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The Prognostic Value of Cerebral Blood Flow Measurement in Patients with the Apallic Syndrome

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INTRODUCTION

Improvements in resuscitative and supportive measures have led to increased efforts to save those whose brains are severely injured by trauma or by any other form of damage affecting the central nervous system. Sometimes these efforts have only partial success in individuals who have continuous heart action but irreversibly damaged brains. If patients survive this acute stage of brain damage, the deep coma may be followed by a peculiar clinical state referred to as the "apallic syndrome" (Kretschmer 1940), "akinetic mutism" (Cairns, Oldfield, Pennybacker and Whitteridge 1941) or "coma vigile" (Alajouanine 1957). The outcome of this clinical state is variable: many of the severely damaged patients die within weeks or months from late complications or secondary diseases; others may survive and show progressive improvement after an apallic syndrome lasting for several months. This improvement may lead to a state with persistent dementia and with major neurological deficit. Some patients recover from their severe brain damage with only minor mental and neurological deficits and may be fully resocialized.

A comparison between the clinical and anatomical features noted in patients who died during or after the development of an apallic syndrome indicates the high pathogenetic and prognostic importance of lesions in the rostral brain stem (Jellinger and Seitelberger 1970). Multiple lesions of the cortex, cerebral white matter, other subcortical regions and upper brain stem structures are commonly present also and modify the clinical picture. These anatomical lesions are reflected in alterations in the electroencephalogram (EEG) of the patients and during a period of recovery, the EEG may give some information about the functional state of the central nervous

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system. Anatomical lesions within the brain and the brain stem may be visualized by means of pneumoencephalography. This diagnostic procedure gives morphological but no functional information and may be hazardous for patients in a vegetative labile state such as the apallic syndrome. Usually, the clinical state of the patients shows a change for the worse after this investigation; the process of recovery may be arrested for some time and the patients are more susceptible to complications.

As shown by Baldy-Moulinier and Frèrebeau (1969) and Shalit, Beller, Feinsod, Draphin and Cotev (1970) measurements of cerebral blood flow may be used to judge the prognosis in acute states of coma. In the present study cerebral blood flow (CBF) was measured in patients suffering from chronic brain lesions after severe head trauma or other forms of damage to the central nervous system. The CBF values were correlated with the clinical outcome and stage of recovery, which these patients eventually reached. The target was to find out how far the CBF value could be used as a prognostic index in patients with severe brain damage, especially with the apallic syndrome.

METHODS

For the measurement of the cerebral blood flow the Xenon clearance method was used (Lassen and Ingvar 1963). After local anaesthesia the internal carotid artery was punctured directly or catheterized via the common carotid artery. Correct placement of the needle or catheter was checked by injection of dye (Evans blue) and by the scintiphoto taken during the investigation. 4–10 mCi 133-Xenon in saline solution (1–3 ml) were injected and the activity over the head was recorded by means of a scintillation camera (Nuclear Chicago Pho/Gamma III). Direct connection of the camera to a dual ratemeter and writer allowed the registration of the flow in one or both hemispheres. Regional cerebral blood flow of small areas of 12×12 mm was simultaneously measured by connecting the camera to a dual analog to digital converter and a 1600-word memory. The activity of small registration areas was accumulated for short periods of time (2.4 sec for the initial recording and 18 sec for the final recording) and transferred to digital magnetic tape. During one washout study of 10 min the information of 70 sampling periods was stored. Blood flow values of all the single areas (50–100 in one hemisphere) were computed off line by an IBM 1800 data acquisition and control system. A detailed description of the system used together with the important parameters, such as energy resolution, spatial resolution (about 20 mm for Xe in the system used), count loss, statistical error of the results (2–10%) and reliability of the measured values are described elsewhere (Heiss, Prosenz, Roszuczky and Tschabitscher 1968; Heiss, Prosenz and Roszuczky 1972).

