Management of Patients with Ischemic Stroke

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Abstract:

In a case with embolic occlusion of cerebral artery, residual cerebral blood flow (CBF) in symptomatic ischemic region is distributed heterogeneously and cerebral infarction is developed gradually from ischemic core to penumbra. Ischemic core is defined as a region with irreversible tissue damage due to fairly poor collateral circulation, and ischemic penumbra is defined as a region with preservation of tissue reversibility in a certain time. Reversibility of ischemic penumbra is also depending on both residual CBF and time from stroke onset, and the existence of ischemic penumbra is essential for thrombolytic therapy. Ischemic penumbra is thought to be the first therapeutic target in management of patients with acute cerebral ischemia. Using ^{133}Xe SPECT imaging, penumbral flow is estimated as 15-30 ml/100g/min within 3 hours from stroke onset and 20-30 ml/100g/min during 3-6 hours from stroke onset. Ischemic penumbra could be diagnosed accurately by both negative findings on DWI and critical flow level in brain perfusion SPECT or other perfusion image.

Hemodynamic cerebral ischemia could be stratified into Stage I and Stage II (Misery perfusion). According to vasodilatory and metabolic compensation toward reduction of cerebral perfusion pressure, Stage I ischemia is defined as both preservation of resting CBF and reduction of vascular reserve (VR). Stage II ischemia is defined as reduction of resting CBF associated with loss of VR. The vasodilatory response to acetazolamide provides an effective parameter of VR: (acetazolamide-activated CBF / resting CBF − 1) ×100%. Stage II ischemia is quantitatively defined as both CBF less than 80% of normal mean CBF and VR less than 10%. Stratification of hemodynamic cerebral ischemia could be important to determine future risk of stroke. Stage II ischemia is thought to be the second therapeutic target in management of patients with hemodynamic cerebral ischemia. The characteristics and kinetics of brain perfusion radiotracers should be considered in quantitative stratification of hemodynamic cerebral ischemia using brain perfusion SPECT.

Introduction

On pathophysiological basis, prompt flow restoration to salvage neurons in the ischemic penumbra[1,2] and protection from the cascade of cellular injury, appear the rational approaches to an effective treatment of acute ischemic stroke. Early reperfusion by means of thrombolytic agents is tried at the first therapeutic target (ischemic penumbra). The potential benefit of thrombolytics is counterbalanced by the risk of hemorrhagic complications and cerebral edema associated with reperfusion. The results of rt-PA stroke study of NINDS support the efficacy of thrombolytic thera-

py within 3 hours from the stroke onset[3]. However, therapeutic window of thrombolytic therapy may depend on not only the duration of cerebral ischemia but also the intensity of cerebral ischemia[4,5]. Additionally, diffusion-weighted MRI (DWI) could show early ischemic changes in acute stroke[6]. Brain perfusion SPECT and DWI could provide the informations on both the intensity of cerebral ischemia and tissue viability, and these modalities could open the therapeutic window over 3 hours from the stroke onset.

Hemodynamic cerebral ischemia is one of mechanisms of stroke associated with arteriosclerosis of cerebral artery. The vascular system of the brain is controlled by autoregulatory response. When cerebral perfusion pressure is reduced under a lower limit of the autoregulation by the occlusion or stenosis of major cerebral artery, the ability of vasodilatory response (cerebrovascular reserve: VR) is compromised[7,8], and "misery perfusion[9]" does occur. Measurements of CBF and VR using quantitation of brain perfusion SPECT may be particularly effective in assessing the

degree of hemodynamic cerebral ischemia[10]. Hemodynamic cerebral ischemia could be quantitatively stratified into Stage I and Stage II (Misery perfusion), and the stratification could be important to determine future risk of stroke. A surgical intervention such as EC-IC bypass surgery is tried at the second therapeutic target (misery perfusion: Stage II ischemia). At present, Japanese EC-IC Bypass trial (JET Study) is organized and ongoing to clarify surgical benefit for Stage II ischemia.

Recent management of patients with ischemic stroke should be based on the evidence on effective treatments and carried out by stroke team informed about multimodality.

