Bull Yamaguchi Med Sch 35(3-4) : 69-75, 1988

Cerebrovascular Reactivity to CO_2 in Patients with Metabolic Encephalopathy

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(Received March 22, revised June 28, 1988)

Abstract The effects of hypocapnic-hyperventilation on cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) were evaluated in 7 patients with hepatic or septic encephalopathy. A positive linear relationship between CBF and $PaCO_2$ was observed in hepatic patients ($CBF=3.12PaCO_2-81.4$, $r=0.739$) and in septic patients ($CBF=1.96PaCO_2-36.1$, $r=0.535$). Although these regression equations were not statistically different from that of awake patients ($CBF=0.87PaCO_2+12.0$, $r=0.866$), a tendency to augment the cerebrovascular reactivity to CO_2 was observed in patients with hepatic or septic encephalopathy. Therefore, hypocapnic-hyperventilation produced a reduction in CBF below the level required to meet the demand in 4 of 7 patients. As an index of cerebral ischemia, the ratio of CBF to $CMRO_2$ was examined in the same patients during alteration of $PaCO_2$. A good linear correlation was observed between $CBF/CMRO_2$ and jugular venous PO_2 ($JPvO_2$) ($CBF/CMRO_2=0.97JPvO_2-15,4$, $r=0.917$).

It is concluded that cerebrovascular reactivity to CO_2 was preserved in patients with hepatic and septic encephalopathy, therefore, intentional or inadvertent hyperventilation may produce cerebral ischemia in these patients. The $JPvO_2$ may be useful as a monitor for cerebral oxygenation in patients with metabolic encephalopathy.

Key Words : Metabolic encephalopathy, CBF, CO_2 response, Hyperventilation, Brain hypoxemia

Introduction

Conscious disturbance is often the leading symptom in metabolic diseases, i. e., acute severe hepatic disease or sepsis. Mechanical respiratory support is one of the best interventions for the adequate management of these patients.

Cerebrovascular reactivity to $PaCO_2$ is less susceptible to damage[1], so that inadvertent hypocapnic-hyperventilation may produce brain hypoxemia due to a reduction in cerebral blood flow which is not sufficient to meet the demand. However, Chodobski and co-workers[2] demonstrated that cerebrovascular reactivity to CO_2 was diminished or abolished in cats with experimental hepatic coma by the intravenous infusion of ammonium acetate. In patients with metabolic encephalopathy, including hepatic or septic encephalopathy, it has not yet been proven that cerebrovascular reactivity to $PaCO_2$ is presented or not, and furthermore, it is not clear as to what level the $PaCO_2$ can be reduced without producing brain tissue hypoxia when the patients are put on a mechanical ventilator.

In this study, CBF was measured by the

Kety-Schmidt method using nitrous oxide[3] and then the cerebral metabolic rate for oxygen was calculated to examine the cerebrovascular reactivity to $PaCO_2$ in 7 patients with metabolic encephalopathy. In addition, an attempt was made to clarify whether jugular venous PO_2 can provide information regarding adequate cerebral oxygenation during mechanical ventilation.

Materials and Methods

Seven patients, 3 patients with hepatic encephalopathy (HE) and 4 with septic encephalopathy (SE) were studied. Tables 1 and 2 show the clinical data for the two groups. Hepatic encephalopathy was graded according to the clinical severity of neuropsychiatric features using the criteria of Sherlock[4] ; all patients showed Grade 5 ; deep coma with no response to painful stimuli. Septic encephalopathy was graded according to the Glasgow Coma Scale[5] ; on admission, all patients showed 3-4 points. Sanction for the investigation was obtained from the Ethical Committees of the Hospital, and written informed consents were obtained from the patient's relatives.

The cerebral blood flow (CBF) was measured in all 7 patients and 8 observations of CO_2 -response were made in 7 patients with HE or SE on admission day and in a steady state following mechanical ventilation. All patients were intubated and placed on a mechanical ventilator to maintain their PaO_2 values above 80 mmHg, applying positive end-expiratory pressure (PEEP) as needed. In all patients, EEGs were recorded using front-parietal silver-silver chloride electrodes. The radial artery was cannulated for measurement of arterial pressure and for blood sampling. Using ultrasonic guidance[6], an 18-gauge Medicut catheter was placed in the left jugular bulb for blood sampling and CBF measurement, and the position of the catheter was confirmed by X-ray. The CBF was measured by the Kety-Schmidt technique using 15% nitrous oxide (N_2O) as previously reported[7]. After taking arterial and jugular bulb venous blood samples, N_2O was added to the inspired oxygen. Simultaneous arterial and jugular bulb venous blood samples were obtained 1, 3, 5, 7, 10, 12, and 15 min after the initiation of N_2O inhalation.