RESULTS

Material

Forty-eight patients with severe brain damage were investigated and their individual clinical courses were correlated with the CBF values. Thirty-three of these individuals suffered from an apallic syndrome; in 28 cases this apallic syndrome was a sequel of severe head trauma and in 5 patients it was due to other forms of brain

damage (2 cases of intracerebral haemorrhage and 1 each with thrombosis of intracranial veins, asphyxia resulting from asthmatic attacks and subacute sclerosing panencephalitis). The patients with an apallic syndrome were divided into 4 groups according to the clinical outcome and the grade of recovery achieved after prolonged rehabilitation. The groups were as follows:

Group 1: 8 patients who died without signs of recovery from a complete apallic syndrome within $1\frac{1}{2}$ to 4 months after injury.

Group 2: 10 patients whose clinical state improved slightly to a state with severe neurological and mental deficits (6 cases) or who died after slight recovery because of secondary complications (4 cases). These patients could not exist without free medical and nursing care.

Group 3: 9 patients, who recovered from their apallic syndrome to a state with a moderate degree of residual deficit. These patients were able to take care of their own personal needs, to communicate and to walk.

Group 4: 6 patients, who recovered from their severe brain injury and a subsequent apallic syndrome either completely or with only some minor deficits sometimes resulting from primary brain lesions (slight paresis of limbs, residual aphasia, slight dementia) and in whom effective rehabilitation was possible. In a fifth group of 15 cases who suffered severe head trauma without the development of an apallic syndrome CBF was also measured. This group 5 was further subdivided according to the clinical course: 6 patients showed signs of permanent severe post-traumatic brain damage (group 5a) and 9 patients showed good recovery with only slight neurological deficits (group 5b).

Typical case histories illustrating each group are given to demonstrate the different types of clinical course (for details concerning the different stages in the development of recovery from an apallic syndrome, see Gerstenbrand 1967).

Group 1

Case 1. K.P., a 46-year-old man, was admitted after suffering a severe head injury in a traffic accident. He was deeply comatose and showed all the symptoms and signs of an acute midbrain syndrome (oculomotor disturbance, generalized extensor spasms, vegetative imbalance).

By angiography a left-sided epidural haematoma was diagnosed and the patient was operated upon 6 hr after the accident. Three days later the midbrain syndrome resolved and developed into an apallic syndrome, which was fully developed on the 10th day. The patient showed then a coma vigile, appearing alert but lacking the ability to comprehend and to respond to the environment in any meaningful way; the eyeballs were divergent, the upper limbs were fixed in a flexed position, the lower limbs were extended; there were pathological reflexes, extrapyramidal Parkinsonian symptoms and primitive reflexes (snout and sucking, groping and grasping, chewing movements, postural reflexes). This fully-developed apallic syndrome remained unchanged until death occurred 124 days after the accident.

Cerebral blood flow was measured 66 and 122 days after the accident. The values obtained (21.8 and 19.5 ml/100 g/min, respectively) were very low. Patho-anatomical findings: primary traumatic lesion of the right insula Reilii and of the right occipital lobe with haemorrhagic residua; cortical contusions in the left temporobasal, frontobasal and temporopolar cortex (contre-coup); primary traumatic lesions of the corpus callosum, of the fornix and of both medial thalamic nuclei; residua of haemorrhages and necroses in both unci hippocampi resulting from tentorial compression; symmetrical lesions in the dorsolateral rostral pontine tectum and also in the middle pontine tegmentum.

Group 2

Case 2. E.X., an 11-year-old girl, suffered from a right parietal fracture of the skull. Within 6 hr an acute midbrain syndrome with extensor spasms (decerebrate rigidity), dilated pupils, divergent squint and vegetative imbalance developed. After 5 days a transient stage of the apallic syndrome appeared; this was fully developed after 12 days and remained so for 9 weeks. Then, as a first sign of improvement, primitive emo-

tional reactions (fright reaction) appeared. Seven weeks later optic fixation and following was possible, after another 4 weeks primitive instructions ("close your eyes", "open your mouth", etc.) could be executed. An EEG, soon after admission, showed general slowing and ϑ–δ activity over both occipital regions. In successive recordings a right parieto-occipital focus became more and more predominant and finally the EEG stabilized.

CBF was measured as 23.8 ml/100 g/min 100 days after the accident during the first phase of recovery; a control recording 283 days after the accident showed only an insignificant increase in blood flow (25.6 ml/100 g/min) in spite of the slight clinical improvement.

