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Cerebrovascular Disease and O-15 PET

Measurement of Hemodynamic Parameters Using O-15 PET

Positron emission tomography (PET) and O-15 tracers have been used for greater than 30 years to evaluate human cerebral hemodynamics in patients with cerebral vascular disease (CVD). Quantitative measurement of cerebral blood flow (CBF) and metabolism is important because critical impairment of cerebral circulation induces irreversible damage to the cerebral cortex, causing neuronal deficits or functional damage. The cerebral regions of impaired hemodynamics, "misery perfusion" are visualized by mismatch between oxygen metabolism and CBF [1, 2], which is usually delineated by the elevation of oxygen extraction fraction (OEF) in O-15 gas PET [2–6]. Because patients with misery perfusion show a significantly higher incidence rate of stroke or recurrent stroke [7–9], evaluation of hemodynamic status in CVD patients is very important to determine indication of neurosurgical treatment. To quantitatively evaluate cerebral hemodynamic status, methods for precise measurement were developed and its accuracy has also been improved with the progression of PET scanner resolution.

The historic development of PET measurement of cerebral hemodynamic parameters is shown in Table 14.1 [10–25]. The impaired hemodynamic status of misery perfusion was at first determined using a count-based semiquantitative method [1, 2]. Quantitative methods for cerebral circulation and oxygen metabolism were proposed in the early 1980s, and the two common methods based on a single compartment model are known as the steady-state method and the bolus inhalation method (so-called 'autoradiographic' or 'three-step' method) (Fig. 14.1a). A quantitative steady-state method with continuous inhalation of O-15 labeled gases such as $^{15}O_2$, $C^{15}O_2$ and $C^{15}O$ was proposed [15, 16]. Lammertsma et al. corrected the effect of cerebral blood volume (CBV) on OEF in the O-15 gas steady-state method [17]. OEF is usually overestimated when CBV correction is not applied. Although this method is simple and easier than the bolus tracer administration method, specific equipment must be installed to keep radioactive gas at a constant rate of concentration during PET scans, and patients cannot avoid high exposure to radioactive gas. The autoradiographic method developed for measurement of CBF using O-15 water was applied [18, 19] to

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Table 14.1 Measurements of CBF and oxygen metabolism using O-15 tracers

Authors	Tracers	Method	Parameters	Year	References
Ter-Pogossian et al., Raichle et al.	$H_2{}^{15}O$, $^{15}O_2$	Bolus (No. image)	CBF, $CMRO_2$	1969–1976	[10–13]
Jones et al.	$^{15}O_2$, $C^{15}O_2$	Steady-state	Qualitative	1976	[14]
Frackowiak et al., Lammertsma et al.	$^{15}O_2$, $C^{15}O_2$	Steady-state	CBF, OEF, $CMRO_2$	1980, 1981	[15, 16]
Lammertsma et al.	$^{15}O_2$, $C^{15}O$	Steady-state(OEF-CBV correction)	OEF, $CMRO_2$	1983	[17]
Herscovitch et al., Raichle et al.	$H_2{}^{15}O$	Bolus, (ARG)	CBF	1983	[18, 19]
Mintun et al.	$H_2{}^{15}O$, $^{15}O_2$, $C^{15}O$	Bolus, (3-step)	CBF, CBV, OEF, $CMRO_2$	1984	[20]
Lammertsma et al.	^{11}CO, ^{11}C-HSA	Equilibrium	CBV, Htc ratio	1984	[21]
Gambhir et al.	$H_2{}^{15}O$	Bolus, (2-CM)	CBF, V_d	1987	[22]
Lammertsma et al.	$C^{15}O_2$	Build-up	CBF	1989	[23]
Ohta et al.	$^{15}O_2$, $H_2{}^{15}O$	Bolus, (1-step, 2-CM)	$CMRO_2$, OEF, CBF, V_0	1992, 1996	[24, 25]

CBF cerebral blood flow, *$CMRO_2$* cerebral metabolic rate of oxygen, *OEF* oxygen extraction fraction, *CBV* cerebral blood volume, *V_d* distribution volume, *Htc ratio* cerebral-to-large vessel hematocrit ratio, *V_0* arterial-to-capillary volume, *ARG* autoradiographic method, *CM* compartment model

the measurement of oxygen metabolism with bolus administration of O-15 tracers (three-step method) [20]. This method does not require the specific equipment to maintain a constant concentration rate of radioactive gas.

