Importance of the Hematocrit as a Risk Factor in Cerebral Infarction

HIDEO TOHGI, M.D., HIROSHI YAMANOUCHI, M.D.,
MOTOTAKA MURAKAMI, M.D., AND MASAKUNI KAMEYAMA, M.D.

SUMMARY. The relationship between the incidence of cerebral infarction and the hematocrit was studied using 432 consecutive autopsied patients with the average age of 77.1 years. The incidence of cerebral infarction was higher in patients with hematocrit values of more than 46%, (the average in younger adult subjects). The increase in the frequency of cerebral infarction with high hematocrit values was more conspicuous in patients with severe cerebral atherosclerosis than in those with slight cerebral atherosclerosis. High blood pressure per se did not influence the relationship between the hematocrit value and the incidence of cerebral infarction. With hematocrit values of more than 41%, cerebral infarction occurred more frequently in patients over 78 years of age than in the younger patients, but the difference was not significant statistically. High hematocrit values are associated with a higher risk of cerebral infarction in deep subcortical structures of the brain than for cortical infarctions. The pathogenetic and preventive implications of these results are discussed in the light of blood rheology.

STUDY of the pathogenesis of cerebral infarction should deal not only with atherosclerotic vascular changes, but also the nature of the blood flowing through the vascular system. Of particular importance, from the rheological viewpoint, is blood viscosity which depends largely on hematocrit value.

The increased risk of cerebral infarction has been well recognized in patients with an abnormally high hematocrit value, as in polycythemia vera. The relationship, however, between the risk of cerebral infarction and the hematocrit value within its normal range drew little attention until the Framingham study by Kannel and co-workers in 1972.

The purpose of this study is to show the relationship between the incidence of cerebral infarction and the hematocrit value, and to investigate how this relationship varies according to the degree of cerebral atherosclerosis, blood pressure, patient age, and infarction site.

Materials and Methods

We studied 432 consecutive patients who came to autopsy from August 1972 to November 1974. There were 218 males and 214 females, ranging from 60 to 92 years of age, with an average of 77.1 years. During this period 81.5% of total deaths were autopsied. Of 432 autopsied cases, 76 had cerebral infarction and 31 cerebral hemorrhage. One had a large infarction in the occipital lobe and a fresh cerebellar hemorrhage, which was believed to be the cause of death and thus included in the group with hemorrhage. The patients with stroke were admitted to the hospital within 36 hours of onset. In all patients blood pressure and the hematocrit value were measured at the time of admission.

The hospital (Tokyo Metropolitan Geriatric) receives almost exclusively elderly patients who live in the home for the aged or in the city of Tokyo. The incidence of stroke in this series (25%) is slightly lower than that in other reports from Japan. For example, 31.1% of deaths over 60 years in Japan in 1974 were due to cerebrovascular disease (Ministry of Health and Welfare), and 34.1% of deaths over 40 years were due to cerebrovascular disease (5-year follow up study by Okinaka et al., 1962-1967). Acutely ill patients with stroke are usually admitted to local hospitals in their neighborhood. The difference in source of patients may have biased the results of this study to some extent.

The degree of atherosclerotic changes in cerebral arteries was defined at autopsy according to the modified method of the World Federation of Neurology Code for grading atherosclerosis: (−) for less than 25% stenosis, (+) for 25-50% stenosis, and (+++) for more than 50% stenosis.

The distribution of the age of patients, systolic blood pressure, and hematocrit value is shown in figure 1a, b, c. The average and standard deviation of the systolic blood pressure were 146.1 ± 32.6 mm Hg, and of hematocrit were 37.0 ± 6.4%.

Results

1) Incidence of Cerebral Infarction in Relation to Degree of Cerebral Atherosclerosis, Blood Pressure, Hematocrit

Among the 432 consecutive autopsy cases, 69 had grade (−) atherosclerosis of cerebral arteries, 128 grade (+), and 235 grade (++). The incidence of cerebral infarction was 8.7% with grade (−), 10.9% with grade (+), and 23.0% with grade (+++). The incidence of cerebral infarction in cases with grade (+++) was 2.6 times that for grade (−). The incidence of cerebral hemorrhage in cases with grade (+++) (28%) was 3.1 times that of cases with grade (−) (9%).

The incidence of cerebral infarction increased in relation to the systolic blood pressure up to 180 mm Hg, but showed only a slight increase in the range over 180 mm Hg (fig. 2b). The incidence of cerebral infarction in patients with a systolic pressure of 160-180 mm Hg (28.6%) was 5.1 times that of patients with a systolic pressure of less than 100 mm Hg (5.6%).