Table 1 Clinical data of patients with hepatic encephalopathy.

Patient No.	Age (years)	Sex	Diagnosis	NH_3 (μg%)	Bilirubin (mg%)	EEG	Conscious level*	Outcome	Lenght of stay in ICU (days)
1	43	M	Esophageal varix	193	18.7	Burst& Supression	5	Died	10
2	32	M	Fulminant hepatitis	>400	40.1	50μV 2 – 3 Hz	5	Died	30
3	42	M	Fulminant hepatitis	212	20.5	70-100μv 2 – 3 Hz	5	Died	17

*Scherlock's criteria

Table 2 Clinical data of patients with septic encephalopathy.

Patient No.	Age (years)	Sex	Diagnosis	Limulus test	EEG	Outcome	Length of stay in ICU (days)
1	72	M	Unkown origin of infection	+	2 – 4 Hz 30–50μV	Survived	18
2	53	M	Perforation of the colon	+	nearly flat	Died	8
3	85	F	Perforation of the colon	+	flat	Died	7
4	67	M	Perforation of the colon	+	nearly flat	Died	12

Then the concentration of N_2O in the blood was measured by gas chromatography (Shimadzu, GC4APTF, Tokyo, Japan). The CBF was calculated by a modification of the Kety-Schmidt method, which included prolongation of the N_2O saturation phase and extrapolation of the arterio-venous difference of N_2O concentration to infinity.

Mean arterial pressure (MAP) was defined as the cerebral perfusion pressure (CPP), and cerebral vascular resistance (CVR) as the ratio of CPP to CBF. The PO_2, PCO_2, and pH were measured with a blood gas analyzer (178 pH/Blood Gas Analyzer, Corning Medical and Scientific, Mass. U. S. A.), and oxygen saturation (SaO_2, SvO_2) and hemoglobin (Hb) with a Hemoximeter (OSM2, Radiometer, Copenhagen, Denmark). To maintain $PaCO_2$ constant during the CBF measurement, end-tidal CO_2 was monitored with a CO_2 Analyzer (CD300, Datex, Helsinki, Finland). These values were measured before and 7 min, and 15 min after the start of N_2O inhalation ; the mean values of the three samples were used.

Oxygen content was calculated from the hemoglobin oxygen-carrying capacity and the amount of dissolved oxygen, as estimated from PO_2 and oxygen solubility. The $CMRO_2$ was calculated from the product of CBF and the oxygen content difference ($C(a-jv)O_2$) between the arterial (CaO_2) and the jugular bulb blood ($JCvO_2$).

In both patients with HE and those with SE, after the first measurement (normocapnia), relative hyperventilation (hypocapnia) was mechanically performed to provide mild hypocapnia monitoring end-tidal CO_2 during the measurement of CBF. The CBF on hypocapnia was calculated as $CMRO_2$ obtained during normocapnia divided by $C(a-jv)O_2$ by Fick's principle on the assumption that during hypocapnia the $CMRO_2$ was the same as that during normocapnia. Within such a range, $PaCO_2$ has been shown to have no measurable effect on $CMRO_2$[8]. The regression equations of CO_2-responses of CBF in the two groups were compared with that in awake patients reported previously[7]. The ratio of CBF to $CMRO_2$ ($CBF/CMRO_2$) was calculated as the index for the CBF value which adequately meets the cerebral metabolic demand, and the correlation between $CBF/CMRO_2$ and $JPvO_2$ was examined. Dopamine was infused intravenously at a rate of 3-5 μg/kg/min in patients from both groups throughout the period of this study to maintain a stable hemodynamic state. Of the three patients with HE, one was tested for the autoregulation of CBF by raising MAP from 105 mmHg to 115 mmHg by an increase in the dose of intravenously infused dopamine. Body temperature was maintained at 37 ± 0.3℃.