Because various quantitative methods for measurement of CBF using O-15 water PET were proposed, the method for quantitative measurement was improved, as well as several methods for image calculation and correction of parameters to improve the image quality and calculation time [25–35]. A two-compartment (one-tissue compartment) model analysis increased the accuracy of CBF values by separating the vascular component from the blood flow value as shown in the following equation (Fig. 14.1b) [24, 25]:

$$C_b(t) = K_1 \cdot C_a(t) \otimes e^{-k2t} + V_0 \cdot C_a(t).$$

where $C_b(t)$ and $C_a(t)$ are the concentrations of tracer in the brain and arteries, K_1 and k_2 are rate constants, V_0 is arterial-to-capillary blood volume, and $\otimes$ denotes operation of convolution. A single-compartment model analysis can be described with elimination of the second term in this equation [18, 19]. Rate constant of K_1 linearly correlates with blood flow, which can be corrected by extraction of the tracer ($K_1 = E \cdot F$; E = extraction, F = blood flow). If this method is applied to the bolus $^{15}O_2$ inhalation method, the cerebral metabolic rate of oxygen ($CMRO_2$) can be calculated without measuring CBF and CBV by the equation of $CMRO_2 = tO_2c \cdot K_1$, where tO_2c is total arterial O_2 content (one-step method) [24]. This method includes an assumption that the metabolized and recirculating radioactivity of O-15 water is negligible during the scanning time. The $CMRO_2$ values tend to be overestimated because of this assumption as well as the fact that venous radioactivity cannot be eliminated completely despite separation of V_0 [24, 36]. This simple method, however, can evaluate changes in oxygen metabolism during neural stimulation by repeated measurement of $CMRO_2$ in activation studies [37]. Recently, a report from 11 PET centers in Japan, in which several representative methods for O-15 PET were used, showed no significant differences in quantitative values of hemodynamic parameters among the methods [38]. In this study, overall mean ± SD (standard deviation) values in