Group 3

Case 3. A.H., a 38-year-old female, was hospitalized following severe head injury with a fracture of the left frontal bone. She was unconscious immediately after the accident, developed an acute midbrain syndrome within 12 hr; this lasted for 3 days and developed thereafter into an apallic syndrome which was fully-developed on the 6th day. Recovery started on the 13th day with a primitive fright reaction; during the next week optic fixation and following movements and grasping and groping were observed. Forty-five days after the accident the patient showed forced grasping and sucking of all objects within the visual field, chewing and biting, a pathological increase in appetite but no sexual disinhibition. Sixty days after the accident a Korsakow syndrome developed and lasted for another month. After this a stage of permanent deficit developed with mainly frontobasal symptoms (affective lability, loss of intellectual capability, loss of intellectual drive, etc.). After the initial diffuse disturbance (α-rhythm with superimposed ϑ–δ activity) the EEG stabilized showing a right temporoparietal ϑ–δ focus. CBF was measured during the second phase of recovery (65 days after the accident) and was 32.6 ml/100 g/min; 9 weeks later with further improvement CBF was about the same (30.8 ml/100 g/min).

Group 4

Case 4. H. W., a 22-year-old male, was admitted unconscious following head injury to the left forehead. An acute midbrain syndrome developed after 3 hr and lasted for 2 days. Then an apallic syndrome developed lasting until the 22nd day. Recovery started thereafter, proceeding in typical phases until a minor deficit stage with a slight dementia and a slight frontal syndrome due to the primary lesion of the brain was reached 8 weeks after the accident. Further rehabilitation for 2 months enabled the patient to work again in his former position. The EEG improved from a diffuse α–ϑ activity with a δ-focus over the left frontal lobe to a left frontal δ–ϑ focus and normal activity over the other regions. Pneumoencephalography performed 47 days after the onset showed a dilatation of the 3rd ventricle, the basal cisterns and the left temporal horn. CBF was studied 46 days after the accident during the recovery phase and gave a value of 41.1 ml/100 g/min; this value is slightly below that found in patients without lesions of the central nervous system ($n=30$, 50.1 ± 5.7 ml/100 g/min, see Table 1).

Group 5

Case 5. To illustrate the group of patients showing no development of an apallic syndrome during the clinical course, the history of J. E., a 31-year-old male, is given; he was admitted after a head injury to the left side, was conscious but in shock and suffered immediately after the accident from a right hemiparesis, expressive aphasia and symptoms of frontal lobe damage. Four weeks later the patient started to improve neurologically to a point where a slight hemiparesis, some expressive dysphasia and marked frontal lobe symptoms remained. The EEG showed immediately after the injury a focus over the left frontotemporal area which did not subsequently change. Pneumoencephalography was performed $8\frac{1}{2}$ months after the accident and revealed focal atrophy of the left frontal lobe. CBF was recorded twice: on the 25th day a value of 30.9 ml/100 g/min and $7\frac{1}{2}$ months after the accident a value of 39.3 ml/100 g/min was recorded.

CBF-values

The results of the studies of *hemispheric CBF* are summarized in Table 1. The measurements were performed in similar clinical circumstances, *i.e.* during a stable state of the apallic syndrome or during the early stages of recovery. Later the patients were classified individually according to their subsequent clinical course. Unfortunately it was not possible to study the patients at the same time after the injury or after the onset of the apallic syndrome. That this handicap does not limit the validity of flow values may be deduced from the results of repeat studies in 9 patients. In spite of a marked clinical recovery in 6 cases flow values were identical or only insignificantly

TABLE 1

CBF VALUES IN DIFFERENT GROUPS OF PATIENTS WITH AN APALLIC SYNDROME (GROUPS 1–4), IN HEAD INJURY PATIENTS WITHOUT APALLIC SYNDROME (GROUPS 5a and b) AND IN A CONTROL GROUP WITHOUT CEREBRAL LESIONS

Significant differences are described in the text. Mean values ± standard deviation.

