Cerebral Hematocrit Decreases With Hemodynamic Compromise in Carotid Artery Occlusion
A PET Study
Hiroshi Yamauchi, MD, PhD; Hidenao Fukuyama, MD, PhD; Yasuhiro Nagahama, MD, PhD; Yukinori Katsumi, MD; Hidehiko Okazawa, MD, PhD

Background and Purpose—This study investigated whether in patients with internal carotid artery occlusion the regional cerebral hematocrit correlates with cerebral hemodynamics or metabolic state and, if so, how the regional cerebral hematocrit changes in the hemodynamically compromised region.

Methods—We used positron emission tomography to study seven patients with unilateral internal carotid artery occlusion and no cortical infarction in the chronic stage. The distributions of red blood cell and plasma volumes were assessed using oxygen-15–labeled carbon monoxide and copper-62–labeled human serum albumin-dithiosemicarbazone tracers, respectively. The calculated hematocrit value was compared with the hemodynamic and metabolic parameters measured with the oxygen-15 steady-state technique.

Results—In the cerebral cortex, the value of the cerebral hematocrit varied but was correlated with the hemodynamic and metabolic status. Stepwise regression analysis revealed that the large vessel hematocrit, the cerebral metabolic rate of oxygen, and the cerebral blood flow or the oxygen extraction fraction accounted for a significant proportion of variance of the cerebral hematocrit. The oxygen extraction fraction and the cerebral metabolic rate of oxygen negatively correlated with the cerebral hematocrit, whereas the cerebral blood flow correlated positively: patients with reduced blood supply relative to metabolic demand (decreased blood flow with increased oxygen extraction fraction) showed low hematocrit values.

Conclusions—In carotid artery occlusion in the chronic stage, regional cerebral hematocrit may vary according to cerebral hemodynamics and metabolic status. Regional cerebral hematocrit may decrease with hemodynamic compromise unless oxygen metabolism concomitantly decreases. (Stroke. 1998;29:98-103.)

Key Words: carotid artery diseases ■ cerebral ischemia ■ hematocrit ■ tomography, emission computed
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Subjects and Methods

We studied seven patients with unilateral ICA occlusion in whom no cortical infarctions were demonstrated on MRI. These patients were five men and two women, aged 61 to 74 years (mean±SD, 65±5). The diagnosis of ICA occlusion was based on conventional angiography, which also disclosed no significant arterial disease contralateral to the ICA occlusion in any patient. One patient had no symptoms, one had transient ischemic attacks, and five had minor hemispheric stroke with mild disability. All symptoms were related to the affected carotid distribution. In the asymptomatic patient, ICA occlusion was suspected because of the observation of flow void loss on MRI performed because of hoarseness. In each of the six symptomatic patients, T1-weighted MRI disclosed only one minor subcortical infarction, defined as a well-demarcated hypointense area in the middle cerebral artery (MCA) territory or watershed area of the hemisphere with ICA occlusion. The size of the infarct ranged from 70 to 240 mm². On T2-weighted MRI, punctate or patchy high-intensity areas were observed in the cerebral white matter with ICA occlusion in all of the patients. Four patients showed a confluent high-intensity lesion in the centrum semiovale ipsilateral to the ICA occlusion that was considered to be ischemic change in the deep watershed area due to low flow. The punctate or patchy high-intensity areas of lesser degree were found on the nonaffected side in three patients, but no patient showed confluent high-intensity areas. The clinical and neuroradiological data are summarized in Table 1. All patients were treated with antplatelet therapy (aspirin or ticlopidine HC3), but none took medication that might specifically affect blood rheology such as pentoxifylline. The interval between the PET and MRI evaluations and the latest ischemic event ranged from 2 to 64 months (mean±SD, 28±21). In the asymptomatic patient, ICA occlusion was confirmed on angiography 28 months before the PET study. All patients and their relatives gave informed consent to the conventional angiography and PET studies.

