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Aspects of Regional Cerebral Circulation Measurements in Patients with intracranial Tumours

Aspecten van de regionaal gemeten hersencirculatie bij patiënten met intracraniële tumoren

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Summary

The regional cerebral circulation was measured by means of the Xenon[133] clearance method in 16 patients with intracranial space-occupying lesions.
A summary of the results obtained is given as well as some illustrative examples.
Intracranial tumors may influence many aspects of the cerebral blood flow and its regulation.

Samenvatting

Bij 16 patiënten met een intra-cranieel ruimte innemend proces werd de regionale cerebrale bloeddoorstroming gemeten met de Xenon[133] uitwasmethode.
Na een kort overzicht van de literatuur wordt een samenvatting gegeven van de resultaten en deze worden geïllustreerd met enkele voorbeelden.
Intra-craniële tumoren kunnen invloed hebben op vele aspecten van de cerebrale bloeddoorstroming en op de regulatie hiervan.

Introduction

The neurological symptoms in patients with intracranial tumors are determined by many factors.
Apart from the volume of the tumor and its localisation, the following factors are of importance:

a) Increase in intracranical pressure and the rate of increase in this pressure.
b) The extent of the existing oedema of the brain in the tissue around the tumor — especially severe in metastasis.
c) The relationship between the tumor and the regional cerebral blood flow (rCBF).

The last three factors are interdependent, having a strong mutual relationship.
The degree of this relationship is variable and difficult to predict in the individual case.
Hence, it is understandable that, though diagnostic methods which are routinely used (arteriography, pneumoencephalography, positive contrast-encephalography, brainscanning) give fairly exact information with regard to localisation and anatomical extent of the process, they do not provide exact information concerning the patho-physiological processes in and around the tumor. Until a few years ago, the only technique available for the study of the cerebral patho-physiology in patients was electroencephalography.

The electroencephalogram (EEG) is an extremely sensitive device for the detection of cortical functional disturbances.
However, it gives little (or, at least, no specific) information about the functional state of subcortical structures.
Moreover, the electroencephalogram seldom gives explicit information about the cause of a functional disturbance and its localising value is limited (Cooper 1965).
It is for this reason that there is a widely growing interest in the measurement of intracranial pressure (Lundberg 1965, Jennett 1972) as well as in regional cerebral blood flow measurements.

Methods

The technique of regional cerebral blood flow measurements using radioactive gases has been described in detail elsewhere (see among others Lassen 1963, Høedt-Rasmussen 1965, Jonkman 1968). Broadly speaking, the investigations are conducted as follows: a physiologically inert radioactive gas (Xenon[133]) is injected through a teflon catheter into the internal carotid artery. (The gas is dissolved in a saline solution).
A few seconds after the injection the gas will have completely diffused throughout the whole brain tissue.
The injection is given very quickly and the clear-

ance of the xenon from the brain tissue begins immediately. The clearance curve can be observed with the aid of extracranially placed detectors. We used 16 detectors with crystals of 1.2 cm and Philips XP 1110 photomultipliers.
It is possible to measure in a fairly restricted local area if a narrow collimator is used.
From the clearance curves obtained, a number of parameters can be calculated (see also Høedt-Rasmussen 1965, Pálvölgyi 1968, Wilkinson 1968, Olesen 1971):

1. Regional cerebral blood flow through grey, as well as through white, matter (in cc/100 g. min.).
2. Mean regional blood flow through grey and white matter (in cc/100 g. min.).

This latter value can be obtained by several methods:

a. Weighted mean flow.
b. "Height over area" analysis.
c. Initital flow measurements.

For the undermentioned observations only the so-called rCBF (initial) (Paulson, 1969) was used.

