Serial Measurement of Regional Cerebral Blood Flow in Patients with Middle Cerebral Artery Stem Occlusion

—Report of Two Cases—

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Abstract

Regional cerebral blood flow (rCBF) in two patients with middle cerebral artery stem occlusion (one characterized by persistent occlusion and the other by spontaneous recanalization) was measured repeatedly by dynamic single-photon emission computed tomography and ^{133}Xe gas steady-state inhalation. With the exception of complete recanalization in one patient, the pathophysiology in the two cases appeared essentially the same. These cases are described and the problems of measuring and interpreting rCBF in cerebral infarction are addressed. The concept of a "homeostatic mechanism of cerebral energy supply" is also discussed.

Key words: regional cerebral blood flow, cerebral infarction, luxury perfusion, misery perfusion, matched perfusion, computed tomography

Introduction

In two representative patients with middle cerebral artery (MCA) stem occlusion (one with persistent occlusion and the other with spontaneous recanalization), the final tomographic images of regional cerebral blood flow (rCBF) were surprisingly similar, despite the markedly peculiar rCBF dynamics ("luxury perfusion") in the patient with recanalization.

The data from these serial observations strongly support the hypothesis that there is a homeostatic mechanism with respect to the cerebral energy supply and imply that rCBF is regulated by this mechanism according to the brain metabolic requirement. This principle has been well documented in positron emission tomographic (PET) studies.^{2,3,8,17,22,44} The rCBF dynamics of our two cases are discussed with special reference to this hypothesis.

Patients

Case 1: A 58-year-old male with no previous neurological disorder was hospitalized with sudden,

complete right hemiplegia and total aphasia without impairment of consciousness. He recovered from this episode and was able to walk with a cane within 2 months of its onset, although paralysis of right upper extremity, and severe motor and moderate sensory aphasia remained.

A computed tomographic (CT) scan obtained on the day after onset showed a large low-density area in the left MCA-perfused region (Fig. 1). Angiography on the 3rd day after onset revealed complete occlusion of the left MCA stem just beyond the divergence of a few medial branches of the lenticulostriate arteries (Fig. 2). Persistent occlusion was demonstrated by digital subtraction angiography on the 44th day, but details of the perforating arteries were unclear because of poor resolution.

Case 2: A 60-year-old male with a history of myocardial infarction was hospitalized with sudden onset of moderate right hemiparesis and total aphasia without impaired consciousness. The hemiparesis had almost completely disappeared within 2 weeks after onset, but severe motor and slight sensory aphasia remained.

A CT scan on the 9th day after onset disclosed a large low-density area in the left MCA-perfused territory (Fig. 3). Angiography 2 days after onset dem-

Fig. 1 Precontrast CT scan in Case 1 (persistent occlusion of the left MCA stem), obtained on the day after onset.

Fig. 3 Precontrast CT scan in Case 2 (left MCA stem occlusion followed by subsequent recanalization), obtained on the 9th day after onset.

Fig. 2 Case 1. Angiograms obtained on the 3rd day show complete occlusion of the left MCA stem (arrow). A: anteroposterior view, B: lateral view.

onstrated neither occlusion nor stenosis of the left MCA, but showed a small arterial plaque, which stenosed the left internal carotid artery (ICA) by 25% (Fig. 4). This finding suggested transient embolic occlusion of the MCA stem and subsequent recanalization.

Both patients were treated conservatively, without fibrinolytic or hemodilution therapy.

Methods

The rCBF was measured at 5 cm above the orbito-meatal plane by means of dynamic single-photon emission CT (D-SPECT) with 32 rotating detectors containing NaI scintillators (Tomomatic-32, Medimatic Ltd., Denmark).

^{133}Xe gas was administered by inhalation through a mouthpiece for the initial 1.5 minutes, and exhaled for the next 3 minutes for reconstruction of four consecutive ^{133}Xe distribution maps of the brain. A mixture of oxygen and 60 to 80 mCi of ^{133}Xe gas was prepared in 4-l rubber bag according to the lung permeability of each patient, so that a stable head count rate of 160 to 240×10^3 counts/min/32 detectors was obtained in the second 1-minute period.

