaired neural transmission leading subsequently to longer periods of multiregional deactivation. Together with the aging factor this may facilitate the loss of otherwise active neuronal tissue. It could best be studied by combining rCBF and CT methods with histological data from animal experiments.

The results of the present study indicate the potential of the present method for providing information toward a better understanding of cerebral dysfunction linked to exposure to organic solvents. That discriminatory criteria could be obtained between two groups differing only in their length of chronic exposure gives a good indication of the sensitivity and utility of the rCBF method in clinical and experimental studies of the neurotoxic effects of organic solvents upon cognitive processes.

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