3. The relative weight of grey and white matter in the region under the detector (in % of 100 g. tissue).

Our procedure differed only in detail from the techniques used by other investigators.
A special apparatus was developed to determine the exact localisation of the detectors in relation to the arteriograms previously made.
One must realize that, in patients with large tumors, it is possible that some detectors measure only the circulation through the tumor, and not through the brain tissue (see figure 1). An additional complication is that the diffusion-coefficient is known for grey and white matter, but unknown for tumor tissue. Because we were very interested in the relationship between the EEG and the results of the rCBF measurements, an EEG was registered continuously throughout the experiments, using standard methods (16 channels, 10-20 system; Jonkman 1970).
With this procedure, the regional cerebral circulation was studied in 16 patients with brain tumors. At the time of the investigation, all patients were hospitalized at the St. Ursula Clinic.
In all but 2 cases, the diagnosis was verified, not only by arteriography, but also by operation and/or autopsy.

Results

The mean normal value of the rCBF values is, according to other authors, 55 cc/100 g. min. (SD = 5.9).
In previous experiments performed on a group patients of different ages, results indicated that in old age there is a decrease in the mean rCBF.
This decrease is difficult to acertain since it is almost impossible to obtain normal values for older people.
But, even taking into account the physiological decrease in old age, we can state that we found *a very marked decrease in mean regional cerebral blood flow* in all our tumor patients. The lowest values were found in patients with extensive, dif-

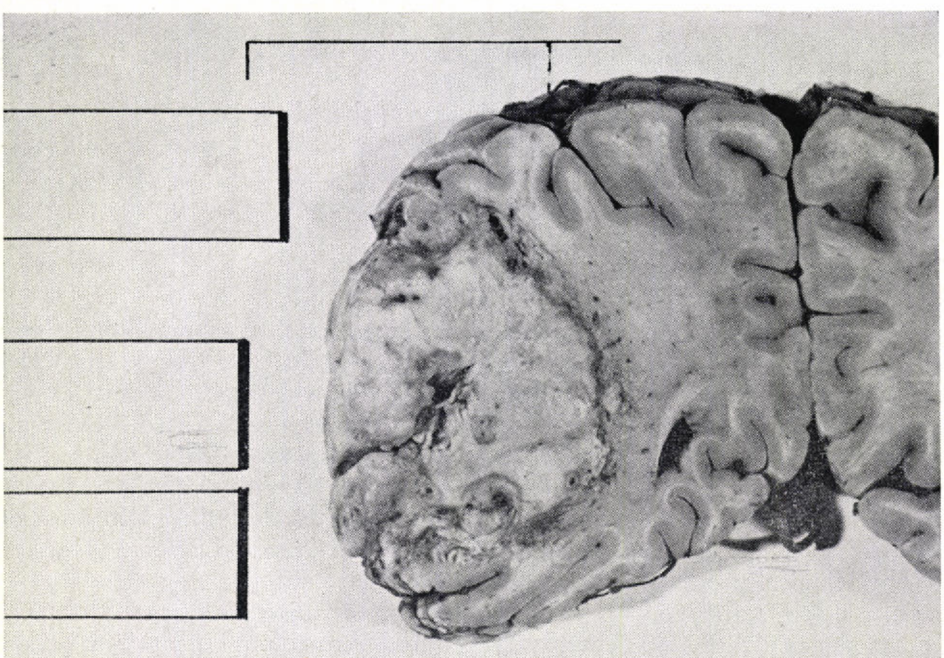

Fig. 1. Large cerebral tumor (astrocytoma). The contour of three detectors is outlined.