The spatial resolution (FWHM) obtained with this apparatus in an ^{133}Xe phantom study was 20 to 25 mm axially and transversely, depending on the distance from the detector system. The energy discrimination level was adjusted at 20% below the photo-

Fig. 4 Case 2. Angiograms obtained on the 2nd day show 25% stenosis of the left ICA (A, arrow) and the left MCA branches after recanalization (B, lateral view).

peak of 81 keV. A brain-blood partition coefficient of 1.0 ml/gm was employed in all areas of the brain.

The rCBF values were calculated tomographically on the basis of the four consecutive ^{133}Xe distribution maps by the use of two algorithms^{5,14,37} — the “early picture” and “sequence of pictures” methods. The limit of application of these two algorithms was 70% of ^{133}Xe accumulation. The results were displayed on a tomographic rCBF distribution map on 128 matrix with a graded, 16-color scale, and the absolute values were also printed out on a 32×32 matrix, each pixel corresponding to a brain area of approximately $7 \times 7 \text{ mm}^2$. Thus, each hemisphere comprised 150 to 190 pixels, depending on the head size.

With these measurement techniques, normal hemispheric CBF was estimated to be $68.5 \pm 9.8 \text{ ml/100 gm/min}$ [$n = 11$, mean age = 40.4 ± 11.8 years, arterial CO_2 tension (PaCO_2) = $42.8 \pm 5.7 \text{ mmHg}$, mean arterial blood pressure (MABP) = $105 \pm 17 \text{ mmHg}$]. No significant right-left hemispheric difference ($1.1 \pm 0.8\%$) was observed (Fig. 5A).^{8,17,22} Reproducibility was demonstrated in a patient with a left temporal arteriovenous malformation by repeating measurement 50 minutes later, when the remaining ^{133}Xe activity had dropped below 7.3% (Fig. 5B and C).

Results

Case 1: Resting rCBF was measured on the 2nd, 10th, 13th, 38th, and 52nd days after onset (Fig. 6). MABP and PaCO_2 were described in the legends of Fig. 6. The rCBF values calculated from the 80 pixels corresponding to the MCA-perfused cortical regions of both (ipsilateral/contralateral) hemispheres were as follows: 21.2/42.5, 28.1/48.8, 39.7/64.4, 34.8/65.8, and 28.5/62.0 ml/100 gm/min (Fig. 7).

Less recoverable rCBF reduction in the left (ipsilateral) hemisphere and prominent diaschitic rCBF reduction in the right (contralateral) hemisphere were characteristic of this case of persistent occlusion.

Case 2: Similarly to Case 1, measurements were obtained on the 8th, 10th, 15th, 22nd, and 43rd days after onset (Fig. 8). The rCBF values were as follows: 119/51.5, 86.8/52.4, 54.5/57.0, 33.9/56.9, and 31.1/59.5 ml/100 gm/min (Fig. 7).

The black areas in the rCBF tomograms of days 8 and 10 represent high rCBF values ($> 112 \text{ ml/100 gm/min}$), which went beyond the color scale. Time-dependently recoverable “luxury perfusion” in the left (ipsilateral) hemisphere was the noteworthy finding in this case of recanalization. On days 8 and 10, the number of pixels indicating rCBF values of

more than 90 ml/100 gm/min were 67 and 38, respectively, and their mean values were 137 and 112 ml/100 gm/min, respectively. The maximum rCBF value indicated by any pixel was 200 ml/100 gm/min and occurred on day 8.

Discussion

I. Methodological considerations

Along with the many advantages of combining three-dimensional visualization with a noninvasive procedure, the low energy of ^{133}Xe and its slow passage to the brain give rise to the two unavoidable problems of limited spatial resolution, especially of the deep structures, and unreliability of rCBF calculations for white matter (which are overestimated by a factor of approximately 2.5).

Nevertheless, the information this system offers is quite reproducible throughout the brain, provided that the head is precisely positioned, the dose of ^{133}Xe is sufficient, and the patient's tidal exchange is stable. Therefore, not only the right and left hemispheric difference^{21,22} but also absolute rCBF values obtained at different times from a given cortical area in the same patient can be compared.

However, great care should be taken, in selecting the homolateral and/or homologous region of interest (ROI) on the print-out, to minimize errors of artificial manipulation. Also, the statistical unreliability of individual pixels must be kept in mind. In general, the larger the ROI, the greater the reliability.²² In fact, a ROI larger than 4×4 pixels (a tomographic brain area of $28 \times 28 \text{ mm}^2$) is recommended, taking the spatial resolution of this apparatus (20 to 25 mm of FWHM) into account.