Clinical group (see text)	*Number of patients*	*Age (years)*	*Days after accident*	f_A[a]	f_B	f_G	f_W	W_G	W_W
1	8	38 ± 14	65 ± 34	22.0 ± 3.0	23.2 ± 3.2	41.3 ± 9.2	17.1 ± 2.0	28.0 ± 8.0	72.0 ± 8.0
2	10	29 ± 18	103 ± 93	29.3 ± 7.1	30.6 ± 6.2	54.6 ± 12.2	19.3 ± 3.1	35.0 ± 12.0	65.0 ± 12.0
3	9	23 ± 8	166 ± 144	34.4 ± 6.8	34.4 ± 5.5	57.0 ± 10.0	22.6 ± 5.5	35.0 ± 8.0	65.0 ± 8.0
4	6	32 ± 11	66 ± 18	36.3 ± 4.8	37.2 ± 3.5	66.9 ± 6.6	18.9 ± 2.2	36.0 ± 6.2	64.0 ± 6.2
5a	6	43 ± 9	91 ± 41	28.4 ± 4.5	28.0 ± 2.9	49.0 ± 5.9	18.9 ± 2.5	30.9 ± 5.2	69.1 ± 5.2
5b	9	32 ± 15	56 ± 32	34.3 ± 5.3	33.9 ± 5.0	57.6 ± 10.8	19.2 ± 2.1	38.1 ± 5.9	61.9 ± 5.9
normal controls	30	38 ± 14		50.1 ± 5.7	49.8 ± 5.8	81.9 ± 11.9	21.8 ± 3.6	47.2 ± 7.4	52.8 ± 7.4

[a] For meaning of symbols, see text.

different after a mean time period of 74 days between the measurements (f_A*: 23.7 and 25.7 ml/100 g/min; f_B: 25.4 and 25.9 ml/100 g/min; f_G: 54.8 and 47.1 ml/100 g/min; f_W: 17.7 and 17.4 ml/100 g/min; W_G: 23.4 and 29.4%; W_W: 76.6 and 70.6%). When the CBF was recorded in a state which represented the highest level of recovery, the values obtained were not different from those which were obtained at an earlier stage after injury from other patients of the same clinical group (2 in group 3, 1 in group 4). Because of the critical state and the vegetative irritability of the patients, no studies were performed during the first 3 weeks. In group 5, CBF was taken during the subacute stage or during the early phase of recovery.

The flow values recorded in the different groups showed no correlation with the minor differences in arterial blood pressure recorded by sphygmomanometer from the brachial artery (mean value ± standard deviation in group 1: 119±14/77±9, 2: 121±14/74±6, 3: 118±8/72±7, 4: 127±12/70±6, 5a: 118±8/76±4, 5b: 123±11/81±13 mm Hg). Arterial pCO_2 was measured in 6 patients during the blood flow studies; the values obtained were in the normal range (37.2±1.5 mm Hg).

As may be seen in Table 1 by comparing the mean values of different groups, the clinical course is reflected in the corresponding total flow values (f_A: flow calculated according to the height over area method, f_B: mean flow calculated with bicompartmental analysis) and in the flow of the fast component (f_G). Differences between the relative weights of the fast or slow component (W_G and W_W) and of the flow of the slow component were only small. The significant differences of the groups in relation to f_A, f_B and f_G could be proved by an analysis of variance (Table 2). Also, groups were

TABLE 2

ANALYSIS OF VARIANCE OF THE 4 GROUPS OF PATIENTS WITH APALLIC SYNDROME

	f_A	f_B	f_G	f_W	W_G	W_W
Square sums between groups, $df=3$	934.57	820.16	2361.62	136.44	348.38	315.09
Mean squares	311.52	273.39	787.20	45.48	116.13	105.03
Square sums within groups, $df=29$	1134.27	816.81	3323.30	426.49	2846.52	2727.67
Mean squares	39.11	28.17	114.60	14.71	98.16	94.06
Total square sums, $df=32$	2068.84	1636.98	5684.92	562.93	3194.90	3042.76
F	7.965[a]	9.706[a]	6.869[a]	3.093	1.183	1.117
η	0.672	0.708	0.645	0.492	0.330	0.322

[a] $P<0.01$; $[F_{3,29}(0.01)=4.55]$.