Difference in the regression equations of the CBF and $PaCO_2$ were tested between both groups and awake patients using the Students' t test for an unpaired comparison.

Results

Tables 3 and 4 show the cerebral hemodynamics during normocapnia and hypocapnia in patients with HE and SE, while table 5 and 6 show the blood gas data for the two groups. The CBF on hypocapnia in

Table 3 Cerebral hemodynamics in patients with hepatic encephalopathy.

Patient No.	$Paco_2$ (mmHg)	MAP (mmHg)	CBF (ml/100g/min)	CVR (mmHg/CBF)	$CMRO_2$ (ml/100g/min)	$CBF/CMRO_2$ (ml blood/ml O_2)	$C(a-jv)O_2$ (vol%)
1	35	70	18.4	3.8	0.81	23	4.4
	30	70	(15.9)	4.4	−	20	5.1
2	43	105	48.3	2.2	1.81	27	3.8
	34	105	(24.0)	4.4	−	13	7.5
	47	115	112.4	1.0	1.35	83	1.2
	34	115	(29.4)	3.9	−	22	4.6
3	52	130	54.6	2.4	2.07	26	3.8
	39	130	(28.0)	4.6	−	15	7.4

Abbreviation : mmHg/CBF=mmHg/ml/100g/min. Others : see text.
(CBF)=CBF in parenthesis was calculated from the ratio of $CMRO_2/C(a-jv)O_2$, where $CMRO_2$ was the same as the initial value.

Table 4 Cerebral hemodynamics in patients with septic encephalopathy.

Patient No.	$PaCO_2$ (mmHg)	MAP (mmHg)	CBF (ml/100g/min)	CVR (mmHg/CBF)	$CMRO_2$ (ml/100g/min)	$CBF/CMRO_2$ (ml blood/ml O_2)	$C(a-jv)O_2$ (vol%)
1	38	68	16.6	4.1	1.05	16	6.3
	36	77	24.1	3.2	2.19	11	9.1
2	43	60	82.0	0.7	1.89	43	2.3
	34	60	(22.5)	2.7	–	12	8.4
3	38	84	63.3	1.3	1.90	33	3.0
	29	84	(18.8)	4.5	–	10	10.1
4	46	70	39.7	1.8	2.18	18	5.5
	43	70	(37.6)	1.9	–	17	5.8
	29	70	(28.7)	2.4	–	13	7.6

Abbreviation : mmHg/CBF=mmHg/ml/100g/min. Others : see text.
(CBF)=CBF in parenthesis was calculated from the ratio of $CMRO_2/C(a-jv)O_2$, where $CMRO_2$ was the same as the initial value.

Table 5 Blood gas data in patients with hepatic coma during normocapnia and hypocapnia.

Patient No.	A or V	PO_2(mmHg)		PCO_2(mmHg)		pH		B.E.(mEq/l)		CO_2(vol%)	
		N	H	N	H	N	H	N	H	N	H
1	A	177	127	34	30	7.52	7.58	6	8	9.5	11.3
	V	33	29	45	39	7.44	7.51	7	9	5.1	6.2
2	A	417	125*	43	34	7.41	7.50	3	5	17.8	17.8
	V	54	34	49	42	7.36	7.43	2	4	14.0	10.3
	A	403	161	47	34	7.32	7.46	−2	2	18.3	16.9
	V	88	41	52	44	7.29	7.39	−2	2	17.1	12.3
3	A	524	599	52	39	7.44	7.55	9	11	23.0	23.1
	V	58	37	59	53	7.41	7.47	9	11	19.2	15.7

Abbreviations ; N : Normoventilation, H : Hyperventilation
A : Arterial blood, V : Jugular venous blood
$F_IO_2=0.85$, $F_IO_2{}^*=0.4$

parenthesis in Tables 4 and 5 was determined by calculating the ratio of $CMRO_2$ obtained during normocapnia to $C(a-jv)O_2$.