Ischemic penumbra and core

Evaluation by brain perfusion SPECT

In a case with embolic occlusion of cerebral artery, residual cerebral blood flow (CBF) in symptomatic ischemic region is distributed heterogeneously and cerebral infarc-
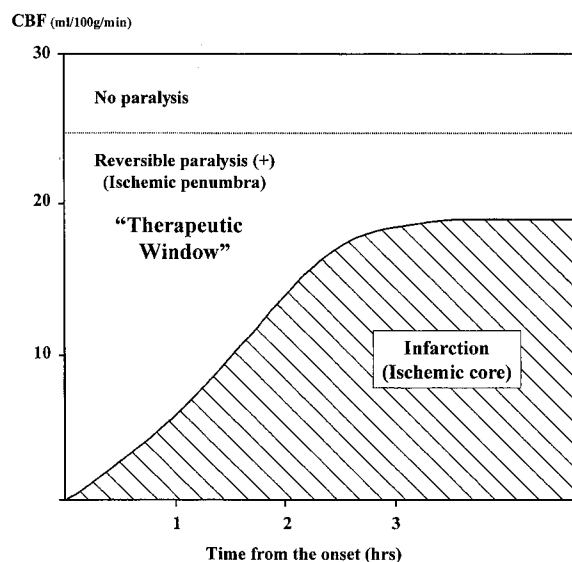

Fig.1 Reversibility of neurological signs and ischemic brain tissue estimated by both time from stroke onset and residual CBF
Ischemic penumbra could be the therapeutic window for thrombolytic therapy, and ischemic core could extend depending on both residual CBF and time from stroke onset.
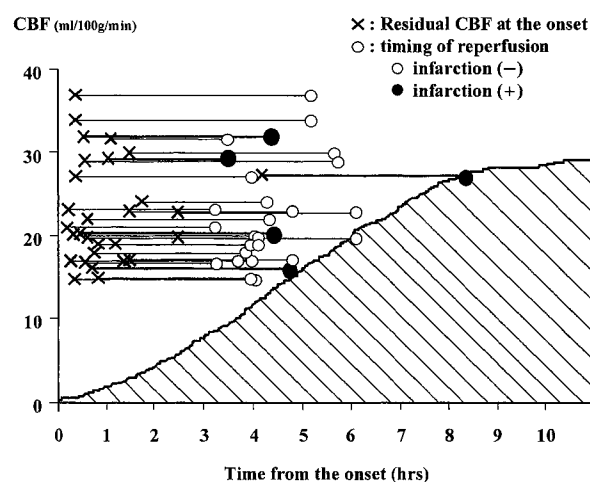

Fig.2 Residual CBF level and time to reperfusion and the appearance of infarction in successful reperfusion areas.
Using ^{133}Xe SPECT imaging, penumbral flow is estimated as 15-30 ml/100g/min within 3 hours from stroke onset and 20-30 ml/100g/min during 3-6 hours from stroke onset
×: Residual CBF level, ○: time to reperfusion

tion is developed gradually from ischemic core to penumbra[1]. Ischemic core is defined as a region with irreversible tissue damage due to fairly poor collateral circulation, and ischemic penumbra is defined as a region with preservation of tissue reversibility in a certain time. Ratio of ischemic penumbra to core is depending on both residual CBF and time from stroke onset. Therefore, in acute stroke case it is important to assess not only ischemic penumbra but also ischemic core by brain perfusion SPECT. Reversibility of ischemic penumbra is also depending on both residual CBF and time from stroke onset[4, 5], and the existence of ischemic penumbra is essential for thrombolytic therapy. Ischemic penumbra is thought to be the therapeutic window for cerebral reperfusion (Fig. 1).

