Hematocrit as a Risk Factor of Cerebral Infarction: Long-Term Prospective Population Survey in a Japanese Rural Community

Yutaka Kiyohara, M.D., Kazuo Ueda, M.D., Yutaka Hasuo, M.D., Ichiro Fuji, M.D., Toshiro Yanai, M.D., Junichi Wada, M.D., Hideo Kawano, M.D., Tatsuru Shikata, M.D., Teruo Omae, M.D.,* and Masatoshi Fujishima, M.D.

SUMMARY To elucidate the relation of hematocrit (Hct) to the incidence of cerebral infarction, a prospective follow-up study of 16 years (1965-81) was performed in a general population sample of 1220 Hisayama residents aged 44 and over, of both sexes. Most of the subjects who died during the follow-up period were autopsied, the rate being 89.0%.

Hct decreased with advancing age in men, but not in women. The average value for Hct was significantly lower in women than in men. According to the mean value ± 1 SD of Hct, the subjects were grouped into 3, in each sex as follows: low (<35%), normal (35-45%) and high (≥45%) for men, and, low (<30%), normal (30-40%) and high (≥40%) for women.

During the follow-up period, cerebral infarction occurred in 117 patients. The cumulative incidence of cerebral infarction in the low Hct group for men was the lowest, even after adjustments for age and blood pressure. Conversely, the incidence in the low Hct group of women was significantly higher than that in the normal Hct group and was consistently increased with time during 2-5 years of the follow-up. After the 6th year or later, however, the incidence was gradually but significantly increased in the high Hct group, compared with the normal Hct group. Since Hct levels were related with other variables such as serum total cholesterol, serum total protein, Quetelet index and prevalence of hypertension in both sexes, heavy alcohol consumption in men, and glucose intolerance in women, such variables were taken into account using Cox's proportional hazards regression model. The low Hct in women remained important as an independent risk factor of cerebral infarction.

The sex difference in the role of Hct as a cause of cerebral infarction was discussed, taking into consideration the interrelationship between Hct and other risk factors.

IN 1972, THE FRAMINGHAM STUDY1 showed that a higher level of hemoglobin might be a risk factor for cerebral infarction, and since then, several clinical and clinicopathological observations indicated that high hematocrit (Hct) may be associated with the occurrence of cerebral ischemia.2-3 On the other hand, in patients with iron deficiency anemia secondary to chronic blood loss, cerebral ischemia and hemiparesis are often observed.4-5 Concerning the relationship between either hemoglobin or Hct and subsequent cerebral infarction, however, there are few data on a population-based study.

The incidence of cerebral accidents in Japan is higher than in the U.S.A., thereby leading to discussion as to whether risk factors of stroke differ between the two populations.6

In the early 1960s, iron deficiency anemia was one of the major problems in public health for Japanese, particularly for women in rural areas. This phenomenon was assumed to be related to an indigent nutritional state, heavy physical labor, or hookworm infections.7

On the basis of the data from the prospective community study conducted in Hisayama town, a rural area in Kyushu Island, Japan, we found a dual effect of Hct on the incidence of cerebral infarction.

Material and Methods

The prospective epidemiological study on cerebrovascular diseases was initiated in 1961 in the community of Hisayama town.8 The study included 1621 residents of both sexes aged 40 and over. These same subjects have been followed from November 1961 to the present time. The age-, sex- and occupational distributions of this group were similar to those of the entire Japanese population, according to national census in 1960, implying a representative sample of the Japanese race.