TABLE 1. Clinical and Radiographic Data for 7 Patients with ICA Occlusion

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Age, y/</th>
<th>Sex</th>
<th>Hematocrit, %</th>
<th>Associated Condition</th>
<th>Angiography (Collateral)</th>
<th>Infarct Site and Size on T1-Weighted MRI (mm×mm)</th>
<th>Confluent High-Intensity Lesion in the Centrum Semiovale on T2-Weighted MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61/F</td>
<td>40</td>
<td></td>
<td>No symptom (more than 2.3 years)</td>
<td>Old MI</td>
<td>R ICAO (A com.)</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>61/M</td>
<td>41</td>
<td></td>
<td>Transient, L, visual disturbance (2.5 years)</td>
<td>DM, HT</td>
<td>L ICAO (Leptomeningeal)</td>
<td>L frontal subcortex (7×10)</td>
</tr>
<tr>
<td>3</td>
<td>63/M</td>
<td>35</td>
<td></td>
<td>Minor, R, hemisphere stroke (2 months)</td>
<td>None</td>
<td>R ICAO (A com.)</td>
<td>R frontal subcortex (30×8)</td>
</tr>
<tr>
<td>4</td>
<td>70/M</td>
<td>37</td>
<td></td>
<td>Minor, L, hemisphere stroke (3 months)</td>
<td>None</td>
<td>L ICAO (A com., Oph.)</td>
<td>L centrum semiovale (11×8)</td>
</tr>
<tr>
<td>5</td>
<td>74/M</td>
<td>39</td>
<td></td>
<td>Minor, R, hemisphere stroke (2.2 years)</td>
<td>None</td>
<td>R ICAO (A com.)</td>
<td>R corona radiata (10×5)</td>
</tr>
<tr>
<td>6</td>
<td>62/F</td>
<td>35</td>
<td></td>
<td>Minor, R, hemisphere stroke (3.4 years)</td>
<td>DM</td>
<td>R ICAO (A com., Oph.)</td>
<td>R frontal subcortex (15×10)</td>
</tr>
<tr>
<td>7</td>
<td>67/M</td>
<td>34</td>
<td></td>
<td>Minor, L, hemisphere stroke (5.4 years)</td>
<td>HT</td>
<td>L ICAO (A com., P com.)</td>
<td>L centrum semiovale (20×10)</td>
</tr>
</tbody>
</table>

Pt indicates patient; M, male; F, female; Hematocrit, hematocrit for blood from the radial artery; DM, diabetes mellitus; HT, hypertension; MI, myocardial infarction; L, left; R, right; ICAO, internal carotid artery occlusion; A com., anterior communicating artery; Oph., ophthalmic artery; and P com., posterior communicating artery.

*The times in parentheses indicate the interval between the onset of each symptom and the PET scan. In patient 1, right internal carotid artery occlusion was found incidentally on MRI more than 2.3 years before the PET study.

Selected Abbreviations and Acronyms

- CBF = cerebral blood flow
- CHct = cerebral Hct
- CMRO2 = cerebral metabolic rate of oxygen
- CPV = cerebral plasma volume
- CRBV = cerebral red blood cell volume
- 62Cu-HSA-DTS = copper-62 labeled human serum albumin–dithiosemicarbazone
- FWHM = full width at half maximum
- Hct = hematocrit
- ICA = internal carotid artery
- MCA = middle cerebral artery
- OEF = oxygen extraction fraction
- ROI = region of interest
- Tb = mean transit time of blood
- Tp = mean transit time of plasma
- Tr = mean transit time of red blood cells

("misery perfusion") may be at high risk for recurrent ischemic stroke. Thus, it is especially important to identify the relationship between regional cerebral Hct and cerebral hemodynamics or metabolic state, for application of the rheologically oriented therapy for patients with ICA occlusion to prevent recurrent stroke.

Our preliminary study in seven patients with major cerebral arterial occlusion, including five of the patients with ICA occlusion in this study, suggested a reduction in cerebral Hct distal to the major cerebral arterial occlusion site but with variation among patients. The purpose of this study was to determine whether in patients with ICA occlusion in the chronic stage regional cerebral Hct correlates with cerebral hemodynamics or metabolic state and, if so, how the regional cerebral Hct changes in the hemodynamically compromised region. We selected the patients with unilateral ICA occlusion and no cortical infarction, and examined the relationship between the cerebral Hct and the other hemodynamic and metabolic parameters in the cerebral cortex using PET.
Cerebral Hematocrit in ICA Occlusion

All patients were scanned with a PCT-360W system (Hitachi Medical Co). A detailed description of this PET scanner has been published previously.11 This system acquires 15 slices with center-to-center distance of 7 mm and transaxial resolution of 6.5 mm FWHM at the center. The slice thickness at the center is 6.9-mm FWHM and 5.9-mm FWHM, respectively, for in-plane and cross-plane slices.

The subject’s head was immobilized with a head-holder and positioned with light beams to obtain transaxial slices parallel to the orbitomeatal line. As part of the scanning procedure but before the PET study, Germanium-68–Gallium-68 transmission scanning was performed for 20 minutes for attenuation correction.