To confirm the hemodynamic criteria of thrombolytic therapy, timing of reperfusion and residual CBF in successful reperfusion areas was investigated in 29 ROI of patients with MCA occlusion. Fig. 2 showed that cerebral infarction was avoided in 24 areas out of 29 reperfused ROIs. These results imply that cerebral tissue viability could depend on both residual CBF level and timing of reperfusion under conditions that residual CBF might be maintained steadily during the treatment[11]. In our institute, therapeutic window for thrombolytic therapy was established from brain perfusion SPECT based on quantitative measurement. Using ^{133}Xe SPECT imaging (Kanno-Lassen[12]), penumbral flow is estimated as 15-30 ml/100g/min within 3 hours from stroke onset and 20-30 ml/100g/min during 3-6 hours from stroke onset[13]. Semiquantification of CBF imaging by ^{99m}Tc-HMPAO or ECD SPECT suggested 35-70%CBF asymmetry as penumbral flow level within 6 hours from stroke onset[14].

Evaluation by DWI

Diffusion weighted MRI (DWI) could indicate early pathological changes in ischemic stroke. In clinical situation, hyperintensity areas on DWI within the early ischemic brain should be considered as irreversible tissue changes equal to ischemic core[15]. To investigate tissue viability of hyperintensity areas on DWI, both ^{133}Xe-SPECT and DWI was performed in 23 patients with acute stroke within around 6 hours. As to the areas with hyperintensity (n=23) and the areas without hyperintensity (n=17) on DWI, residual CBF
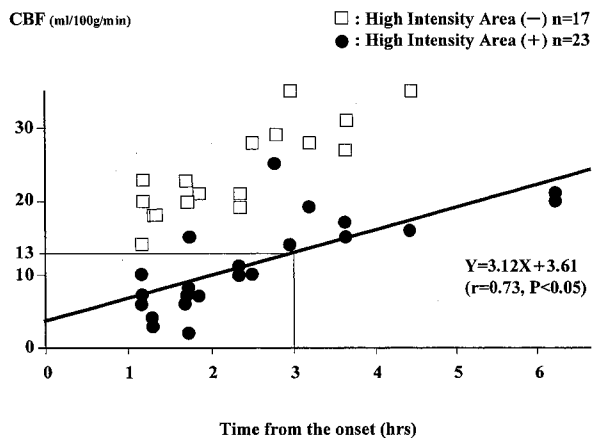

Fig.3 Relationship between time from onset (X) and residual CBF (Y) in hyperintensity areas on DWI
Linear regression line of the areas with hyperintensity (Y=3.12X+3.61, r =0.73, p < 0.05) could imply that the appearance of hyperintensity area may depend on not only the intensity of cerebral ischemia but also the duration of cerebral ischemia. Residual CBF suspected from the linear regression line in hyperintensity areas could not be enough to maintain cerebral tissue viability.
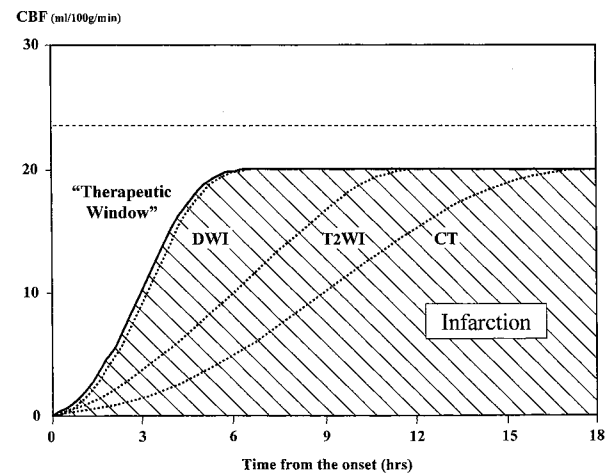

Fig.4 Identification of early ischemic changes by CT, T2WI, DWI (An assumption)
DWI could be more suitable for detecting ischemic core, but ischemic penumbra should be identified using both DWI and brain perfusion SPECT (or other perfusion image).

(Y-axis) and time from onset (X-axis) were plotted as Fig. 3. Fig. 3 showed that residual CBF was significantly lower in the areas with hyperintensity on DWI than in the areas without hyperintensity. Linear regression line of the areas with hyperintensity (Y=3.12X+3.61, r =0.73, p < 0.05) could imply that the appearance of hyperintensity area may depend on not only the intensity of cerebral ischemia but also the duration of cerebral ischemia. Residual CBF suspected from the linear regression line in hyperintensity areas could not be enough to maintain tissue viability. Early ischemic sign on neuroimagings has important role in management of patient with ischemic stroke. Concerning on identification of irreversible changes by neuroimagings, DWI was superior to not only CT but also MRI (T2WI)(Fig. 4). DWI was more suitable for detecting ischemic core, but ischemic penumbra should be identified using both DWI and brain perfusion SPECT (or other perfusion image). Ischemic penumbra could be diagnosed accurately by both negative findings on DWI and critical flow level in brain perfusion SPECT or other perfusion image.