Out of the original cohort, 1220 persons of both sexes with no history of cerebral stroke were entered into this study, because Hct was initially measured at the survey in 1965. Consequently, the subjects aged 44 and over were included in the new cohort. They were followed from November 1, 1965 to October 31, 1981, mainly by repeated cross-sectional examination every 2 years. Moreover, a daily monitoring to detect any newly developed cerebral accident was established by the study team and by local physicians or by members of the central town health office. At the cross-sectional examination in 1965, the following information in addition to Hct, was obtained as possible predictors of cerebrovascular diseases; age, blood pressure, serum total cholesterol, serum total protein, Quetelet index (weight in kilograms/height² in meters), ECG abnormalities (Minnesota code of III-1, IV-1,2,3), daily alcohol intake and cigarette smoking. Glucose intoller-
ance was assessed by the oral glucose tolerance test. Details of the methods of the examinations and the criteria for diagnosis of cerebral stroke have been described elsewhere.8-10 All of the 1220 subjects were followed for 16 years. During the observation period, 408 subjects of the cohort died of various diseases and 363 (89.0%) were autopsied. The first episode of cerebral infarction occurred in 117, 85 died, and 81 were autopsied (95.3%).

A small number with cerebral embolism was included in the category of cerebral infarction.

Hct was determined by Wintrobe’s method.11 Taking into account the sex difference in Hct, the subjects were grouped into 3, based on mean value ± 1 SD respectively; low (<35%), normal (35-45%) and high Hct (≥45%) groups for men, and low (<30%), normal (30-40%) and high Hct (≥40%) groups for women (fig. 1).

Statistical analyses were made as follows: a relationship between age and Hct level in each sex by using analysis of variance with Bonferroni’s multiple comparisons, and the relation between sex and Hct in each age group by Student’s t-test. Average values for variables, as well as prevalence of other risk factors, were compared among Hct groups in each sex. Adjustments for age were made in each group. To estimate the statistical significance, analysis of covariance was used for the comparison of average values, and Mantel-Haenszel’s χ² analysis for prevalence.12 Age- and blood pressure-adjusted cumulative incidence of cerebral infarction was calculated by means of Hankey-Myers’ method13 over 16 years of follow-up by Hct groups in each sex. To eliminate the influence on Hct of confronted factors, multivariate analysis was performed by using Cox’s proportional hazards regression model.14 Continuous variables were directly entered into the equation. Categorical variables were transformed into the ordinal number by the coding system as follows: ECG abnormalities; 0-absence, 1-presence, glucose intolerance; 0-absence, 1-borderline, 2-over, smoking; 0-nonsmoker, 1-fewer than 10 cigarettes per day, 2-10 and over but fewer than 20 per day, 3-20 and over per day. Alcohol intake was converted to the daily equivalent and scored in terms of the equivalent number of GO, a traditional Japanese unit of volume for SAKE (1 GO contains 28 ml of alcohol: - as 0-nondrinker, 1-less than 1.5 GO per day, 2-1.5 GO and over per day. When the Hct group was selected as an independent variable in the Cox’s model, coding number for high Hct or for low Hct was altered by the purpose of analysis. In the case of analysis for high Hct, 1 was given to the high Hct group, 0 was given to the low and the normal Hct groups. Meanwhile, analyzing the effect of low Hct, 1 was allotted to the low Hct group, 0 to other two groups.

Results
Average values for Hct were 39.8 ± 5.0 (SD)% for men and 35.8 ± 4.2% for women, the difference being significant (p < 0.0001). As demonstrated in figure 1, the frequency of distribution of Hct was normal in pattern. Mean values of Hct by age and sex are presented in table 1. Hct was decreased with increasing age by Bonferroni’s method in men, while it remained unchanged in women. In each age group, except for the 9th decade, the Hct value was significantly lower in women than that in men.

Table 2 shows the age-adjusted average values for variables and the prevalence of possible risk factors of cerebral infarction in the Hct groups, in each sex. Systolic (SBP) and diastolic blood pressures (DBP), serum total cholesterol, total protein and Quetelet index were significantly increased with a rise of Hct levels in both sexes, except for SBP and DBP for men. Prevalence of hypertension by WHO criteria (SBP ≥ 160 mm Hg and/or DBP ≥ 95 mm Hg) for both sexes, and of glucose intolerance for women, and of heavy alcohol drinking (≥1.5 GO) for men were also significantly increased in the high Hct groups compared with those with a normal Hct. Prevalence of heavy smoking (≥20 cigarettes per day) for men tended to increase.
HEMATOCRIT AND CEREBRAL INFARCTION/Kiyohara et al. 689