The CBF was determined while the subject continuously inhaled 300 MBq of CO15O per minute through a mask, and the CMRO2 and OEF were measured during continuous inhalation of 500 MBq of O2O per minute. Data were collected for 5 minutes. For measurement of CRCV, 1.20 GBq of C 15O was inhaled, and the PET scan was started 30 seconds after the arrival of the peak count of the brain tissue and continued for 5 minutes. We calculated CBF, CMRO2, and OEF based on the steady-state method.12

The cerebral blood volume was calculated from the data of the C15O scan and was incorporated into the correction of the CMRO2, and OEF.13.14 In the calculation of the cerebral blood volume, a conventional Hct ratio of 0.85 was used. Functional images were reconstructed as 128×128 pixels, with each pixel representing an area of 2.0×2.0 mm.

After the completion of the 15O-gas study, 296 to 740 MBq of 62Cu-HSA-DTS was injected intravenously over 15 seconds in a total volume of 8 mL to obtain CPV images. A 22Zn/24Cu generator was prepared with 22ZnCl2 aqueous solution (1.1 GBq, pH 5.0), and HSA-DTS was synthesized by the method reported in the previous studies.15.16 62Cu-labeling of HSA-DTS was performed by simple mixing of 4 mL of HSA-DTS solution (5 mg/mL in saline buffer at pH 6.0) and 4 mL of the 62Cu-generater eluate. 62Cu-HSA-DTS was readily obtained by a ligand-exchange reaction.17 PET data acquisition was started 3 minutes after administration of 62Cu-HSA-DTS and continued for 8 minutes. Blood samples were obtained at 1, 5, and 7 minutes after injection of 62Cu-HSA-DTS, and both whole-blood and plasma radioactivity were counted.18

Regional CRCV and CPV were calculated using the PET images acquired in the C15O and 62Cu-HSA-DTS studies according to the following equations: CRCV= Cco/(Aco/AHct) (mL/g) and CPV= CHSA/PHSA (mL/g), where Cco and CHSA are the cerebral plasma radioactivity and cerebral hematocrit, respectively, and Aco and AHct are the arterial concentrations of the indicator and the arterial hemoglobin concentration of the indicator, respectively.

We compared the mean hemispheric values of the PET variables for each patient, using Wilcoxon signed-rank test. Statistical significance was accepted at P<.05. Stepwise regression analysis was used to test the independent predictive value of hemodynamic or metabolic parameters on cerebral Hct. We applied this analysis to the hemispheric values of cerebral Hct as the dependent variable and the value of large vessel Hct and the hemispheric values for the PET parameters including CBF, CMRO2, and OEF as the independent variables. We adopted data pairs from the two hemispheres for each patient to analyze the factors that determine the hemispheric difference of cerebral Ht values at the same large vessel Hct, although the data are not independent from each other despite the unilateral nature of the ICA disease. In addition, the values of CBF, OEF, and CMRO2 are not strictly independent, because CMRO2 is calculated from CBF and OEF.

Results

The value of large vessel arterial Hct in the patients ranged from 0.34 to 0.41 (mean±SD, 0.37±0.03). No patient showed a significant change in PaO2 or Paco2 during PET scanning.

In the group as a whole, the value of cerebral Hct in the cerebral cortex ipsilateral to the ICA occlusion was not different from that in the contralateral cortex, whereas significant decreases of CBF and CMRO2 with an increase of OEF were found (Table 2).

Analysis of data for individual patients revealed that the values of cerebral Hct varied among patients or between hemispheres in the same patient but were correlated with parameters of cerebral hemodynamics and metabolic status. When the values of CBF, OEF, CMRO2, and large vessel Hct were entered in a stepwise regression analysis, it produced a model including the values of OEF, CMRO2, and large vessel arterial Hct with a correlation coefficient of .864 for the cerebral Hct: [model A], Hct=0.47AHct−0.003OEF−0.047CMRO2+0.444, P=.0025, or a model including the values of CBF, CMRO2, and large vessel arterial Hct with a correlation coefficient of .867 for the cerebral Hct: [model B], Hct=0.715AHct+0.004CBF−0.091CMRO2+0.173, P=.0023 (Table 3). The CMRO2 and the CBF or OEF accounted for 32% of variance of the cerebral Hct, although AHct was the most heavily-weighted factor, which accounted for 42% of the variance. The CBF was negatively correlated with the OEF (r=−.89, P<.001), indicating that in the hemisphere with decreased CBF the OEF was increased. In these models, the CBF value positively correlated with the cerebral Hct value, whereas the OEF value correlated negatively. Thus, in patients with reduced blood supply relative to
metabolic demand (decreased CBF with increased OEF), the value of cerebral Hct was low (Figure).