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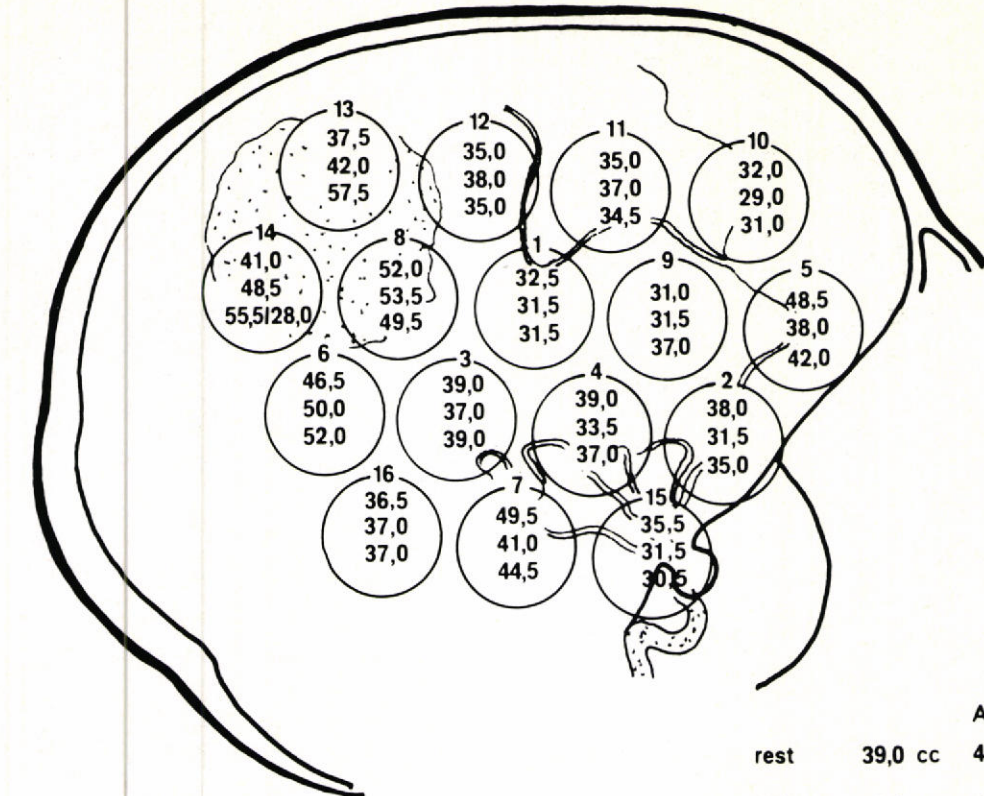

		$ApCO_2$
rest	39,0 cc	48,5 mm Hg
HV	39,0 cc	44,5 mm Hg
after HV	40,5 cc	50,0 mm Hg

Fig. 2. Astrocytoma IV parietal. First measurement during resting state; second measurement after hyperventilation; third measurement again in the resting state (there was a spontaneous increase of A Pco_2: 50 Torr!). Signs of inversed steal during the second injection (detector 5, 14, 13). In the resting state a relatively high rCBF is seen over a part of the tumor (8). (rCBF in cc/100 g. min.).

fuse, growing malignant tumors (almost all mean values were between 25 and 35 cc/100 g. min.).

The best circulation (relatively) was found in a patient with an epidermoid cyst in the middle cerebral fossa (42.5 cc/100 g. min.). Apparently, the cerebral circulation can adapt if the tumor is not destructive and is of slow growth.

In the literature, there are reports that the cerebral blood flow is diminished in the contralateral hemisphere also. We did not have the opportunity to verify this.

In all 16 patients *regional differences* were found. However, one must realize that there are tumors with a higher perfusion rate than normal brain tissue, and there are also poorly vascularised tumors. This means that it is often impossible to localise a tumor when only rCBF values are taken into account.

If the localisation of the tumor is known, one can conclude from the rCBF pattern wether the tumor is highly or poorly vascularised.

There was very good agreement between the values obtained by the cerebral blood flow measurements and the result of the angiography. That is, tumors which were highly vascularised angiographically also showed regions with high rCBF values.

When a detector is placed over a region with arterio-venous anastomosis, one will obtain a curve with an *abnormal configuration*.

The rapid increase in radio-activity after the injection is then not followed by the normal slow decrease, but by a very rapid decrease. These so-called "shuntpeaks" are found because a portion of the radio-active material does not take part in the normal diffusion/clearance process, but leaves the brain tissue immediately through the anastomosis.

According to the literature, such shuntpeaks can be found over many kinds of tumors (Pávölgyi 1969).

