Relationship between Hematological Parameters and Incidence of Ischemic Heart Diseases among Japanese White-Collar Male Workers

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Abstract: Relationship between Hematological Parameters and Incidence of Ischemic Heart Diseases among Japanese White-Collar Male Workers: Toshio KOBAYASHI, et al. —The determination whether high hematocrit (Hct) and hemoglobin (Hb) are risk factors for ischemic heart diseases (IHD) remains controversial in Japan. To examine whether hematological parameters are independent risk factors for IHD, we conducted a case control study among 3,924 Japanese male white-collar workers aged 35–60 yr. IHD cases were defined as men with a first episode of acute myocardial infarction or angina pectoris during the investigation period (from April 1995 to April 2000). Five controls without a history of IHD were assigned for each case, matching for age and smoking status. Twenty-two IHD cases were developed during the study period and 110 controls were assigned. Hematological parameters, obtained from periodic health examinations undergone before the onset of the disease, were analyzed with the conditional logistic regression model. Multivariate adjusted odds ratios (OR) with 95% confidence interval (95%CI) were estimated, controlling for Body Mass Index, total cholesterol, alcohol use, hypertension and fasting blood sugar. Crude OR (95%CI) for Hct, Hb, red blood cell count (RBC) and Mean corpuscular volume (MCV) were 1.21 (1.03–1.42), 2.04 (1.17–3.56), 1.09 (0.96–1.24) and 1.09 (0.98–1.22), respectively. The multivariate adjusted OR (95%CI) for Hct, Hb, RBC and MCV were 1.28 (1.06–1.54), 2.75 (1.39–5.46), 1.08 (0.92–1.28) and 1.09 (0.97–1.24), respectively. These results suggest that Hct and Hb are independent risk factors for ischemic heart diseases among Japanese middle-aged male white-collar workers. (J Occup Health 2001; 43: 85–89)

Key words: Hematocrit, Hemoglobin, Ischemic heart disease, Cardiovascular risk factor, Japanese male worker

The periodic health examination of workers in Japan traditionally includes hematological parameters as an essential component. First instituted because of the poor nutritional status of Japanese workers, hematological parameters were also expected to detect diseases caused by hazardous substances such as lead¹. But the general nutritional status of Japanese workers has improved significantly, and the National Nutritional Survey² revealed a higher intake of fat and protein, suggesting that malnutrition is no longer a prevalent problem for current Japanese workers. Additionally, specific examinations for hazardous substances such as lead have been developed³ and introduced into routine examinations for workers handling toxic substances, so that there is little rationale for continuing to include hematological parameters in the periodic health examinations of Japanese workers. The systematic reviews of Canadian and US clinical preventive services⁴, ⁵ also concluded that there is insufficient evidence to recommend for or against routine testing for anemia in asymptomatic persons, with the exception of pregnant women and infants. Simply following the reports from North America, it seems also reasonable to exclude routine screening for anemia in Japan. However, in general, once a system is abolished it is not easy to reintroduce, even if it is found to have some other benefit. Although hematological parameters may not be useful for the detection and treatment of anemia among workers, they can still be useful in predicting increased
cardiovascular risk.

In fact, increased hematocrit (Hct) and hemoglobin (Hb) are considered to be possible risk factors for ischemic heart diseases (IHD)\textsuperscript{6–12}, but several studies have not supported this\textsuperscript{13–17}. The conflicting results may be explained by differences in ethnicity\textsuperscript{13–16, 18} and sex\textsuperscript{19}. Therefore, it is worthwhile to further examine the validity of the hematological parameters as independent risk factors for IHD in Japan, where the relationships between IHD and hematological parameters have rarely been examined. If an association between high Hct or Hb and the risk of IHD exists, it may be explained either as the result of an increase in other well-known risk factors such as high cholesterol, hypertension and obesity, or as an independent effect of hematological parameters per se.

The aim of the present study was to examine, by a matched case-control study among male white-collar workers, the relationship between hematological parameters and the incidence of acute myocardial infarction or angina pectoris with adjustment for other cardiovascular risk factors.

\textbf{Methods}

\textbf{Subjects and study design}

The study subjects were 3,924 male white-collar workers aged 35–60 yr working in a life insurance company in Tokyo. The cases were subjects with a first episode of acute myocardial infarction (AMI) or angina pectoris (AP) during the study period (from April 1995 to April 2000). They were assigned according to the medical certificates which were submitted to the health insurance society of this company. Diagnoses of AMI and AP were made when electrocardiographic changes and/or coronary angiographic findings were matched with typical clinical symptoms (chest discomfort and/or pain). Five male controls without a past history of IHD or abnormal ECG finding were randomly selected for each case from a pool of workers who participated in periodic health examinations in the study period. Controls were matched for age and smoking status (non smoker, 1–9 cigarettes per day, 10–19 cigarettes per day, $\geq$ 20 cigarettes per day), because smoking is strongly correlated with polycythemia through increased blood carboxyhemoglobin levels\textsuperscript{19, 20}. The diagnoses were confirmed and agreed upon by two physicians. Subjects with recurrence of IHD, obstructive or restrictive pulmonary diseases and those with other anemic diseases were excluded from the case and control group.

\textbf{Hematological parameters}

Subjects underwent a periodic health examination at least once during the study period. The data related to hematological parameters of Hct, Hb, number of red blood cells (RBC) and mean corpuscular volume (MCV) were obtained from the last periodic health examination before the onset of IHD. Blood was collected from the antecubital vein. Hematological parameters were measured in an automatic hematological analyzer (NE-8000, Toa Medical Co.), which measures Hct, Hb and RBC by the erythrocyte pulse height detection method, oxyhemoglobin method and sheath flow DC detection method, respectively. MCV was computed from the Hct and RBC values. The maximum coefficients of variation of each parameter were 1.5%, 1.0%, 1.5% and 1.5% for Hct, Hb, RBC and MCV, respectively.