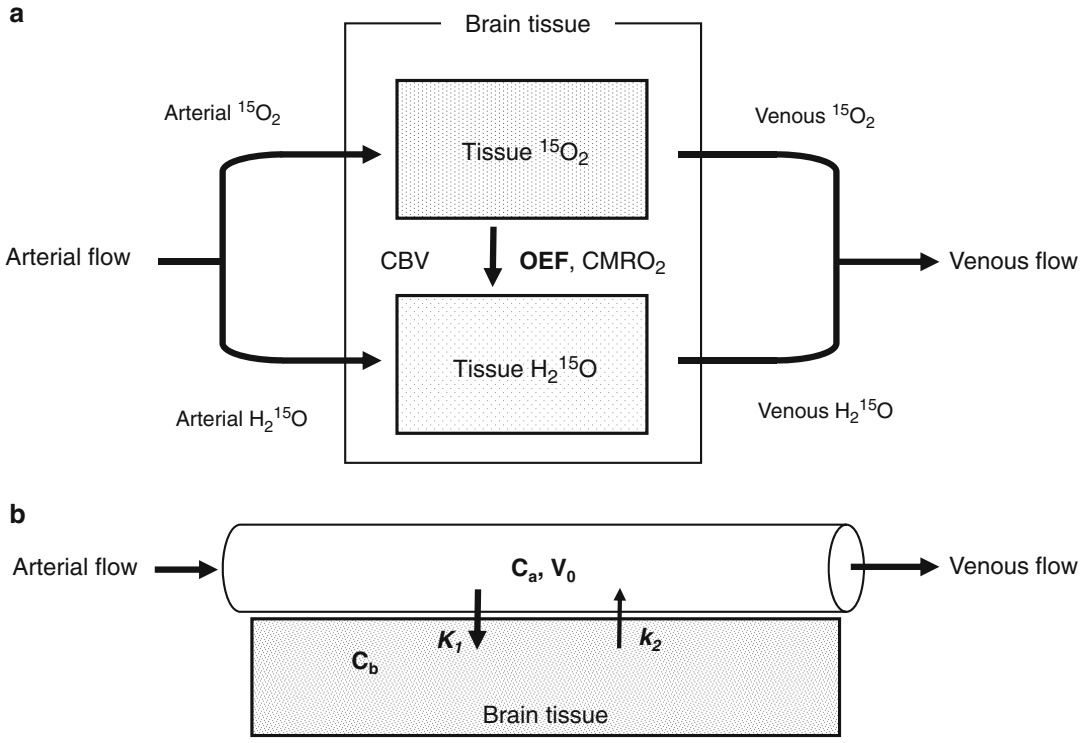

Fig. 14.1 Schematic of one-compartment (**a**) and two-compartment (one-tissue compartment) (**b**) models for calculation of CBF and oxygen metabolism. In model (**a**), CBF calculation using $H_2{}^{15}O$ or $C^{15}O_2$ can be explained by neglecting $^{15}O_2$ elements. C_a and C_b are the concentrations of arterial and brain tissue radioactivity, K_1 and k_2 are rate constants of tracers, and V_0 is the arterial-to-capillary blood volume

cerebral cortical regions for healthy human subjects were CBF = 44.4 ± 6.5 mL/100 g/min, CBV = 3.8 ± 0.7 mL/100 g, $CMRO_2$ = 3.3 ± 0.5 mL/100 g/min, and OEF = 0.44 ± 0.06.

Contrary to the development of precise quantification methods, one long-term prospective study reported that the diagnostic accuracy for misery perfusion was similar to, or rather, better with the count-based method compared with the quantitative evaluation [39, 40]. Recent reports on the application of count-based semi-quantitative methods have been controversial. A normalized method using cerebellar counts showed poor agreement with quantitative OEF elevation [41]. However, another study employing a simplified ipsilateral-to-contralateral asymmetry index (AI) comparison method using count-based ratio images showed good accordance with the AI of quantitative OEF in CVD patients [42, 43]. The advantage of these simplified methods is that the scanning protocol is simple and the procedure is noninvasive without arterial blood sampling. For precise evaluation of hemodynamic changes in the brain, quantitative methods with arterial blood sampling are required; however, in clinical studies, the simplified method is preferable for assessment of the hemodynamic status.

Chronic Cerebrovascular Disease

CBF autoregulation is the mechanism by which CBF is maintained during changes in systemic blood pressure. This physiologic function also can be applied to the relationship between changes in cerebral perfusion pressure (CPP) and CBF. CBF is maintained by autoregulatory vasoconstriction and vasodilatation of arterioles when CPP is changed; however, CBF decreases when