Table 2. Age-Adjusted Average Values (A) or Prevalence (B) of Risk Factors for Cerebral Infarction by Sex and Hematocrit (Hct) Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Males (n = 78)</th>
<th>Females (n = 530)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (n = 361)</td>
<td>Normal (n = 75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (Means ± SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>144 ± 3</td>
<td>145 ± 1</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>82 ± 2</td>
<td>84 ± 1</td>
</tr>
<tr>
<td>Total cholesterol (mg/100 g)</td>
<td>153 ± 4</td>
<td>156 ± 2</td>
</tr>
<tr>
<td>Total protein (g/100 g)</td>
<td>7.2 ± 0.0</td>
<td>7.2 ± 0.0</td>
</tr>
<tr>
<td>Quetelet index</td>
<td>21.3 ± 0.2</td>
<td>21.9 ± 0.1</td>
</tr>
<tr>
<td>B (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension†</td>
<td>34.5</td>
<td>34.1</td>
</tr>
<tr>
<td>ECG abnormalities§</td>
<td>38.1</td>
<td>25.2</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>15.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>22.3</td>
<td>24.9</td>
</tr>
<tr>
<td>Heavy smoker†‡</td>
<td>23.6</td>
<td>24.9</td>
</tr>
</tbody>
</table>

†By WHO criteria (SBP ≥ 160 mm Hg and/or DBP ≥ 95 mm Hg). §Minnesota code III-1 and/or IV-1,2,3. † ≥ 1.5 Gd/day. ‡ ≥ 20 cigarettes/day.

Statistical significance: *p < 0.05, **p < 0.01, comparison among three Hct groups by analysis of covariance; †p < 0.05, ‡p < 0.01 vs normal Hct group by Mantel-Haenszel χ².

with Hct. The number of women who drank alcohol or smoked cigarettes was too small to reach statistical significance.

In Table 3, average annual incidence of cerebral infarction for 16 years of follow-up was calculated by Hct levels. Cerebral infarction most frequently occurred in the high Hct group, and sequentially in order of the normal and the low Hct groups in men. But there was no statistical difference in the incidence of cerebral infarction among the three determined by Mantel-Haenszel's χ² test. Cerebral infarction occurred more frequently in both high and low Hct groups of women, than in the normal Hct group. A statistical significance was obtained between the high and the normal Hct groups.

Figure 2 shows the age- and blood pressure-adjusted cumulative incidence of cerebral infarction for men. The incidence tended to be lower in the low Hct group, throughout the follow-up period, while the incidence in the high Hct group was slightly high compared with that in the normal Hct group after the 6th year of follow-up. In contrast, the incidence in women was considerably different, as shown in Figure 3. In the low Hct group (<30%), the incidence consistently increased with time during the 5 years of follow-up, and the development of infarction was clustered in this period. Meanwhile, the incidence in the high Hct group was gradually increased and the difference became significant compared with that in the normal Hct group after the 6th year of follow-up.

Since Hct interacts with other factors, a multivariate analysis should be done to investigate the net effect of Hct on cerebral infarction. In men, neither low nor high Hct was an independent risk factor of cerebral infarction throughout the follow-up period, after age, SBP, ECG abnormalities, glucose intolerance, serum cholesterol, serum protein, Quetelet index, daily alcohol intake and smoking habits were taken into account (Table 4). Age, SBP and ECG abnormalities were significant and independent precursors of cerebral infarction in men during 16 years of follow-up (Table 5). In contrast, as shown in Table 4, low Hct in women still remained a significant risk factor of cerebral infarction for 5, 10 and 16 years of follow-up, after the adjustment of various factors, although the magnitude of significance tended to decrease in the later period of follow-up. For 16 years of follow-up, important risk factors of cerebral infarction for women were age, SBP, low Hct and glucose intolerance (Table 5). High Hct never contributed to the evolution of cerebral infarction in women, determined by multivariate analysis.