According to the recent investigations, brain protection such as mild hypothermia or free radical scavengers could open the therapeutic window for prompt restoration of regional CBF. To establish hemodynamic criteria for thrombolytic therapy, brain perfusion SPECT and DWI could provide adequate information on tissue viability.

Stratification of hemodynamic cerebral ischemia and Misery perfusion

Evaluation by brain perfusion SPECT

Hemodynamic cerebral ischemia could be stratified into Stage I and Stage II (Misery perfusion) [7),8)]. According to vasodilatory and metabolic compensation toward reduction of CPP, Stage I ischemia is defined as both preservation of resting CBF and reduction of vascular reserve. Stage II ischemia is defined as reduction of resting CBF, loss of vascular reserve and elevation of oxygen extraction fraction (OEF)(Fig. 5). The vasodilatory response to acetazolamide, a carbonic anhydrase inhibitor, provides an effective parameter of cerebrovascular reserve [17)]. Recently, quantitative measurement of CBF and cerebrovascular reserve (VR):

(acetazolamide-activated CBF / resting CBF - 1) × 100% is introduced in clinical use and hemodynamic cerebral ischemia can be quantitatively stratified into Stage I and Stage II. Both ^{123}I-IMP-microsphere method[18)] and ^{123}I-IMP-ARG method[17)] indicate acceptable accuracy, and can be commonly used as quantitative brain perfusion SPECT imaging. In a case of ^{123}I-IMP-ARG method (Fig. 6), Stage I ischemia is defined as follows: resting CBF more than 34ml/100g/min (this value corresponds to 80% of mean CBF of normal subjects) or VR from 10% to 30%, Stage II ischemia is defined as follows: rCBF less than 34ml/100g/min and VR less than 10%. Hemodynamically normal subjects are
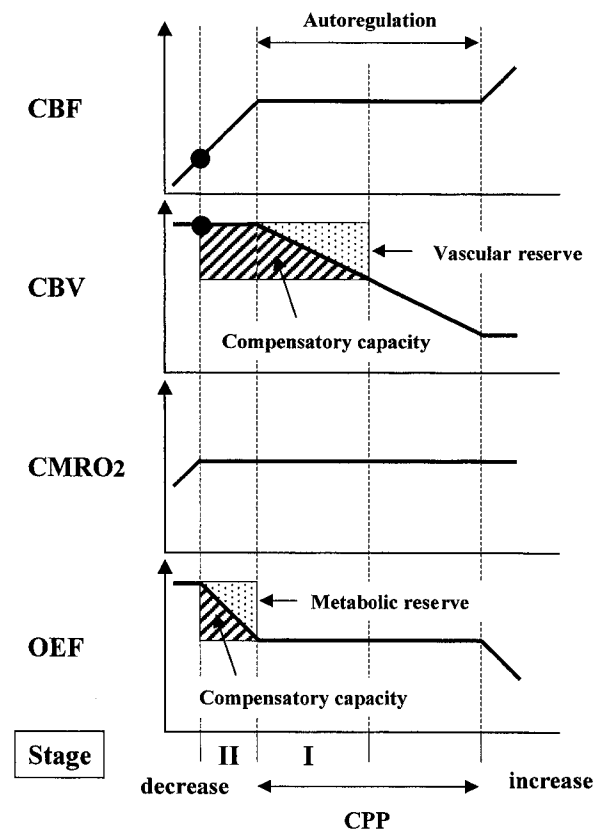

Fig.5　Stages of hemodynamic cerebral ischemia and compensatory capacity by vascular reserve and metabolic reserve
Stage I : maintenance of CBF and reduction of vascular reserve
Stage II : reduction of CBF and loss of vascular reserve and reduction of metabolic reserve(misery perfusion)

involved in VR more than 30% (Stage 0) [13].