compared mutually using Student's t test and the Duncan t test; significant differences could be found between the f_G of groups 1 and 2 ($t=2.548$, $P<5\%$), of groups 2 and 4 ($t=2.256$, $P<5\%$) and of groups 1 and 3 ($t=3.348$, $P<1\%$), between the f_B of groups 1 and 2 ($t=3.010$, $P<1\%$), 1 and 3 ($t=4.989$, $P<1\%$) and 2 and 4 ($t=2.363$, $P<5\%$) and between the f_A of groups 1 and 2 ($t=2.702$, $P<2\%$) and 1 and 3 ($t=4.775$, $P<1\%$). In groups 5a and 5b, f_A ($t=2.231$, $P<5\%$), f_B ($t=2.568$, $P<5\%$) and W_G ($t=2.394$, $P<5\%$) were significantly different. Assuming an increase of the values from group 1

* For meaning of symbols, see next para.

to group 4, the relation between the category scales of the prognostic groups and the ratio scales of the individual blood flow parameters was estimated with η, which is a measure to express the dependency of the single prognostic groups from the blood flow values. The significance of this measure of dependency is indicated by the highly significant F values from the analysis of variance (Table 2).

Studies of *regional CBF* revealed generally decreased values all over the brain corresponding to the hemispheric CBF. In patients with evidence of a primary lesion of the cortex, areas with further impaired circulation could be observed (Fig. 1). These regions showed a good correlation with clinical evidence of permanent or long-lasting neurological deficits or with patho-anatomical findings in autopsy cases (compare Fig. 1 with the history of Case 1).

The regional CBF measurements revealed the differences between patients with the apallic syndrome (groups 1 to 4) and patients suffering from head trauma without the development of an apallic syndrome (groups 5a and b). In cases belonging to group 5 CBF was not usually decreased all over the brain, but circumscribed areas of low perfusion were observed corresponding to the localization of the primary lesion in the brain, which all of these patients had suffered (Fig. 2). The low values of hemispheric blood flow in some such cases, similar to the CBF values of groups 2 and 3, as shown in Table 1, were mainly due to the impaired blood supply to damaged brain areas. In some older patients the head injury was superimposed upon the effects of pre-existing cerebrovascular disease. In the patients of group 5, the total CBF usually increased with improvement in the focal brain lesion (as may be seen from the results of the repeated measurements in case 5).

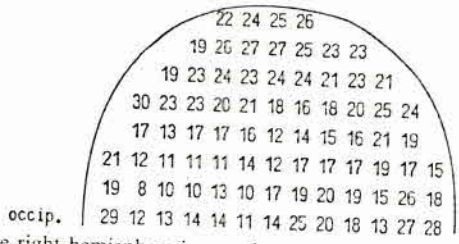

Fig. 1. rCBF map of the right hemisphere in a patient suffering from a post-traumatic apallic syndrome (Case 1). Measurement was performed on the 66th day after the head injury and revealed a hemispheric blood flow of 21.8 ml/100 g min. The map shows rCBF generally decreased all over the brain; in temporal and occipital areas the blood flow values are extremely low.

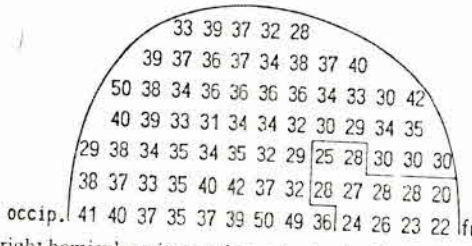

Fig. 2. rCBF-map of the right hemisphere in a patient, who had suffered from an open fracture of the frontal bone accompanied by destruction of frontal brain tissue. Investigation was performed on the 139th day after the trauma and revealed a hemispheric blood flow of 30.7 ml 100 g min calculated from the total count rate over the brain. This relative low value was influenced by the circumscribed frontal lesion with a decreased blood supply.