In our material, shuntpeaks were registered only in patients with meningeoma (2 cases).

The localisation of the shuntpeaks coincided very well with the localisation of the tumor.

These shuntpeaks were of much lower amplitude than those found in patients with congenital arterio-venous malformations. More important than the abnormalities in the resting state, or an abnormal configuration of the curve, is often an abnormal pattern during *reactivity testing procedures*.

The reactivity testing procedures can be devided into:

1. *Testing of the autoregulation*

Autoregulation is the capacity of the normal cere-

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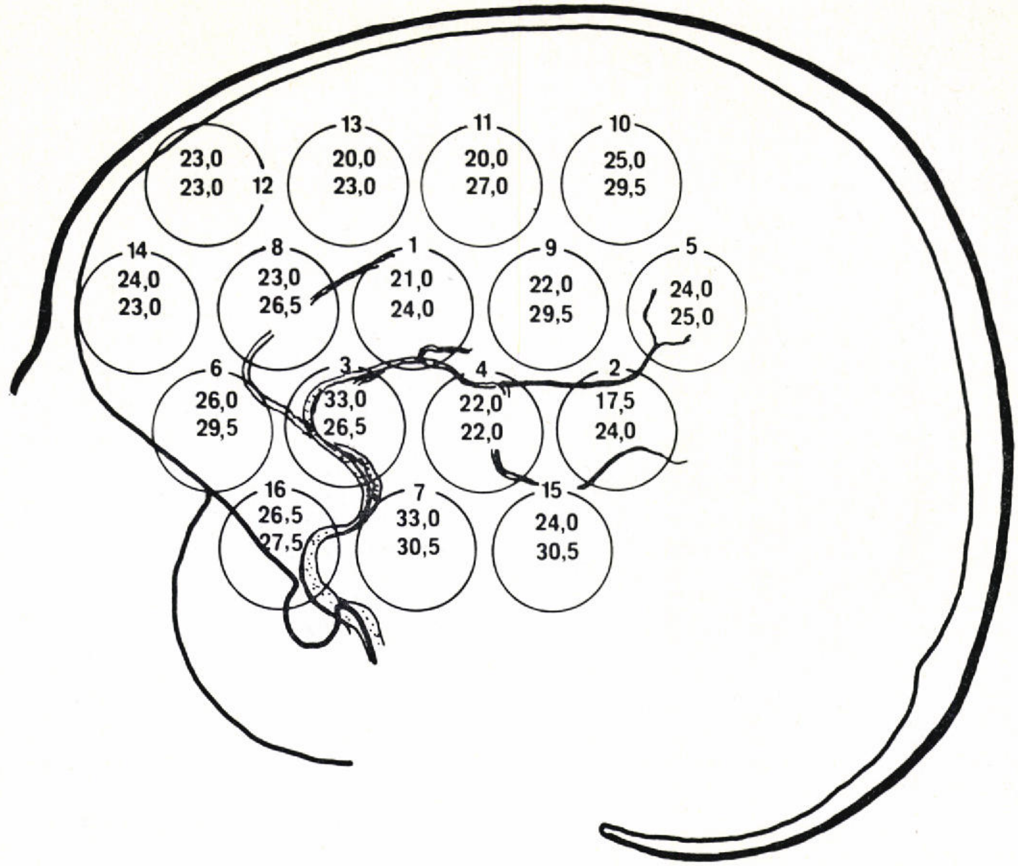

Fig. 3. Large astrocytoma IV in the left hemisphere. Diffuse marked decrease in rCBF. Minimal reaction to intra-arterial papaverine. Paradox reaction present (3). (rCBF in cc/100 g. min.)