Stratification of hemodynamic cerebral ischemia could be important to determine future risk of stroke. Twenty-four patients with hemodynamic stroke were selected for recent EC-IC bypass study. In this study, EC-IC Bypass surgery was performed in patients with Stage II and I (nearly II) ischemia using ^{123}I-IMP-ARG methods. In the affected territories, the mean values of resting CBF and VR after surgery (35.0 ± 7.2ml/100g/min, 32.9 ± 15.2%) were significantly improved in comparison with the values before surgery (29.6 ± 5.3ml, -4.5 ± 12.4%). In the unaffected territories, the mean values of resting CBF and VR after surgery (38.8 ± 7.9ml/100g/min, 40.8 ± 15.8%) were not significantly different to those values before surgery (Fig. 7). The degree of stage after surgery (Stage 0 in 16, Stage I in 8, Stage II in 0) was
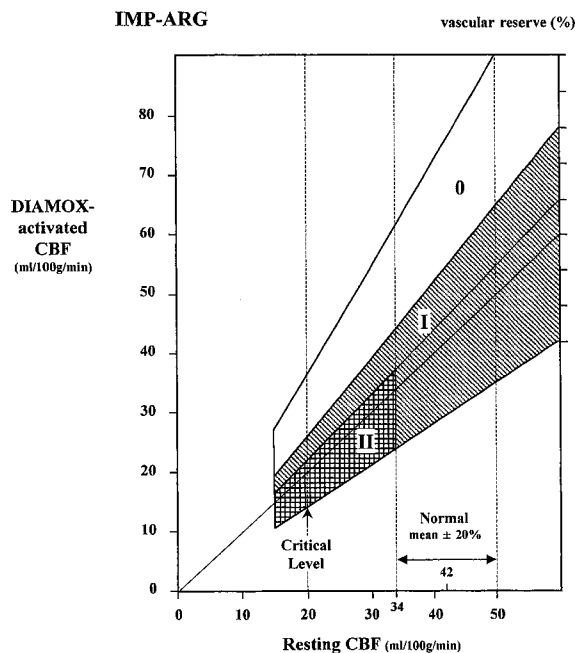
statistically restored in comparison with the degree of stage before surgery (Stage 0 in 0, Stage I in 7, Stage II in 17)(Fig. 8). Stage II hemodynamic cerebral ischemia defined by quantitative brain perfusion SPECT imaging could be reversed to Stage I or 0 by EC- IC Bypass surgery. At present, Japanese EC-IC Bypass trial (JET Study) is organized and ongoing to clarify surgical benefit for Stage II ischemia, and quantitative measurement of CBF and VR has been recognized to be essential for the inclusion criteria for this trial.

Fig.6 Quantitation of stages of hemodynamic cerebral ischemia using resting and acetazolamide-activated CBF (^{123}I-IMP-ARG method)
Stage 0 : normal vascular reserve; (>30%)
Stage I : reduction of vascular reserve; (+ 30% > ,
     > + 10%)
     OR resting CBF; (normal mean ± 20%)
Stage II : loss of vascular reserve; (≤ + 10%)
     OR resting CBF; (≤ normal mean − 20%)