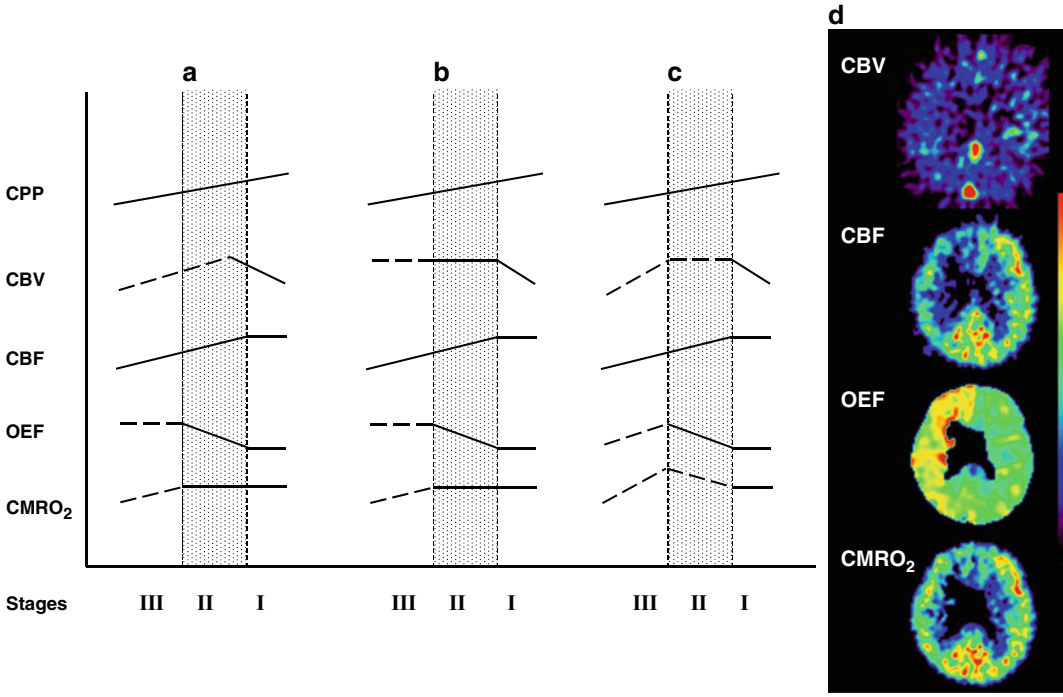

Fig. 14.2 Graph explaining changes in hemodynamic parameters induced by decreases in perfusion pressure (CPP). Powers et al. initially proposed the basic concept of hypothesis (**a**), and later revised the model with a minor change in CBV (**b**) [3–6, 40, 46]. Nemoto et al. modified this model based on their two-compartment analysis (**c**) [47]. *Dotted* area in the graph shows stage II impairment. Representative PET images for patients with misery perfusion (stage II) are presented in the right column (**d**). Misery perfusion shows a slight decrease in $CMRO_2$ at the region of CBF decrease and OEF elevation

CPP decreases below the lower limit of autoregulation (Fig. 14.2). Experiments on cerebrovascular autoregulation have shown an increase in the diameter of resistance arteries as a function of the decrease in systemic blood pressure [44, 45]. Although this vasodilatory change caused by a reduction in blood pressure is a well-known physiologic reaction in the acute phase, it is not clear whether the cerebral circulation in patients with chronic CVD shows similar vasodilatory compensation in the resistance arteries. To explain the cerebral hemodynamic changes in CVD patients, Powers et al. originally presumed that the dilatory change in resistance vessels continues even after the vasodilatation can no longer compensate for CBF autoregulation as described in animal experiments (Fig. 14.2a) [3, 5, 6]. They later modified this model with respect to hemodynamics in chronic CVD patients (Fig. 14.2b) [39, 46] and reported the importance of neurosurgical treatment for stage II ischemia. Recently, Nemoto et al. slightly corrected this hemodynamic assumption based on their analysis using a two-compartment model (Fig. 14.2c) [47]. However, most patients with misery perfusion usually show a slight decrease in $CMRO_2$ (Fig. 14.2d) as described by Powers et al. in their reports [3–5].

Several researchers and neurosurgeons reported that the extracranial-to-intracranial (EC/IC) bypass surgery is efficient for patients with misery perfusion caused by cerebral arterial occlusive lesions [3–6, 48]. However, the multicenter cohort study conducted in the mid-1980s for evaluation of prognosis of CVD patients contradicted the effectiveness of the EC/IC bypass