Although considerable scatter was observed in the CBF values of patients with HE and SE (16.6 ml/100g/min to 112.4 ml/100g/min), all of their $CMRO_2$ values were significantly lower ($p < 0.05$) than those of awake patients (3.1 ± 0.6 ml/100g/min)[7]. There were positive linear relationships in patients with HE and SE between CBF(y) and $PaCO_2$(x), the regression line being $y=3.12x-81.4$ ($r=0.739$) in patients with HE, and $y=1.96x-36.1$ ($r=0.535$) in patients with SE. There were no significant differences in the regression equations between HE, SE and that of awake patients ($y=0.87x+12.0$, $r=0.866$). Following the reduction in $PaCO_2$, $CBF/CMRO_2$ decreased below normal values (14-15 ml blood/ml O_2)[9] in one of three patients with HE and in all three patients with SE. There was a close linear relationship between $CBF/CMRO_2$(y) and $JPvO_2$(x) ($y=0.97x-15.4$, $r=0.917$) (Fig 1). In one patient with HE (patient No. 2), CBF increased from 48.3 ml/100g/min to 112.4 ml/100g/min as MAP rose from 105

Table 6 Blood gas data in patients with septic coma during normocapnia and hypocapnia.

Patient No.	A or V	PO_2(mmHg)		PCO_2(mmHg)		pH		B.E.(mEq/l)		CO_2(vol%)	
		N	H	N	H	N	H	N	H	N	H
1	A	234	248	38	36	7.55	7.49	10	5	15.1	13.2
	V	30	21	51	46	7.48	7.38	14	4	8.7	4.1
2	A	245	284	43	34	7.39	7.49	1	4	16.4	16.4
	V	55	31	46	45	7.37	7.41	1	4	14.1	8.0
3	A	313	275	38	29	7.58	7.74	14	22	15.4	16.7
	V	47	22	41	39	7.56	7.60	15	17	12.4	6.6
4	A	311	294	46	43	7.29	7.37	−4	6	14.9	15.8
	A		95*		29		7.54		4		15.0
	V	39	38	55	52	7.24	7.30	−5	−1	9.4	10.0
	V		26*		42		7.42		3		7.4

Abbreviations ; N : Normoventilation, H : Hyperventilation
A : Arterial blood, V : Jugular venous blood
$F_IO_2=1.0$, $F_IO_2{}^*=0.5$

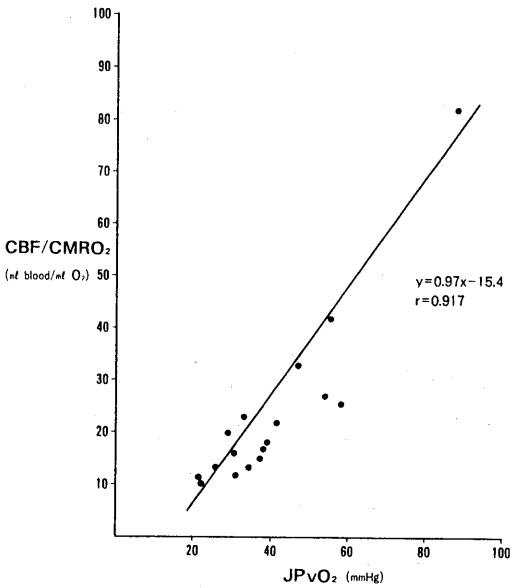

Fig. 1 The relationship between $JPvO_2$ and $CBF/CMRO_2$ in patients with metabolic encephalopathy

mmHg to 115 mmHg. EEG data were consistent with the generalized slowing seen in all patients with HE and SE, with one exception, the patient whose EEG showed burst and suppression.

Discussion

The major findings of this study were 1) $CMRO_2$ values were generally reduced below normal and CBF values were scattered, resulting in an increase in $CBF/CMRO_2$, 2) cerebrovascular reactivity to CO_2 was preserved in patients with ME, including HE and SE, as well as awake patients, 3) a reduction in $PaCO_2$ produced below normal $CBF/CMRO_2$ values (14-15 ml blood/ml O_2)[9] in 4 of 7 patients.

There are many reports concerning CBF and $CMRO_2$ in patients with HE[10-14]. These reports demonstrated that CBF values showed considerable scatter, perhaps due to the alteration of $PaCO_2$ and/or CPP, but that the $CMRO_2$ values were consistently reduced below normal values. Our CBF and $CMRO_2$ results in HE corresponded with these previous studies. However, studies which examined the relationship between CBF and $CMRO_2$ in patients with SE can not be found. In this study, CBF and $CMRO_2$ values in patients with SE were similar to those in patients with HE. Therefore, we discuss here the changes in CBF and $CMRO_2$ with respect to ME, including HE and SE.