Discussion

This study revealed that in patients with ICA occlusion in the chronic stage regional cerebral Hct correlates with cerebral hemodynamics and metabolic status and that it is decreased in the part of the hemodynamically compromised region examined. We found that in the cerebral cortex, which escaped infarct, the large vessel Hct, the CMRO$_2$, and the CBF or OEF accounted for a significant proportion of variance of the cerebral Hct. These hemodynamic and metabolic parameters independently contributed to the prediction of the cerebral Hct, although the large vessel Hct was the most heavily weighted factor. Because of the strong negative correlation between the CBF and OEF in our patients, entering of either value into the model resulted in a similar degree of correlation. The CBF value positively correlated with the cerebral Hct value, whereas the OEF value correlated negatively. Thus, in patients with reduced blood supply relative to metabolic demand (decrease in CBF with increase in OEF), the value of cerebral Hct was low. The value of CMRO$_2$ was negatively related to the value of cerebral Hct. Therefore, as a whole, no significant hemispheric asymmetry in cerebral Hct was found in our patients, who showed a significant decrease in CMRO$_2$, a decrease in CBF, and an increase in OEF. Regional CHct may decrease with the severity of hemodynamic compromise unless oxygen metabolism concomitantly decreases.

The reason for the decrease in Hct in the hemodynamically compromised region is uncertain from this study. However, we found that the total blood volume was increased in this region and that the more pronounced increase in CPV than in CRCV caused the decrease in Hct. In addition, because CBF was decreased in this region, the calculated mean transit time of blood was increased, with a greater increase in the Tr than in the Tp. Therefore, one possible cause of the decrease in Hct is that the lesser decrease in the velocity of red blood cells than in that of plasma may result in concentration of red blood cells in the centers of vessels with an increase in marginal cell-free plasma layer. A study of cerebral microvessels in the cat demonstrated that the thickness of the cell-free plasma layer was increased with a decrease in the pseudo–shear rate defined as the ratio of cell velocity to vessel radius, possibly due to aggregation of red blood cells. Reductions in the perfusion pressure due to ICA occlusion cause vasodilatation and slowing of blood. Thus, in the hemodynamically compromised region with increased blood volume and slow mean transit time of blood, the thickness of the cell-free plasma layer of vessels may increase, resulting in the more pronounced increase in CPV than in CRCV. Another possibility is that the leakage of plasma tracer $^{62}$Cu-HSA-DTS into the cerebral parenchyma due to dysfunction of the blood-brain barrier may cause an artifactual increase in CPV that is disproportionate to any increase in CRCV. Although this effect depends on the actual size of the tracer molecule, none of our patients with only a small subcortical infarction in the chronic stage showed any enhancement of the brain on the MRI study, a negative finding that does not support this mechanism.

There are basic problems with respect to theoretical hemorheology that make our results intrinsically difficult to interpret in terms of either mechanisms or clinical implications. The pathophysiological role of hemorheology in cerebral ischemia is generally viewed as amenable to extrapolation from results of blood viscosity measurements performed with coaxial viscometry. However, the applicability of viscosity values determined by coaxial viscometry to blood flow in the microvascular network of the cerebral circulation is uncertain. Thus, the importance of hemorheological factors per se in cerebral ischemia remains highly controversial. Furthermore, the stress on the importance of viscosity or Hct in the cerebral ischemia, if justified, applies primarily to capillary blood flow. Thus, the clinical importance of our results depends on the validity of the assumption that the Hct in this study, which was estimated for brain tissue overall, reflects the change in capillary Hct.

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**TABLE 3. Multiple Linear Regression Analysis with Cerebral Hematocrit as Dependent Variable**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large vessel Hct</td>
<td>.47</td>
<td>0.131</td>
<td>3.59</td>
<td>.0049</td>
</tr>
<tr>
<td>OEF</td>
<td>-.003</td>
<td>0.001</td>
<td>3.54</td>
<td>.0054</td>
</tr>
<tr>
<td>CMRO$_2$</td>
<td>-.047</td>
<td>0.017</td>
<td>2.83</td>
<td>.0177</td>
</tr>
<tr>
<td>Model B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large vessel Hct</td>
<td>.715</td>
<td>0.142</td>
<td>5.05</td>
<td>.0005</td>
</tr>
<tr>
<td>CBF</td>
<td>.004</td>
<td>0.001</td>
<td>3.61</td>
<td>.0048</td>
</tr>
<tr>
<td>CMRO$_2$</td>
<td>-.091</td>
<td>0.027</td>
<td>3.43</td>
<td>.0065</td>
</tr>
</tbody>
</table>

Large vessel hematocrit indicates the value of hematocrit measured in the blood sample from the radial artery.