Discussion

The most interesting evidence we obtained was the sex difference in the relationship between Hct levels and the subsequent incidence of cerebral infarction. In
women, low Hct was definitely and high Hct was probably related to the occurrence of cerebral infarction, whereas there was no consistent relationship between Hct level and the incidence of cerebral infarction in men. The Framingham study\(^1\) and several clinicopathological observations\(^2\,3\) showed that high levels of hemoglobin or Hct might be associated with the occurrence of cerebral ischemia. We found no documentation of an epidemiological study revealing that low Hct could contribute to the development of cerebral infarction. Elwood et al\(^2\) reported that mortality over a three-year period was related to Hct in 18,740 women. There was evidence of a slight increase in mortality in anemic subjects, most deaths being related to malignant neoplasms, but there was a clear deficiency in the number of deaths due to cardiovascular disease. There is also evidence that cardiovascular disease contributed disproportionately to the increased mortality in cases of higher Hct. It should therefore be elucidated whether low Hct levels in women of our series reflected some underlying disease related to cerebral infarction. Disseminated intravascular coagulation (DIC) frequently occurs in the terminal stage of malignant neoplasms. This state can induce cerebral thrombosis.\(^1\) Cerebral infarction occurred in six women in our low Hct group, and five died from various diseases. At autopsy, the underlying cause of death was cerebral infarction in two, and gastrointestinal bleeding, pneumonia, or congestive heart failure occurred in the others. The only survivor is leading a usual daily life, even with the residual signs of stroke. Thus, there was no definite evidence of the coexistence of malignant neoplasms. We already mentioned the frequency of other risk factors or confounding elements in the three groups classified by Hct level. In case of the six women with cerebral infarction in the low Hct group, there were few abnormalities other than old age and hypertension (atrial fibrillation in one and hypercholesterolemia in one).

In an anemic state, a decrease in the oxygen-carrying capacity of hemoglobin is thought to be compensated for by the increase of cardiac output due to a decrease of blood viscosity and a subsequent increase of venous return to the heart.\(^17\) In addition, a decrease in the affinity of hemoglobin for oxygen is more advanced by an increase of 2,3-diphosphoglycerate in red cells, in the case of anemia.\(^20\) Here, there is a greater likelihood of a dissociation of oxygen from hemoglobin, and the oxygenation of tissue is compensated. However, experimental studies showed that when Hct was as low as 30% or below or hemoglobin was 9 g/100 ml or below, a compensatory mechanism would be no longer suffice to prevent cerebral hypoxia.\(^19\) A few clinical observations revealed that in

### Table 4

<table>
<thead>
<tr>
<th>Follow-up Period</th>
<th>Coeff (β)</th>
<th>p value</th>
<th>Coeff (β)</th>
<th>p value</th>
<th>Coeff (β)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low hematocrit</td>
<td>-0.326</td>
<td>0.160</td>
<td>-0.189</td>
<td>0.201</td>
<td>-0.155</td>
<td>0.233</td>
</tr>
<tr>
<td>high hematocrit</td>
<td>-0.048</td>
<td>0.816</td>
<td>0.020</td>
<td>0.887</td>
<td>0.037</td>
<td>0.767</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low hematocrit</td>
<td>0.639</td>
<td>0.000</td>
<td>0.528</td>
<td>0.000</td>
<td>0.322</td>
<td>0.011</td>
</tr>
<tr>
<td>high hematocrit</td>
<td>0.127</td>
<td>0.577</td>
<td>0.244</td>
<td>0.124</td>
<td>0.116</td>
<td>0.357</td>
</tr>
</tbody>
</table>

Adjusted for age, systolic blood pressure, ECG abnormalities (Minnesota code III-1 and/or IV-1,2,3), serum total cholesterol, serum total protein, Quetelet index, glucose intolerance, smoking and drinking.
the aged, iron deficiency anemia seems to be one of the causes of reversible hemiparesis.\textsuperscript{4,5} Knizley et al\textsuperscript{4} pointed out that transient hemiparesis in anemic patients was related to platelet emboli due to thrombocytosis accompanied by iron deficiency anemia.