surgery [49, 50]. The problem with the cohort study performed by the EC/IC bypass surgery group was that patient entry criteria were inappropriate. All patients with stenotic lesions in the internal carotid arteries were involved in the study, and there was no significant difference in outcome between the surgical treatment and simple medication groups. However, as many recent studies have suggested, if the patients do not show neurologic symptoms, stenoocclusive lesions do not necessarily cause hemodynamic impairment that may induce strokes in the brain [51–53]. Several long-term prospective studies have shown that patients without hemodynamic deficiency did not have a high incidence of subsequent infarction compared with those with misery perfusion. In their 5-year follow-up study ($n=40$), Yamauchi et al. (Kyoto University group) showed that the recurrence rate of stroke was significantly higher in patients with misery perfusion (57.1%) compared with those without OEF elevation (18.2%) [7, 8]. Grubb et al. (Washington University group) also showed a similar result with a larger patient sample ($n=81$) and 3-year follow-up period [9]. Their results suggest that a patient with stenoocclusive lesions in major cerebral arteries may not show neurologic deficits or hemodynamic impairment if the lesion advances slowly enough to generate sufficient collateral circulation.

This evidence shows the importance of evaluation of the cerebral circulation and oxygen metabolism; however, the degree of hemodynamic impairment can be evaluated by a reduction of cerebral vasoreactivity (CVR) after acetazolamide (ACZ) or CO_2 loading [54–56]. The vasodilatory effect of ACZ or CO_2 without changes in systemic blood pressure causes increases in CBF in normal circulation [54, 57, 58]. Recently, several long-term prospective studies were conducted using the quantitative measurement of baseline CBF and CVR to confirm the risk of developing cerebral infarction in hemodynamic impairment [59–67]. The studies were performed to contradict the prospective cohort study that denied the effectiveness and benefits of EC/IC bypass surgery for patients with cerebral arterial occlusion. The aim of the studies was to prove that symptomatic patients with CVD who have hemodynamic impairment should be treated by surgical or interventional methods to avoid recurrent strokes. The studies with alternative methods reported a benefit of measuring CVR to evaluate the hemodynamic condition and to predict the risk of subsequent strokes [59–64]. On the other hand, nonquantitative evaluation of CVR failed to predict any significant difference in recurrent stroke risk between normal and impaired CVR groups [65–67]. A recent study reported that diagnostic accuracy for detecting misery perfusion by using quantitative measurement of CBF and CVR after ACZ administration had a sensitivity of 56.3%, specificity of 88.2%, and accuracy of 78.0% [68].

Figures 14.3 and 14.4 show representative cases of stage I and stage II hemodynamic impairment. A patient with stage I showed a decrease in CVR without elevation of OEF (Fig. 14.3), while a patient with misery perfusion (stage II impairment) showed elevation of OEF as well as a decrease in CVR in the affected hemisphere.

Evaluation of Cerebral Glucose Metabolism Following Stroke

Stroke is caused by a variety of pathologic changes that produce a focal reduction of blood flow or multifocal regions of compromised perfusion. In most of these cases, the end result of reduced CBF and inadequate delivery of oxygen and glucose to the brain is cerebral infarction [69]. In stabilized infarction, [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) PET shows a focal area of hypometabolism in a location consistent with focal cerebral infarction [70]. However, the metabolic impairment in stroke patients is not limited to the area of infarction. PET and single-photon emission computed tomography studies have demonstrated remote effects in regional CBF and metabolism consequent to focal infarction [71]. From the early period after an acute brain lesion, diaschisis can develop because of reduced cerebral function resulting from the interruption of normal input to a region not directly involved in the stroke. Distinguishing between regional ischemia and depressed neurometabolic activity is