The mechanism for the reduction in $CMRO_2$ in patients with ME is unclear.

Dodsworth and colleagues[15] demonstrated that brain norepinephrine synthesis was decreased in acute hepatic coma in rats, and Freund and co-workers[16] observed that in severely septic rats with encephalopathy, norepinephrine and dopamine levels were significantly lower than those in mildly septic rats. There were similarities in the manner of changes in neurotransmitters between the brains of rats in HE or SE. This experimental evidence suggests that the reduction in $CMRO_2$ in patients with ME may be explained by the changes in the brain neurotransmitters. At present, it is unclear whether these changes in brain neurotransmitters are the major cause for the reduction in $CMRO_2$ in patients with ME, or are instead, one more expression of the multiple organ failure occurring during sepsis or acute hepatic failure.

In patients with ME, CBF was much more able to meet the cerebral metabolic demand due to the depression of $CMRO_2$, hence $CBF/CMRO_2$ increased markedly and the oxygen level in blood was higher in jugular venous blood. This phenomena was observed during inhalation anesthsia[9]. In anesthetized patients, $CBF/CMRO_2$ increased as the depth of anesthesia increased, thus providing a higher jugular venous oxygen level. An exact explanation for this phenomenon remains elusive.

It is well known that autoregulation is very sensitive to brain damage, whereas the CO_2 response is less susceptible to damage[1]. The $PaCO_2$ sensitivity of CBF is clearly greater during anesthesia with halothane or cyclopropane than during the awake state[9]. Volatile anesthetics seem to increase the sensitivity of CBF to $PaCO_2$[17]. Chodobski and co-workers[2] demonstrated that cerebrovascular reactivity to CO_2 in cats with ammonia intoxication diminished following elevation of the blood ammonia concentration, and at arterial blood ammonia levels exceeding 500 μmol/l it was virtually abolished. On the contrary, this study suggests that in patients with ME, cerebrovascular reactivity did not diminish, but rather showed a tendency to increase concerning the CBF responsiveness to $PaCO_2$. Apart from species differences, the contradictary results obtained in this study and in animal experimental studies can possibly be explained by differences in the pathophysiology between animal models and the human disease state accompanying multiple organ failure.

Mechanical respiratory support is one of the best interventions for the adequate management of these patients. As a therapeutic application, hypocapnic-hyperventilation has led to its use in several clinical situations of neurological disease[18]. However, for respiratory management of patients with HE or SE whose CBF response to CO_2 is preserved or augmented, intentional or inadvertent hypocapnic-hyperventilation may easily produce brain hypoxia due to a reduction in $CBF/CMRO_2$. In this study, $CBF/CMRO_2$ decreased in proportion to the decrease in $PaCO_2$ in all patients, and in 4 the $CBF/CMRO_2$ values were below the range of normal values for $CBF/CMRO_2$ (14-15 ml blood/ml O_2), indicating that CBF is not sufficient to meet the metabolic demand. It appears from these results that a monitor which indicates brain hypoxia is necessary for patients with ME on a mechanical ventilator. It is difficult to establish whether there is an optimal $PaCO_2$ at which $CBF/CMRO_2$ will be within normal limits. It was examined whether $JPvO_2$ could be used to evaluate the adequacy of the cerebral oxygen supply. It was found that there was a close linear relationship between $CBF/CMRO_2$ and $JPvO_2$ ($r=0.917$) (Fig 1). Therefore, the $JPvO_2$ may be a reliable index as a monitor during mechanical ventilation to avoid brain hypoxia due to inadvertent hyperventialtion.

In this study, CBF and $CMRO_2$ were measured in patients with ME by the Kety-Schmidt method. Previously reported values of CBF and $CMRO_2$ in awake patients in this laboratory corresponded with those reported by many other laboratories, with the CBF and $CMRO_2$ values ranging from 43 to 54 ml/100/min and from 3.0 to 3.3 ml/100/min, respectively[3, 9, 19]. By using the same methodology, the risk and expense of repeating control measurements in awake patients was not necessary. Accordingly, the values obtained from awake patients in a previous study were compared with the CBF responses

to CO_2. For the same reason, the CBF in relative hypocapnia determined by calculating $CMRO_2$, obtained during normocapnia, was divided by $C(a-jv)O_2$ according to Fick's principle based on the evidence that within the range of 20 to 60 mmHg, $PaCO_2$ has no measurable effect on $CMRO_2$[8].