The incidence of cerebral infarction was 6.6% in
patients with hematocrit values less than 30%. It increased to 18.3% in patients with hematocrit values of 36–40% and increased remarkably to 43.6% in patients with hematocrit values of 46–50%. The incidence of cerebral infarction in patients with hematocrit values of more than 51% was 63.6%, 9.6 times that found in patients with hematocrit values of less than 30% (fig. 2c). Cerebral infarction occurred in 13 (18.8%) of 69 patients with hematocrit values of 41 to 45%, and in 17 (50.0%) of 34 patients with hematocrit values of more than 46%. The difference was significant ($\chi^2 = 10.7, p < 0.005$).

A high hematocrit value is an important risk factor of cerebral infarction along with atherosclerosis of cerebral arteries and hypertension.

The incidence of cerebral hemorrhage in patients with hematocrit values of more than 40% was slightly higher than in patients with hematocrit values less...
than 40%, but the rate of increase was far less in comparison with cerebral infarction.

2) Factors Influencing Cerebral Infarction

a) Degree of Atherosclerosis of Cerebral Arteries

The relationship between the hematocrit and cerebral infarction was compared among 3 groups of patients; those with grade (-), (+), and (++) atherosclerosis of cerebral arteries (fig. 3). Cerebral infarction was more common with hematocrit values of more than 46% in patients with grade (+) and grade (+++) atherosclerosis and the increase was most conspicuous with grade (++). In patients with grade (++) atherosclerosis cerebral infarction was found in 35 out of 215 who had hematocrit values of less than 45%, and in 13 out of 20 who had hematocrit values of more than 46%. With grade (+) atherosclerosis, cerebral infarction was found in 12 of 118 patients whose hematocrit values were less than 45%, and in 4 out of 10 with hematocrit values more than 46%. Both of these differences were highly significant ($p < 0.005$). With grade (-) atherosclerosis, cerebral infarction was relatively frequent with hematocrit values of 31-40%, but there was no case of cerebral infarction with a hematocrit value of more than 41%.

b) Systolic Blood Pressure

The patients were divided into 2 groups: normotensives and hypertensives. Normotensives had systolic pressure less than 160 mm Hg and hypertensives more than 160 mm Hg. Cerebral infarction was more common in hypertensives than in normotensives with all levels of hematocrit. The increase of cerebral infarction was much more common with hematocrit values of more than 46% in hypertensives than in normotensives (fig. 4a). This difference was not significant. For patients with hematocrit values of more than 46%, 9 out of 15 hypertensives (60.0%) and 8 out of 19 normotensives (42.1%) had cerebral infarction ($X^2 = 1.07$).

The higher frequency of cerebral infarction in hypertensives may merely reflect the more severe atherosclerosis usually associated with hypertension and may not be related to the hematocrit. To evaluate this point, the study was then limited to patients with grade (++) cerebral atherosclerosis. When this was done the difference between hypertensives and normotensives became far less conspicuous (fig. 4b). The increased frequency of cerebral infarction in hypertensives is believed not to be due to high hematocrit but, for the most part, to atherosclerosis consequent upon hypertension. Figures 3 and 4b indicate that severe atherosclerosis and a high hematocrit show the additive effect on cerebral infarction, but that high blood pressure shows little influence upon the effect of the above 2 factors.

c) Patient Age

The relationship between cerebral infarction and the hematocrit value was compared between 2 age groups; patients over 78 years of age and below 77 (fig. 5a). The frequency of cerebral infarction did not differ between the 2 age groups for hematocrit values less than 40%, but for hematocrit values more than 41%, cerebral infarction occurred more frequently in patients over 78 years. However, this difference was not significant. The frequency of cerebral infarction with hematocrit values of more than 41% was 35.4% in the older age group and 22.4% in the younger age group ($X^2 = 2.19$).

The greater chance of cerebral infarction in the older age group may be the result of augmentation of atherosclerosis with advancing age. When the study was limited to cases with grade (++) cerebral atherosclerosis, the difference in the frequency of cerebral infarction between the 2 age groups became more conspicuous (fig. 5b). For those with hematocrit values of more than 41%, 14 out of 33 cases in the older age group (42.4%) and 9 out of 33 (27.3%) in the younger age group had cerebral infarction. This difference was not significant ($X^2 = 1.67$).

d) Infarction Site

The relationship between the cerebral infarction and the hematocrit value was compared between those with cortical infarctions and those with deep infarctions involving structures of the brain such as basal
ganglia, the internal capsule, and the pons. The increase in the frequency of cerebral infarction with hematocrit values more than 46% was more common with deep infarction than with cortical infarction (fig. 6). Among 210 cases with hematocrit values 36-45%, 24 cases (11.4%) had cortical infarction and 11 (5.2%) deep infarction. Among 34 cases with hematocrit values of more than 46%, 8 (23.5%) had cortical infarction, and 9 (26.5%) deep infarction.