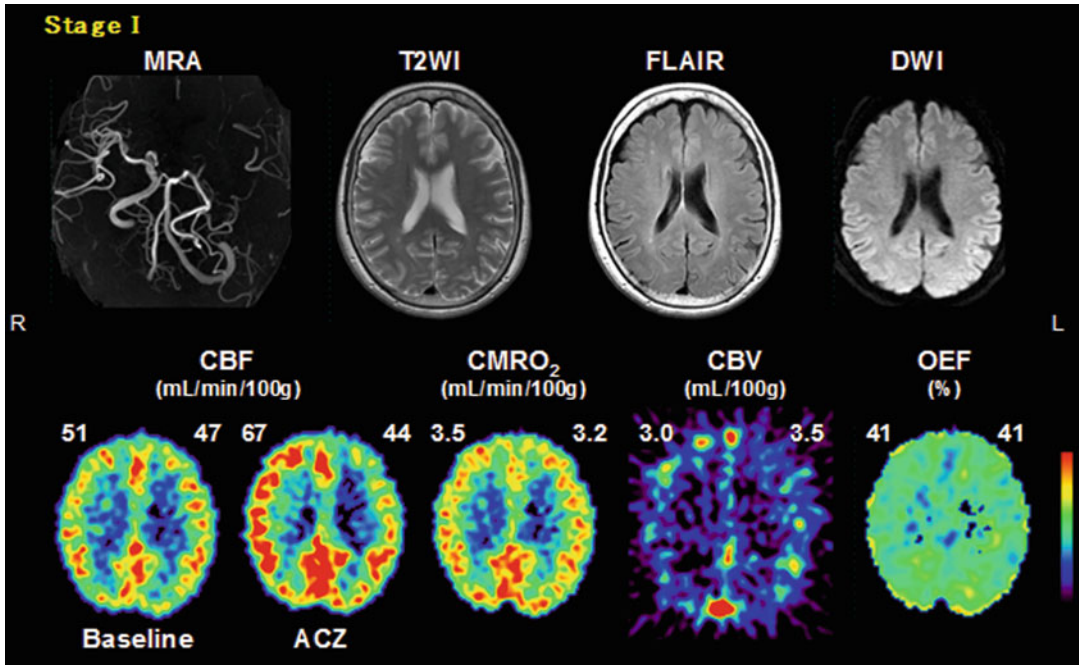

Fig. 14.3 A representative case of a stage I patient with stenosis in the left MCA. CBF and $CMRO_2$ did not show a significant decrease in the affected hemisphere, but CVR after ACZ administration showed the lack of vascular reactivity. Numbers are quantitative values for each hemisphere MRA: MR angiography

aided by the calculation of OEF with $CMRO_2$ and cerebral metabolism [48, 72, 73]. In the regions of diaschisis, the metabolic rate as measured by local glucose consumption was decreased, while OEF and $CMRO_2$ are preserved. Although there are reports of ischemic penumbra and luxury perfusion persisting after stroke [74, 75], normal oxygen extraction surrounding stroke suggests diaschisis [76].

It is likely that diaschisis is associated with functional impairment can determine the severity of the clinical images in the acute stage and its recovery [77]. Diaschisis can occur in the areas surrounding the "infarcted" lesion, in the outside of the lesion in the affected hemisphere as well as in the other hemisphere (e.g., "cross hemispheric" or "cross callosal" diaschisis). A regression of diaschisis is usually, although not invariably, found in the following months and may be related to the clinical recovery [78]. Immediately following stroke, extensive functional depression measured by glucose consumption and associated functional impairment can develop in the bilateral hemisphere [71, 79, 80]. In many reports, the improvement in function after left middle cerebral artery (MCA) stroke, e.g., progression from hand and leg weakness with aphasia to only hand weakness has been observed and seems linked to the anatomy adjacent to the cerebral infarction. Cortical diaschisis is particularly prominent with thalamic infarcts which often lead to pronounced thalamocortical diaschisis with corresponding cognitive deficits [81, 82]. In patients with cortical or subcortical infarction involved in the language area, regression of intrahemispheric and transhemispheric diaschisis may be associated with the recovery of a function that is subserved by an extensive network of interconnected regions in both hemispheres, at least in the first 6 months following stroke [78]. However, in cases of crossed (contralateral) cerebellar diaschisis (CCD) which can occur early after supratentorial ischemic lesions, particularly in the basal ganglia or frontal or parietal corticex, CCD can persist over a long period of time with eventual cerebellar atrophy, but usually lacks