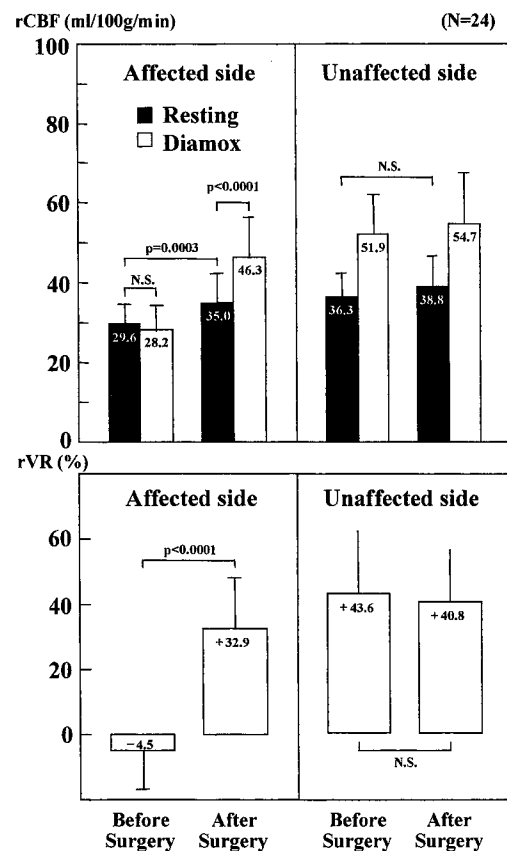Fig.7 Mean value of resting and acetazolamide-activated CBF and vascular reserve (VR) before and after EC-IC bypass
In the affected side, mean values of resting rCBF and vascular reserve (VR) after surgery were significantly improved in comparison with those values before surgery using paired t-test. In the unaffected side, no significant change was observed. (Bars indicated mean ± S.D. of each column.)

Fig.8 Plot shows resting and acetazolamide-activated CBF in 24 patients with STA-MCA anastomosis (Left: before surgery, Right: after surgery).

The degree of stage after surgery (Stage 0 in 16, Stage I in 8, Stage II in 0) was statistically restored in comparison with the degree of stage before surgery (Stage 0 in 0, Stage I in 7, Stage II in 17) (chi-square test : p < 0.0001)

Unaffected side (n=14) Affected side (n=14)

Fig.9 Resting and acetazolamide-activated CBF and vascular reserve using both ^{123}I-IMP-ARG method and ^{99m}Tc-ECD-RVR method. (Bars indicated mean ± S.D. of each column.)

Mean value of resting CBF, acetazolamide-activated CBF and cerebrovascular reserve (VR) using both methods were equivalent in the unaffected territory, however mean value of acetazolamide-activated CBF and cerebrovascular reserve (VR) using ^{99m}Tc-ECD-RVR method were significantly higher than those values using ^{123}I-IMP-ARG method.

Dissociation of quantified brain perfusion SPECT

^{99m}Tc-HMPAO Patlak plot or ^{99m}Tc-ECD-RVR methods could be another option for quantitative brain perfusion SPECT imaging[20), 21)]. Equivalent rCBF values should be quantified using adequate compartment models for different CBF-tracers, however rCBF values could be dissociated between ^{123}I-IMP-ARG method and ^{99m}Tc-ECD-RVR method. To confirm the degree of dissociation of both rCBF value and stage of hemodynamic cerebral ischemia, 14 patients with hemodynamic stroke were selected and resting CBF, acetazolamide-activated CBF and cerebrovascular reserve (VR) were calculated using both ^{123}I-IMP-ARG method and ^{99m}Tc-ECD-RVR method. As a result, mean value of resting CBF, acetazolamide-activated CBF and cerebrovascular reserve (VR) using both methods were equivalent in the unaffected territory, however mean value