I am indebted to Dr. Sari, the Director of the Department of Anesthesia, for his help and encouragement.

References

1) Enevoldsen, E. M. and Jensen, F. T. : Autoregulation and CO_2 responses of cerebral blood flow in patients with acute severe head injury. *J. Neurosurg.*, **48** : 689-703, 1978.
2) Chodobski, A., Szmydnger-Chodobski, J. and Skolasinska, K. : Effect of ammonia intoxication on cerebral blood flow, its autoregulation and responsiveness to carbon dioxide and papaverine. *J. Neurol. Nuerosurg. Psychiatry,* **49** : 302-309, 1986.
3) Kety, S. S. and Schmidt, C. F. : The nitrous oxide method for the quantitative determination of cerebral blood flow in man : theory, procedures, and normal values. *J. Clin. Invest.,* **27** : 476-483, 1948.
4) Sherlock, D. S. : Hepatic encephalopathy. In D. S. Sherlock(ed.), *Disease of the liver and biliary system*, 7th edition, London, Blackwell Scientific Publications, 1985, p. 95-107.
5) Teasdale, G. and Jennett, B. : Assessment of coma and impaired consciousness. *Lancet,* ii : 81-83, 1974.
6) Yonei, A., Nonoue, T. and Sari, A. : Real-time ultrasonic guidance for percutaneous puncture of the internal jugular vein. *Anesthesiology,* **64** : 830-831, 1986.
7) Sari, A., Maekawa, T., Tohjo, M., Okuda, Y. and Takeshita, H. : Effects of Althesin on cerebral blood flow and oxygen consumption in man. *Br. J. Anaesth.,* **48** : 545-550, 1976.
8) Kety, S. S. and Schmidt, C. F. : The effect of altered tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral consumption of normal young men. *J. Clin. Invest.,* **27** : 487-492, 1948.
9) Smith, A. L. and Wollman, H. : Cerebral blood flow and metabolism : Effects of anesthetic drugs and techniques. *Anesthesiology,* **36** : 378-400, 1972.
10) Fazekas, J. F., Ticktin, H. E., Ehrmantraut, W. R. and Alman, R. W. : Cerebral metabolism in hepatic insufficiency. *Am. J. Med.,* **21** : 843-849, 1956.
11) Wechsler, R. L., Crum, W. and Roth, J. L. A. : The blood flow and O_2 consumption of the human brain in hepatic coma. *Clin. Res. Proceeding,* **2** : 74, 1957.
12) Posner, J. B. and Pulm, F. : The toxic effects of carbon dioxide and acetazolamide in hepatic encephalopathy. *J. Clin. Invest.,* **39** : 1249-1258, 1960.
13) Scheinberg, P. : Brain metabolism. *World Neurology,* **2** : 288-293, 1960.
14) Baldy-Moulinier, M. and Bories, P. : CBF and metabolism in hepatic encephalopathy : effects of acute hyperammonemia and of L-DOPA. *Acta Neurol. Scand.* [*suppl*] , **56** : 348-349, 1977.
15) Dodsworth, J. B., James, J. H., Cummings, M. C., and Fischer, J. F. : Depletion of brain norepinephrine in acute hepatic coma. *Surgery,* **75** : 811-820, 1974.
16) Freund, H. R., Muggia-Sullam, M., Peiser, J. and Melamed, E. : Brain neurotransmitter profile is deranged during sepsis and septic encephalopathy in the rat. *J. Surg. Res.,* **38** : 267-271, 1985.
17) Alexander, S. C., Wollman, H., Cohen, P. J., Chase, P. E. and Behar, M. : Cerebrovascular response to $PaCO_2$ during halothane anesthesia in man. *J. Appl. Physiol.,* **19** : 561-565, 1964.
18) Raichle, M. E. and Plum, F. : Hyperventilation and cerebral blood flow. *Stroke,* **3** : 566-575, 1972.
19) Lassen, N. A., Feinberg, I. and Lane, M. H. : Bilateral studies of cerebral oxygen uptake in young and aged normal subjects and in patients with organic dementia. *J. Clin. Invest.,* **39** : 491-500, 1960.