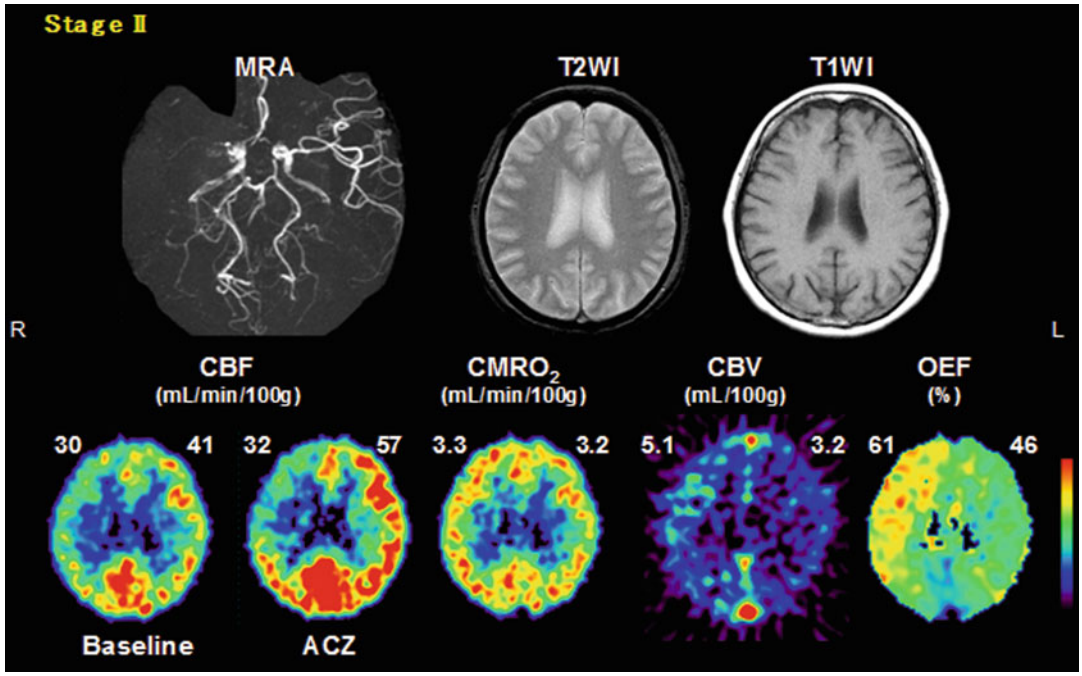

Fig. 14.4 A representative case of chronic CVD with misery perfusion (stage II) in the right cerebral hemisphere as a result of right MCA occlusion (see MRA). This patient did not show decrease in $CMRO_2$ in the impaired region (*right* frontal lobe). Numbers are quantitative values for each hemisphere

major correlates in neurologic functional impairment. The regional glucose metabolism in diaschisis in the early period following stroke may be associated with functional improvement during the recovery phase [83, 84]. Cerebral glucose metabolism in the left hemisphere outside the infarcted region, particularly temporoparietal metabolism, in the acute stage following stroke in the left hemisphere is thought to be the best predictor of recovery of auditory comprehension [85], and suggests an important role for intrahemispheric diaschisis in determining the severity of the clinical picture in the acute stage and its recovery [86].

Bilateral temporoparietal glucose metabolism shows a positive correlation with auditory comprehensive function in patients with aphasia following stroke.

Besides of the resolution of diaschisis, reorganization in the brain plays an important role in poststroke functional recovery. Changes in regional glucose metabolism in the contralateral hemisphere associated with poststroke reorganization have been detected by FDG PET [83]. The parallel change in glucose metabolism and high-energy phosphate metabolism associated with poststroke functional recovery is possibly explained by cerebral reorganization in the contralateral premotor cortex. The resulting cerebral reorganization may account for improved patient functional recovery from stroke. Similar findings can be observed in patients with aphasia following stroke. The changes in neuronal activities measured by glucose metabolism in the surrounding area of the "infarcted" region, in the contralateral mirror area and left Broca's area during activation were highly predictive of the recovery of auditory comprehension, indicating that the possibility to activate an extensive, bihemispheric neural network was crucial for recovery [84]. Hypermetabolism, measured by increased FDG uptake in the contralateral homologous area, indicates that there is increased energy being used, possibly because of increased neuronal plasticity.

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