II. Significance of rCBF dynamics in cerebral infarction

Conventional concept: In an attempt to elucidate the pathophysiology of cerebral infarction, many investigations^{1,11,12,15,16,18–21,23,24,26–29,35,42} have been based on human rCBF dynamics. However, in large part the pathophysiology of cerebral infarction has not been clarified because of the following problems. First, cerebral infarction involves a complicated combination of factors,²² e.g., age, medical history, severity of the primary ischemia, location and extent of the affected brain region, and primary disease of the patient. In particular, the site and severity of the primary ischemia and whether or not it involves the basal ganglia and/or thalamus^{6,38} seem to strongly influence rCBF dynamics, which renders the interpretation of rCBF data very confusing. The second problem concerns time-dependent changes in rCBF

Fig. 5 A: rCBF tomogram of a normal adult in the resting state (MABP = 110 mmHg, PaCO_2 = 45.1 mmHg). B, C: Reproducibility of rCBF tomography after a 50-minute interval in the same patient with an arteriovenous malformation in the left temporal lobe (B: first measurement; MABP = 87 mmHg, PaCO_2 = 48.4 mmHg. C: second measurement; MABP = 88 mmHg, PaCO_2 = 49.4 mmHg). These tomograms are arrayed in a graded, 16-color scale (ml/100 gm/min).

Fig. 6 rCBF tomograms in Case 1 in the resting state at various intervals after onset. A: 2nd day; MABP = 119 mmHg, PaCO_2 = 34.8 mmHg. B: 10th day; MABP = 110 mmHg, PaCO_2 = 37.2 mmHg. C: 13th day; MABP = 100 mmHg, PaCO_2 = 38.9 mmHg. D: 38th day; MABP = 103 mmHg, PaCO_2 = 40.4 mmHg. E: 52nd day; MABP = 117 mmHg, PaCO_2 = 41.7 mmHg. These tomograms are arrayed in a graded, 16-color scale (ml/100 gm/min).

Fig. 7 Sequential changes in rCBF calculated from the 80 pixels corresponding to the MCA-perfused cortical area in both hemispheres. ●: ipsilateral hemisphere, ○: contralateral hemisphere.

dynamics after onset,²²⁾ a phenomenon that was clearly illustrated in the present study. However, conventional methods of measuring rCBF cannot be repeated frequently because of the invasiveness of intra-arterial injection. The third problem requires reassessment of the relationship between rCBF and cerebral metabolism: We do not know for sure what rCBF represents. If the presupposition that rCBF directly reflects cerebral metabolism is not true, rCBF values may be meaningless.

Regarding the relationship between rCBF and metabolism, Kety¹⁶⁾ first reported that cerebral O_2 consumption is confined to a rather narrow range, whereas cerebrovascular resistance tends to fluctuate over a considerable range. Since Kety's report it has been well documented that rCBF and cerebral metabolism are generally as well as regionally interdependent, in normal brain^{2,3,8,13,17,22,30,36,44)} as well

Fig. 8 rCBF tomograms in Case 2 in the resting state at various intervals after onset. A: 8th day; MABP = 107 mmHg, $PaCO_2$ = 40.0 mmHg. B: 10th day; MABP = 99 mmHg, $PaCO_2$ = 39.3 mmHg. C: 15th day; MABP = 90 mmHg, $PaCO_2$ = 42.4 mmHg. D: 22nd day; MABP = 89 mmHg, $PaCO_2$ = 41.5 mmHg. E: 43rd day; MABP = 94 mmHg, $PaCO_2$ = 42.6 mmHg. These tomograms are arrayed in a graded, 16-color scale (ml/100 gm/min).

as in diseased brain at the chronic stage.^{22,30)} In other words, it is safe to assume that each brain has its own "metabolic demand," which fluctuates to some extent in accordance with the status of cerebral function.

Present concept: On the basis of the information we have, it appears reasonable to interpret rCBF dynamics in cerebral infarction in terms of a relationship between "energy supply" and "metabolic demand."

It is no exaggeration to say that the advent of PET, which measures both rCBF and metabolism, has contributed substantially to the establishment of the new concept of cerebral perfusion, which disregards the actual rCBF values and has given rise to the terminology "matched" situation,⁴⁾ "misery perfusion,"^{2,4)} and "luxury perfusion."^{18,22)}

In light of this concept, comparison of the rCBF dynamics in our two cases, in which the only major pathophysiological difference involved recanalization, offers many interesting suggestions about dynamic pathophysiological changes in cerebral infarction.