3) Relationship between Systolic Pressure, Cerebral Atherosclerosis, and Hematocrit

a) Systolic Pressure and Cerebral Atherosclerosis

The distribution of systolic pressure was compared among groups with (−), (+), and (+++) grades of atherosclerosis (fig. 7a). Systolic pressure levels were higher with increasing grades of atherosclerosis. The average and standard deviation of systolic pressure

Figure 4. Relationship between cerebral infarction, hematocrit value, and hypertension.

Figure 5. Relationship between cerebral infarction, hematocrit value and the patient's age.
HEMATOCRIT AS RISK FACTOR IN Cl/Tohgi et al.

was 128.7 ± 28.4 mm Hg with grade (−) atherosclerosis, 137.5 ± 26.8 mm Hg with grade (+) and 154.9 ± 33.4 mm Hg with grade (++). The difference between grade (−) and (+), and grade (+) and (++) were both significant (p < 0.02 and 0.01, respectively).

b) Hematocrit and Cerebral Atherosclerosis

The distribution of the hematocrit value was compared among groups with (−), (+), and (++) grades of cerebral atherosclerosis (fig. 7b). The distribution curves for hematocrit values shifted to higher values with increasing grades of atherosclerosis. The average and standard deviation of hematocrit value was 33.9 ± 7.5% in grade (−), 36.4 ± 6.5% in grade (+), and 37.8 ± 6.5% in grade (++). The difference between grade (−) and grade (+) was significant (p < 0.05), but the difference between grade (+) and grade (++) was not significant.

c) Hematocrit and Systolic Pressure

The correlation coefficient between systolic pressure and the hematocrit value was 0.06. There was no significant correlation between the 2 variables.

Discussion

The present study shows the increased risk of cerebral infarction in patients with a high hematocrit. The risk of cerebral infarction does not change remarkably with the increase of hematocrit values, up to 45%, although the risk was slightly lower in patients with hematocrit values of 36–45% than in those with hematocrit values of 31–35%. The risk of cerebral infarction increased steeply when hematocrit values exceeded 45%.

Blood viscosity does not rise in direct proportion to the hematocrit increase, but it increases sharply as the hematocrit value rises, especially when it exceeds 46%. The hemoglobin content of the blood rises as the hematocrit increases, provided that hemoglobin concentration per unit of packed cell volume is constant. Therefore, the capacity for oxygen transportation per unit volume of blood increases with the increase of hematocrit value. On the other hand, the rise of hematocrit increases blood viscosity and thus reduces blood flow. Theoretical considerations of these 2 factors, i.e., the increase of the hemoglobin content and the decrease of blood flow associated with an increase of the hematocrit value, give an optimum hematocrit value of 45–47%, which coincides with the
average for normal persons. The present results indicate that the risk of cerebral infarction increases remarkably when hematocrit values exceed the optimum value.

The increase in the frequency of cerebral infarction associated with high hematocrit values is influenced by the caliber of the cerebral arteries. Narrow cerebral arteries due to severe atherosclerosis increase the risk of cerebral infarction with high hematocrit values. With high hematocrit values, infarction is more likely in the deep structures of the brain which are supplied by penetrating arteries which have relatively small calibers. High hematocrit values as a risk factor for cerebral infarction are more important when arteries are of small caliber or severely stenosed by atherosclerotic changes.

For the prophylaxis of cerebral infarction, it is of clinical importance to determine the optimum hematocrit value for the aged. Although the prevalence of cerebral infarction was lowest with hematocrit values of less than 30%, this is obviously too low to be the optimum hematocrit value. For hematocrit values of more than 31%, the prevalence of cerebral infarction is slightly lower for hematocrit of 36-45% than for hematocrit of 31-35%. Prevalence of cerebral infarction increases steeply with hematocrit values of more than 46%. Practically, it appears that for the prophylaxis of cerebral infarction the optimum hematocrit value in the aged (up to age 78) is 41-45%; for those over 78 years 36-40% (fig. 5a). The average hematocrit value of elderly patients in this study (37.0%) lies within this range.

In conclusion, a hematocrit value of more than 46% is a risk factor for cerebral infarction in the aged. The risk of cerebral infarction with high hematocrit values is augmented further by severe atherosclerosis and advancing age. High hematocrit values cause more risk for infarctions in deep structures of the brain than in cortical areas. These findings are important for taking preventive measures against cerebral infarction.

References
Importance of the hematocrit as a risk factor in cerebral infarction.
H Tohgi, H Yamanouchi, M Murakami and M Kameyama

Stroke. 1978;9:369-374
doi: 10.1161/01.STR.9.4.369

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://stroke.ahajournals.org/content/9/4/369

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/