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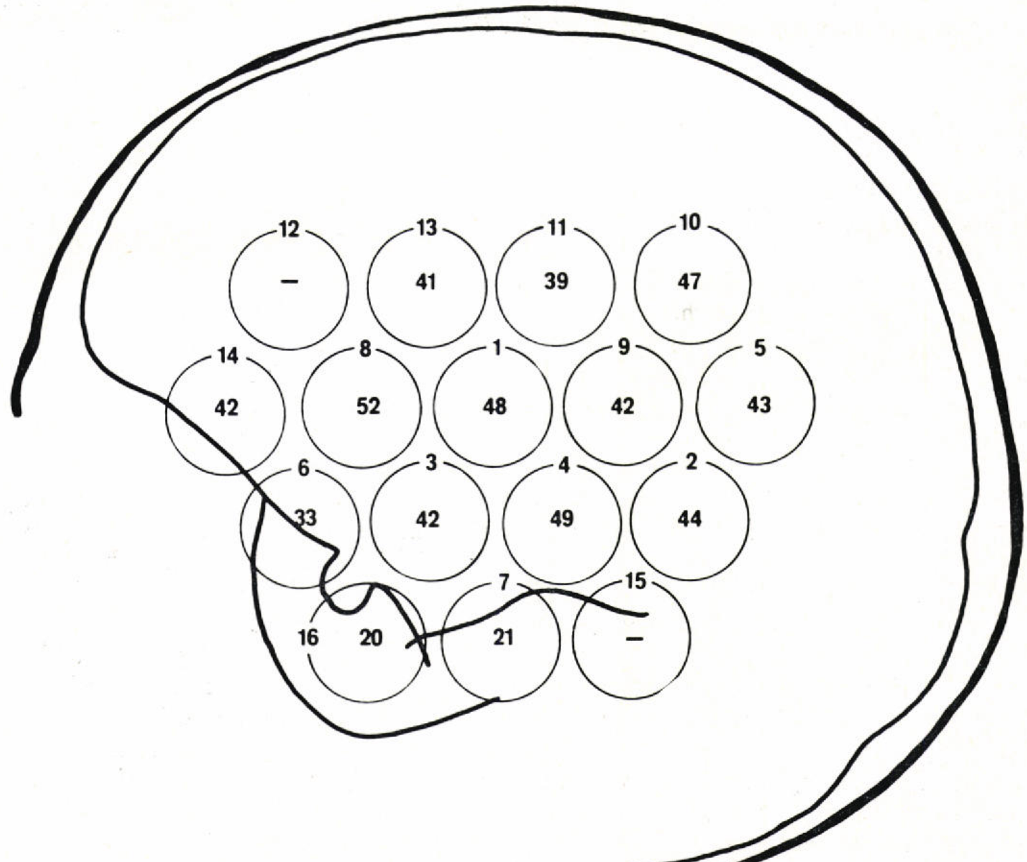

Fig. 4. Epidermoid cyst in the temporal region. Very low relative „weight grey" under detectors 6, 7, 16. (Weight grey in %/100 g. tissue.)

brovascular system to maintain (within certain limits) a constant rCBF with spontaneous or induced changes in perfusion pressure.
Most authors (Pálvölgyi, 1968) describe autoregulation disturbances in patients with cerebral tumors. These disturbances may be localized as well as diffused over the whole hemisphere. We did not repeat these investigations.

2. *Response to changes in arterial carbon-dioxide tension (A Pco_2).*

In normal brain tissue there is a lineair- (Høedt-Rasmussen 1965) or exponential (Olesen 1971) relationship between A Pco_2 and regional cerebral blood flow (increase in A Pco_2 produces an increase in rCBF).
This reponse is frequently lost in a tumor region. The disapearance of this A Pco_2 dependency can induce a so-called intra-cerebral steal:
In this situation, an increase in A Pco_2 leads to a decrease in rCBF in the tumor region due to the fact that the cerebrovascular resistance is lowered in the region around the tumor, but not in the region of the tumor itself, while perfusion pressure remains constant. Under hypocapnia, an inversed steal may come into existence: the rCBF in the tumor region increases because the cerebrovascular resistance in this region does not increase as it does in the surrounding regions.
An example is given in figure 2.
A 60 year old female had an astrocytoma IV in the right parietal region. The first rCBF measurement was made in the resting state: the second measurement after three minutes of hyperventilation. The induced hypocapnia caused a decrease in rCBF in the fronto-temporal region, but an increase in more posterior located regions (detectors 6, 13, 14).
The tumor was highly vascularised according to arteriography. This was demonstrated by the relatively high rCBF in the region of detector 8.