DISCUSSION

Previous investigations of cerebral blood flow (CBF) in patients suffering from the sequelae of severe brain injury were concentrated on the acute stages shortly after the brain damage occurred. In post-traumatic coma, as in most types of coma, the CBF is reduced; this reduction is accompanied by and probably induced by a decrease of oxygen consumption (Kety 1949, Lassen 1959), which is the most important factor indicating brain metabolic activity. In an attempt to obtain prognostic information in comatose patients, Bès, Arbus, Lazorthes, Delpla and Marc Vergne (1969) measured the arteriovenous oxygen difference. Values of below 2 vol. % were found only in cases of coma dépassé, suggesting that patients with such low values cannot survive. Shalit *et al.* (1970) measured blood flow and oxygen consumption in patients suffering from severe brain damage of variable origin. Because of the small number of patients investigated a correlation between $CMRO_2$ levels and prognosis could not be formulated in their cases, but a critical level could be found: when cerebral oxygen consumption reached levels below one-third of the normal value, clinical signs indicating brain death were manifest. Other investigators (*e.g.* Brodersen 1971) concluded from their results, that a $CMRO_2$ value below 10% means brain death. An absence of clearance of ^{133}Xe selectively injected into the internal carotid artery was demonstrated in similar cases (Brock, Schürmann and Hadjidimos 1969). This cessation of cerebral blood flow might be another reliable criterion as well as an isoelectric EEG for establishing brain death.

Baldy-Moulinier and Frèrebeau (1969) measured the CBF in 50 comatose patients by means of the ^{133}Xe clearance method within 5 days of injury. Their first group had an average rCBF of 43 ml/100 g/min; 4 out of 6 patients recovered completely. The second group had an average CBF of 27 ml/100 g/min, but all patients as well as those in their third group, in whom cerebral circulatory arrest was determined by angiography, showed signs of intracranial space-occupying lesions. In patients of the second group clinical improvement was observed when the CBF increased after surgical treatment.

In contrast to these studies the goal of our investigation was to obtain some information concerning the prognosis of patients suffering from the sequelae of severe brain damage. This was achieved by CBF measurements performed after the acute stage, thereby avoiding also the influence of intracranial space-occupying lesions and of oedema on the cerebral circulation. After this acute stage the CBF apparently depends on permanent anatomical changes and does not change with the improving functional performance of the brain. This may be concluded from the repeat and the late measurements made in our patients. Investigations of patients with a long-lasting apallic syndrome were reported previously by Ingvar, Haggendal, Nilsson, Sourander, Wickbom and Lassen (1964) (1 patient), Ingvar, Cronqvist and Granholm (1970) and Heiss, Prosenz, Gloger and Herles (1970) (preliminary results of 16 cases which are included in the present study). The patho-anatomical follow up of the first case of Ingvar *et al.* (1964) confirmed the previous assumption that a lesion critically situated in the brain stem may cause a global depression of brain function (Ingvar and Sourander 1970). In our study a diffuse reduction of CBF could be observed, especially

in patients who had an apallic syndrome after their brain injury. In these patients the reduction of hemispheric CBF was not caused by extremely low rCBF values due to circumscribed brain lesions as seen in patients suffering from head traumas without the development of an apallic syndrome; the severe reduction of CBF was not caused by increased intracranial pressure due to space-occupying lesions. These results as well as the anatomical findings in deceased patients (see the history of case 1) support the assumption of Ingvar and Sourander (1970) and stress the importance of the controlling influence of the brain stem in relation to the function and perfusion of the cerebral cortex.

Despite the limited number of patients studied in each group a significant correlation of the flow values f_A, f_B and f_G to the clinical course and outcome was demonstrable. During the stages of a fully developed apallic syndrome and of early recovery—these stages may last for months—it is almost impossible to distinguish by clinical means between the patients who fail to make any improvement or who will die, the ones who will improve slightly to a defective state of brain function and the ones who will recover more completely. The measurement of CBF provides prognostic information which may encourage one to intensify and continue a programme of rehabilitation in selected cases. In this context the measurement of CBF is an important tool of prognostic value in addition to the information obtained from clinical examination and other investigative techniques.

SUMMARY

Total and regional cerebral blood flow (CBF) was measured in 33 patients suffering from an apallic syndrome following severe brain injury. Using analysis of variance and *t*-test, significant differences in CBF values between 4 groups of patients classified according to the severity of the clinical picture could be demonstrated. A significant correlation between CBF and prognosis was found. Differences between these patients and others suffering from head trauma but without the development of an apallic syndrome, in whom hemispheric blood flow was also decreased, could be shown by regional blood flow studies: in 15 patients without an apallic syndrome the decrease in CBF was mainly due to circumscribed lesions, while in the patients with the apallic syndrome rCBF was usually reduced diffusely all over the brain. The measurement of CBF provides an important tool for estimating the prognosis in patients suffering from the apallic syndrome.

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