III. Interpretation of the present cases

Diaschitic contralateral rCBF reduction: In the contralateral hemispheres in both cases, moderate rCBF reduction was observed within 2 weeks after onset, followed by subsequent recovery to the normal range (Fig. 7). Such a transient functional depression, distant from the circumscribed lesion, was initially described by von Monakow,⁴³⁾ who termed it "diaschisis." Høedt-Rasmussen *et al.*¹¹⁾ described the analogous concept of "transhemispheric depression," which is confined to the contralateral hemisphere and is ascribed to a reduction in cerebral metabolism secondary to disruption of interhemispheric neuronal connections.

Mayer *et al.*,²⁴⁾ Ginsberg *et al.*,⁹⁾ and others using PET^{2,3,17,44,45)} have recently quantitated decreases in rCBF and cortical metabolism and proved that, with few exceptions,^{22,35)} the reductions occur in parallel. Sugiyama³⁸⁾ observed diaschitic rCBF reduction in cases of small intracerebral hematoma without evident mass effect and suggested that destruction of the basal ganglia or thalamus²³⁾ plays an extremely important role in the disruption of interhemispheric neuronal connections. These observations strongly support the postulated concept of diaschisis, whereas morphological evidence of concrete neuronal pathways remains insufficient.^{11,24)}

However, it should be noted that the concept of diaschisis explains only the "metabolic demand." In order to fully understand not only diaschisis, but

also the means of rCBF regulation under various brain conditions, two additional factors must be addressed. One is "energy supply" (perfusion pressure) as a counterpart of metabolic demand. The other is the postulated concept of a "homeostatic mechanism of cerebral energy supply," which intervenes between "demander" and "supplier" to ensure that the rCBF is adequate but not excessive through dynamic control of cerebrovascular resistance within a rather wide but definite range (the authors term such rCBF dynamics "matched perfusion").

On this basis, the conventional concept of "autoregulation" can be regarded as a concretization of the homeostasis of the cerebral energy supply. Diaschitic rCBF reduction, then, can be redefined in terms of a "supplier of energy" and a "homeostatic mechanism" that are intact despite a decreased "metabolic demand." Regarding "recoverability," it might be considered that reversal of the diaschitic rCBF reduction is attributable to restoration of the metabolic demand, but why and how that might occur remains unknown.

Possible explanations include compensatory rearrangement of synaptic configurations *via* the "sprouting" phenomenon of neurons⁴¹⁾ and/or reactivation of "idling" neurons.⁴⁶⁾

Meanwhile, there is still controversy as to what the working components are that achieve homeostasis of the cerebral energy supply and how they so competently control cerebrovascular resistance. The only references are to myogenic³⁹⁾ and chemical factors,^{16,20,34)} vasoactive substances,³⁵⁾ and neurogenic factor.^{7,10,16,20,32,33)} However, in our opinion it is reasonable to assume that this organization comprises several concrete, closely interconnected mechanisms regulated by a feedback system.

rCBF dynamics in the recanalized hemisphere: In the ipsilateral hemisphere in our Case 2, a marked, widespread rCBF increase that exceeded the metabolic demand was observed (Fig. 8A and B). Such an rCBF dynamics was termed "luxury perfusion" by Lassen,¹⁸⁾ and his report was followed by many others^{12,25,27,40,42)} on this phenomenon, in which it was described as rather frequent and transitory in nature. Uemura *et al.*⁴²⁾ presented a case of rCBF alteration in a recanalized infarction followed by luxury perfusion, measured on the 7th and 21st days after onset by the ¹³³Xe intra-arterial injection method, showing a tendency toward rCBF normalization. However, our study may be the first in which the full course of time-dependent dynamic rCBF changes, followed by spontaneous recanalization, have been documented in one patient. The most noteworthy finding is that the luxury-perfused

hemisphere finally recovered to its normal perfusion state (matched perfusion). This course closely paralleled the rCBF reduction pattern that occurred in the patient with MCA stem occlusion about 6 weeks after onset (Figs. 6E and 8E).