3. *Pharmacological reactions*

More rapidly than by means of A Pco_2 changes, a rCBF increase can be induced through intra-arterial injection of papaverine (5-7 mg., diluted in 10 cc saline, rapid injection).
After such an injection under normal conditions the cerebral blood flow rises remarkably (often to 200% of the original value). The effect of papaverine disappears after only 1-2 minutes. The mechanism of this non-physiological increase in cerebral blood flow may be disturbed in the region of the tumor: the reaction may disappear, or even paradoxical reactions may occur.
An example is given in figure 3.
This is the case of a 70 year old man with a large astrocytoma IV in the left hemisphere. The cerebral blood flow in the resting state (values noted in the upper part of each detector field) was extremely low.
After 5 mg. papaverine was injected in the left carotid artery, we found under only a few detectors (6, 9, 11) a slight increase in perfusion. In other regions there was no change, while under detector 3 there was a region with a paradox reaction.
So, it becomes evident that the steal mechanism can also be activated by means of papaverine injection.

As mentioned above, we can calculate the relative weights of grey and white matter from the clearance curves. Although we are doubtful if the calculated values really correlate with the anatomical amounts of grey and white matter, one can say that there are apparently two compartments which have different clearance rates.
The relative weights of these compartments can be estimated. In normal situations, both compartments have about the same weight, and regional differences in normals are small (Wilkinson 1969).
In patients with focal lesions (tumors, vascular lesions), local abnormalitites in the grey/white weight ratio are found in most cases.
An example of this is given in figure 4.
It concerns the same patients who was mentioned in connection with the relatively best circulation: a man of 31 years with an epidermoid cyst in the middle cerebral fossa.
Apart from a (subjective) diplopia and a slight hypalgesia in the region of N. V, the neurological examination was completely normal.
According to the EEG, there were only minor irritative signs in the left temporal region.
Arteriography showed a poorly vascularised space-occupying lesion in the left temporal pole. The mean rCBF was only slightly diminished (42.5 cc/100 g. min.: A $Pco_2 = 40.0$ Torr).
The lowest values were found in the temporal region (in normal individuals the cerebral blood flow is also a little lower in the temporal region than in other locations).
More spectacular was the abnormal ratio of the weights of the two different compartments.
Under detectors 6, 7, and 16 there was an important decrease of the "weight grey". That means that in this region a relatively large compartment with a slow clearance rate has come into existence.
It must be pointed out that this two-compartmental analysis is only feasible when the clearance curves are computer analysed. In our laboratory this was done by a Digital PDP15 computer. The results of the correlation between EEG and cerebral blood flow in these patients will be published elsewhere.
Summarizing the EEG findings, it can be stated:

1. There is generally a good correlation between mean rCBF and the severity of EEG abnormalities.

2. Induced increase in cerebral blood flow (increase of A P_{CO_2}, injection of papaverine) has in general amazingly little influence on the EEG, but pathological signs may become clearer.

Conclusion

Our findings have confirmed the data published by other authors: most intra-cerebral tumors led to disturbances of many aspects of the cerebral blood flow.

The cerebral blood flow measurements do not play an important role in tumor diagnosis, or the localisation of intracranial processes.

The combination of arteriography and rCBF studies can lead to a better understanding of the pathophysiological processes around the tumor, and thus may lead to a better correlation between the pathological process and the clinical signs. For optimal use of the method, we think the following points are of importance:

1. It is necessary to use automatic analysis of the clearance curves.

2. It is essential to calculate all parameters (including the relative weights).

3. The results are more interesting when the regional cerebral blood flow is determined not only in the resting state, but also during hypercapnia, after injections of papaverine, and, if possible, after blood pressure changes.

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