of acetazolamide-activated CBF and cerebrovascular reserve (VR) using ^{99m}Tc-ECD-RVR method were significantly higher than those values using ^{123}I-IMP-ARG method (Fig. 9). The stages of hemodynamic cerebral ischemia were dissociated between ^{123}I-IMP-ARG method (Stage 0 in 2, Stage I in 5, Stage II in 7) and ^{99m}Tc-ECD-RVR method (Stage 0 in 8, Stage I in 3, Stage II in 3 using)(Fig. 10). Therefore ^{99m}Tc-ECD-RVR method can indicate acceptable values of resting CBF but could not demonstrate accurate values of VR activated by acetazolamide challenge. First pass extraction of ^{99m}Tc labeled radiotracers is generally lower in the relative high flow range[22)], therefore quantitative CBF value is tend to be underestimated in the area with normally vasodilatory response under acetazolamide-activated condition. Linearization corrections[23)] should be modified in quantitative brain perfusion SPECT imaging using Patlak
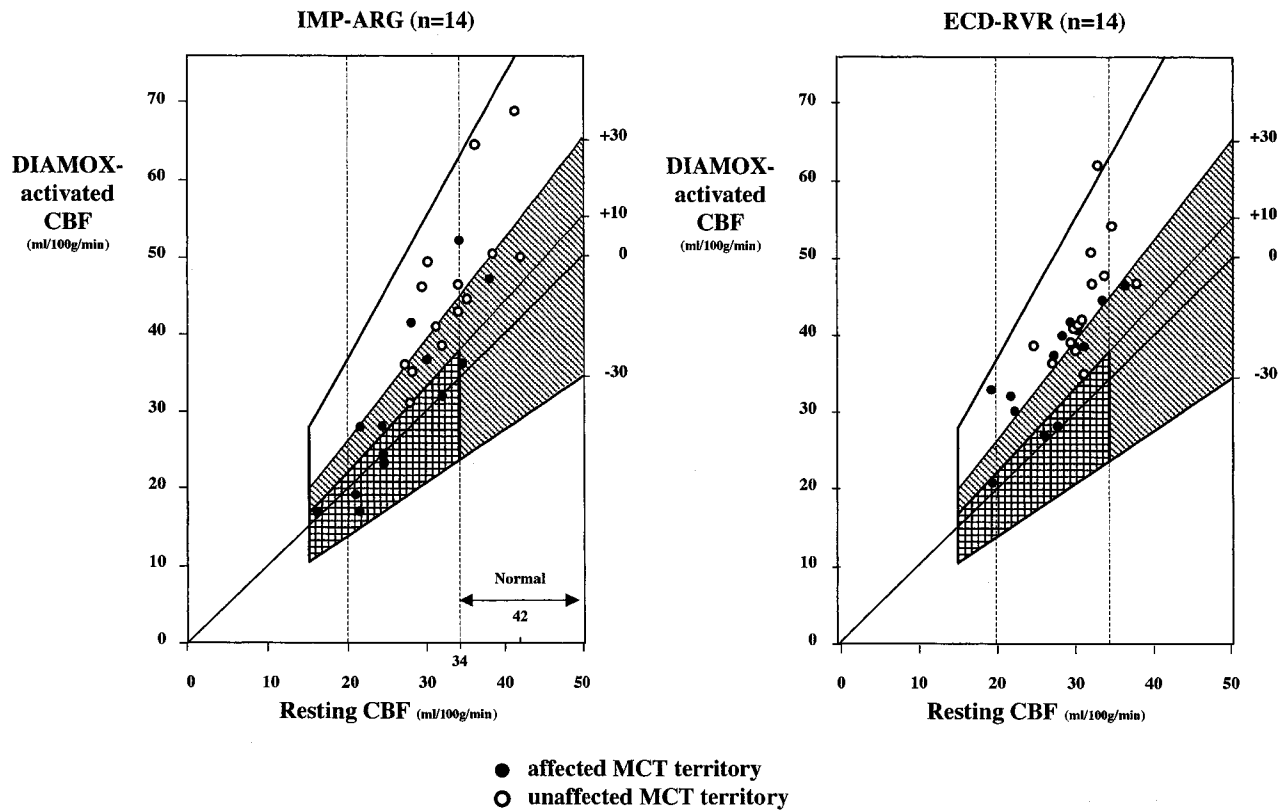
IMP-ARG (n=14)   **ECD-RVR (n=14)**

● affected MCT territory
○ unaffected MCT territory

Fig.10   Plot shows resting and acetazolamide-activated CBF using ^{123}I-IMP-ARG method (left) and ^{99m}Tc-ECD-RVR method (right).
The stages of hemodynamic cerebral ischemia were dissociated between ^{123}I-IMP-ARG method (Stage 0 in 2, Stage I in 5, Stage II in 7) and ^{99m}Tc-ECD-RVR method (Stage 0 in 8, Stage I in 3, Stage II in 3 using).

plot methods, especially using acetazolamide challenge.

Hemodynamic cerebral ischemia could be stratified into Stage I and Stage II (Misery perfusion) and the stratification could be important to determine future risk of stroke. The characteristics and kinetics of brain perfusion radiotracers should be considered in quantitative stratification of hemodynamic cerebral ischemia using brain perfusion SPECT.

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