It seems to be generally accepted that luxury perfusion is caused by interstitial acidosis of surrounding vessels due to delivery of anaerobic metabolites.^{12,18,27-29,42)} However, before discussion of the cause of this phenomenon, it should be mentioned that there are two different types. One is mild and unaccompanied by recanalization at the borderzone surrounding or adjacent to the infarcted region (the "borderzone type")^{12,25,27,28,42)} and the other is moderate to marked and follows recanalization in the infarcted region^{12,25,27,42)} (the authors term this the "focal type"). Indeed, metabolic acidosis plausibly explains the borderzone type of luxury perfusion, as Ogawa *et al.*²⁵⁾ confirmed experimentally. It deserves mention that the brain area suffering luxury perfusion of the borderzone type is functionally as well as morphologically intact and only reacts normally under the acidic circumstance caused by the infarcted region. However, there naturally arises the question of how anaerobic glycolysis could continue in the focal type of luxury perfusion for the long interval⁴²⁾ of 3 to 4 weeks, as happened in our Case 2, in which perfusion was excessive (Fig. 7). A more likely cause of the focal type of luxury perfusion is reversible dysfunction of the homeostatic mechanism of the cerebral energy supply owing to the paralysis of vascular resistance accompanying the primary ischemic event³¹⁾ in the infarcted area. In other words, the focal type of luxury perfusion may merely be an expression of reversible cerebrovascular paralysis manifested under the restored perfusion pressure (supplier of energy). Therefore, the magnitude and duration of this phenomenon must be determined mainly by the severity of damage to cerebral resistance vessels.⁴⁰⁾ On rare occasions severe, necrotizing ischemia may cause a concomitant hemorrhagic infarction.^{12,42)} Thus, the pathophysiological significance of these two types of luxury perfusion may be considered to differ fundamentally.

On the other hand, another significant question is whether or not excessive reperfusion is actually detrimental to brain tissue^{18,25)} and thereby exacerbates the situation.^{12,29,40,42)} It is noteworthy in this regard that Case 2 showed no neurological deterioration during the interval of luxury perfusion. Ogawa *et al.*²⁵⁾ experimentally demonstrated the existence of a brain region between the intact rim and infarcted core that is devitalized following postischemic recirculation. This diversity of results of this problem

may well be attributed to the severity and extent of cerebral tissue damage, determined by "primary" ischemia,⁴⁰⁾ which may change cell-membrane properties¹⁸⁾ so as to accelerate "brain edema" such that the affected region will readily succumb to the restored hydrodynamic pressure following reperfusion.

rCBF dynamics in occluded hemisphere: It is difficult to correctly evaluate the pathophysiology of the occluded hemisphere (Case 2) because no dramatic rCBF alteration took place, in contrast with the contralateral diaschitic rCBF decrease and, in Case 1, the marked ipsilateral rCBF increase. The most severe rCBF reduction, which occurred 2 days after onset, is regarded as reflecting an increased oxygen extraction rate (OER), which was described by Wise *et al.* (misery perfusion).^{44,45)} This compensates for the reduced rCBF supply due to the lowered perfusion pressure (supplier of energy) due to the poor collateral circulation in the "very" acute stage (Fig. 6A). There are two possible reasons why the borderzone type of luxury perfusion was not observed in the acute stage.^{17,22,27,29,42)} the oxygen supply for aerobic glycolysis was adequately compensated for by the increase in the OER, which resulted in no production of anaerobic metabolites or, because of limited resolution, the apparatus failed to detect the existence of mild luxury perfusion of the borderzone type.

The relative rCBF increase on the 13th day (Fig. 6C, *arrow*) is considered the focal type of luxury perfusion. The partial restoration of local perfusion pressure occurs through either intraembolic revascularization or short distal migration of the embolus without a significant change in the angiogram. In any case, emergence of the focal type of this phenomenon implies that insufficiency of the "homeostatic mechanism of the cerebral energy supply" still existed in the infarcted area at this period.

We conclude that there was no significant difference in the essential pathophysiology in these two cases, with the exception of complete recanalization in one patient.

Conclusion

Repeated rCBF measurements by D-SPECT can noninvasively demonstrate the time-dependent alterations in rCBF dynamics in cerebral infarction. The conditions of misery and luxury perfusion are transient phenomena observed in the early period of cerebral infarction, before the brain recovers to a matched-perfusion state in the chronic phase.

Assessment of rCBF dynamics in terms of the

relationships among metabolic demand, perfusion pressure, and the homeostatic mechanism of the cerebral energy supply may advance our understanding of the pathophysiology of the brain.

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