Sex differences in the interrelationship between Hct and other risk factors of cerebral infarction should be taken into account. One reason why the incidence of cerebral infarction did not differ between high and normal Hct groups for men may be related to the fact that Hct is a minor risk factor of cerebral infarction, for males. Hypertension and ECG abnormalities were more frequent in men than in women, and few women smoked or drank alcohol. Meanwhile, major risk factors of cerebral infarction such as hypertension, glucose intolerance were more clearly related to Hct level in women than in men. Namely, the frequency of hypertension or glucose intolerance more sharply increased with increasing Hct levels in women. A causal relationship between high blood viscosity and high blood pressure was suggested.\textsuperscript{22,23} In the multivariate analysis, the more important risk factors were hypertension and glucose intolerance and high Hct no longer had a direct effect on the occurrence of cerebral infarction, in both sexes. Men who drank heavily were more likely to have a high Hct, yet heavy drinking has been pointed out that transient hemiparesis in anemic patients is one of the causes of reversible hemiparesis. Arch Intern Med 129: 483-486, 1972.


Measurement of Regional Cerebral Blood Flow, Blood Volume and Oxygen Metabolism in Patients with Sickle Cell Disease Using Positron Emission Tomography


SUMMARY Regional cerebral blood flow, blood volume, fractional oxygen extraction and oxygen consumption were measured by positron emission tomography in six patients with sickle cell disease to see how oxygen delivery to the brain is maintained in the presence of both anemia and a low oxygen affinity hemoglobin. Both regional cerebral blood flow and blood volume were found to be markedly increased compared to values obtained from 14 normal subjects in the same age range. The mean fractional oxygen extraction was not significantly different in the two groups. Mean oxygen consumption in the two groups was also not significantly different but low values in individual patients with sickle cell disease and the presence of atrophy on the CT-scans of three of them were suggestive of some neuronal loss in patients without any history of nervous system involvement. In view of the known high values of cerebral blood flow and metabolism in childhood, it is suggested that when compounded by anemia and abnormal red cells, a hypercirculatory state may make patients in this age-group particularly prone to ischemic infarction.

STROKE is a relatively common complication of sickle cell disease and contributes substantially to its morbidity and mortality. A recent natural history study, the first in which the nature of the cerebrovascular lesion was established in most patients by CT-scanning, reported a stroke incidence of 6% for all ages. Two thirds of these patients had suffered ischemic cerebral infarction. Infarcts occurred mainly during childhood and adolescence (mean age 7.7 years) and were often repetitive, as had been observed in previous studies. Exchange transfusion regimes have been used with some success to prevent the recurrence of strokes and to improve existing neurological deficits in the survivors even reversing angiographic abnormalities in some cases.

Although some early reports described pathological changes in the walls of the larger intracranial arteries, later authors generally attributed the ischemic infarction in sickle cell disease to small vessel involvement leading to multiple microinfarcts. However, when it had been shown that angiography could safely be performed after prior exchange transfusion, more and more reports again described occlusions and stenosis of major intracranial vessels in the majority of patients with ischemic infarcts studied. Intimal hyperplasia, often combined with medial fibrosis and hyalinization, was found to be causing the obstructions. Explanations of the origin of these changes and of the occurrence of infarction predominantly in the first two decades of life have, however, remained speculative.

Positron emission tomography (PET) now offers the means to measure regional cerebral blood flow (CBF), oxygen extraction ratio (OER), oxygen utilization (CMRO2) and cerebral blood volume (CBV) non-invasively in absolute values. Recently, important information about the pathophysiology of cerebral ischemia has been obtained with this method. In acute stroke it has been shown that when cerebral blood flow falls in relation to the tissue's oxygen requirements, the fraction of oxygen extracted from the blood can rise from
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