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Examples of PET images at the level through the centrum semi-ovale in patient 4 with left (Lt) ICA occlusion and border-zone (centrum semiovale) infarction. The value of large vessel Hct was 0.37. Upper row (from left to right): CBF (according to a pseudocolor scale ranging from 0 to 50 mL/100 g/min), CMRO$_2$ (from 0 to 4 mL/100 g/min), OEF (from 0% to 90%), cerebral hematocrit (Hct, from 0 to 0.6). Lower row: CRCV (from 0 to 5 mL/100 g), CPV (from 0 to 5 mL/100 g), Tr (from 0 to 0.7 minutes) and Tp (from 0 to 0.7 minutes). In the left hemisphere with arterial occlusion, which showed a decrease in CBF (the mean hemispheric value was 22.7 mL/100 g/min) with an increase in OEF (53.7%), the value of cerebral Hct was low (0.32). Also note the more pronounced increase in CPV than in CRCV and the more pronounced increase in Tp than in Tr in the hemisphere with arterial occlusion.

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Although this assumption cannot be verified from these results, it is supported by directly measured data for capillary Hct in animal experiments. In the rabbit bilateral common carotid artery occlusion model, which causes a 48% reduction of CBF without infarct, a decrease in capillary Hct as well as in venous Hct was reported.25 Although the severity of hemodynamic compromise cannot be evaluated by CBF only, the severity of CBF reduction was comparable to that observed in our patients with hemodynamic compromise. The main implication of the observed decrease in Hct in the hemodynamically compromised region is that the often proposed increase of viscosity under low-flow conditions is not supported. In the cerebral cortex, which escaped infarct, there was no vicious cycle wherein elevated blood viscosity caused by an increase in Hct further compromises blood flow and deepens cerebral ischemia, although it is unclear how the plasma viscosity changes. If one considers that an increase in Hct is reported to occur in some patients during the acute stage of stroke,6,27 it may be within the limit of compensation for reduced blood supply that reduced CBF due to ICA occlusion causes a decrease in Hct in the hemodynamically compromised region. In patients with more severe hemodynamic disturbance above the limit of compensation that results in metabolic impairment leading to irreversible ischemic changes, Hct might increase at some stage of acute stroke. Because the extrapolation of the changes in the acute stage from the results in the chronic stage must be made with caution, it should be investigated whether Hct is increased in the hypoperfused but viable areas with increased OEF and preserved CMRO2 in acute stroke.26,27 Another implication of the decrease in Hct in the hemodynamically compromised region with reduced CBF is that it leads to hypoxia due to a reduction in oxygen delivery [product of CBF and oxygen content (Hct)], the degree of which may be greater than is expected from the severity of hypoperfusion. This is among the main disorders to be targeted for therapy in the patients studied. The decrease in Hct does not strongly support the application of rheologically oriented therapy. However, one study demonstrated that the lowering of Hct by isovolemic hemodilution improves oxygen delivery as well as CBF in patients with ICA occlusion showing a compromised hemodynamic state.28 In the ischemic brain, the homeostatic relationship between oxygen content and CBF that maintains oxygen delivery constant under normal conditions is not present, and a direct hemorheological effect is suggested to augment CBF in hemodilution.29 Thus, the decrease in oxygen delivery in the hemodynamically compromised region with decreased Hct might be relieved by a further decrease in Hct by hemodilution, especially in the patients with high large vessel Hct values, although the level of optimal Hct remains to be elucidated.

There are problems in the interpretation of the relationship between cerebral Hct and the other PET variables. The equation for OEF calculated by the steady-state method assumes that the cerebral arterial oxygen content is the same as the peripheral arterial oxygen content. The equation includes, in the denominator, the 15O concentration in the form of hemoglobin-bound molecular oxygen in the arterial blood that may be related to cerebral Hct. Thus, a mathematical phenomenon might in part contribute to the negative relationship between CHct and OEF. The effects of CHct might also affect the calculations of the other PET parameters assessed in this study. Although these potential problems need thorough theoretical and simulation studies for better comprehension of their effects on the various calculations done in this work, preliminary estimations in the previous studies suggested that the effects may not be meaningfully large.13,30

In conclusion, in patients with ICA occlusion in the chronic stage, regional CHct varies according to cerebral hemodynamics and metabolic status. Regional CHct may decrease with hemodynamic compromise unless oxygen metabolism concomitantly decreases. Thus, in the hemodynamically compromised region, the degree of hypoxia may be greater than is expected from the severity of hypoperfusion.

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