\textbf{Other cardiovascular risk factors}

Among cardiovascular risk factors, Body Mass Index (BMI), smoking status, alcohol use, systolic and diastolic blood pressure (SBP and DBP), antihypertensive medication, total cholesterol (T-chol) and fasting blood sugar (FBS) were recorded. BMI and T-chol were treated as continuous variables. Alcohol use was classified into three categorical groups (never drink, 0 to 25 g per day, $\geq$ 25 g per day) and blood pressure was classified as normal blood pressure (SBP $\leq$ 140 mmHg and DBP $\leq$ 90 mmHg and no antihypertensive drug use) vs. hypertension (SBP $>$ 140 mmHg or DBP $>$ 90 mmHg or antihypertensive drug use). Since the distribution of FBS was skewed, FBS was classified into four categorical variables (< 90, 90 to 96.5, 96.5 to 109, and $\geq$ 110 mg/dl) according to the quartile.

\textbf{Statistical analysis}

Crude and multivariate adjusted odds ratio (OR) and 95\% confidence intervals (95\%CI) based on maximum likelihood estimates were calculated with a conditional logistic regression model (SAS PHREG Procedure). BMI, T-chol, alcohol use, hypertension and FBS were included in the multivariate adjusted model. The stepwise variable selection method (inclusion and exclusion criteria: 10\%) was used. All P values are two-tailed.

\textbf{Results}

Twenty-two IHD cases (14 for AMI and 8 for AP) were diagnosed during the investigation period and 110 controls were assigned. Mean ages of the cases and the controls were both 50.8 yr, with a range of 39–59 yr. The proportion of current smoking both in the cases and the controls was 86.4\%. The mean values for the hematological parameters and other cardiovascular risk factors in the cases and the controls are shown in Table 1. The hematological values for the cases were higher than those for the controls. The other established risk factors for IHD were higher in the cases than in the controls. Table 1 shows the crude odds ratio (OR) and 95\%CI for the hematological parameters and cardiovascular risk factors. The relationship between IHD and hematological parameters was significant as evidenced by OR for Hct (1.21, 95\%CI 1.03–1.42) and
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Hb (2.04, 95%CI 1.17–3.56), but not significant for RBC (1.09, 95%CI 0.96–1.24) or MCV (1.09, 95%CI 0.98–1.22). Among other cardiovascular risk factors, SBP (OR 1.46, 95%CI 1.12–1.92), DBP (OR 1.83, 95%CI 1.14–2.94), T-chol (OR 1.18, 95%CI 1.01–1.38), BMI (OR 1.20, 95%CI 1.02–1.41), hypertension (OR 2.99, 95%CI 1.13–7.90) and FBS ʾ110 mg/dl (OR 2.93, 95%CI 1.05–8.16) showed significantly positive relationships with IHD. Multivariate-adjusted OR for hematological parameters after adjusting for BMI, T-chol, hypertension, alcohol use and FBS are shown in Table 2. Even after adjustment, Hct (1.28, 95%CI 1.06–1.54) and Hb (2.75, 95%CI 1.39–5.46) were still significantly related to IHD.

### Table 1. Mean values for the hematological parameters and cardiovascular risk factors in the IHD cases and controls with their unadjusted odds ratio (OR) and 95% confidence interval (95%CI).

<table>
<thead>
<tr>
<th>Case (n=22)</th>
<th>Control (n=110)</th>
<th>OR* 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>48.6 (3.7)</td>
<td>46.6 (3.5)</td>
<td>1.21</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>15.9 (1.0)</td>
<td>15.3 (1.1)</td>
</tr>
<tr>
<td>Red blood cell count (× 10⁴/mm³)</td>
<td>492.9 (42.1)</td>
<td>480.5 (42.7)</td>
</tr>
<tr>
<td>Mean corpuscular volume (µm³)</td>
<td>98.8 (4.2)</td>
<td>97.3 (4.7)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137.9 (24.2)</td>
<td>124.6 (15.3)</td>
</tr>
<tr>
<td>Mean corpuscular volume (µm³)</td>
<td>87.2 (12.8)</td>
<td>79.7 (10.3)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>219.5 (31.0)</td>
<td>203.3 (34.8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.3 (4.2)</td>
<td>23.8 (2.8)</td>
</tr>
<tr>
<td>Hypertension**</td>
<td>54.5% (n=12)</td>
<td>26.4% (n=29)</td>
</tr>
</tbody>
</table>

### Table 2. Multivariate-adjusted* OR in relation to ischemic heart diseases

| Hematocrit (%) | 1.28 | 1.06–1.54 |
| Hemoglobin (g/dl) | 2.75 | 1.39–5.46 |
| Red blood cell count (× 10⁴/mm³) | 1.08 | 0.92–1.28 |
| Mean corpuscular volume (µm³) | 1.09 | 0.97–1.24 |

*Adjusted for Body Mass Index (BMI), total cholesterol (T-chol), alcohol use, hypertension and fasting blood sugar (FBS) by the stepwise method (inclusion and exclusion criteria: 10%). **For hypertension (diagnosed when subjects met at least one of the following: SBP ʾ140 mmHg; DBP ʾ90 mmHg; antihypertensive drug use), percentage (%) of subjects with hypertension and its number (n) are shown. ***For alcohol use and fasting blood sugar, percentage (%) of subjects and its number (n) in each category are shown.

Discussion

In order to examine the relationship between hematological parameters and the onset of IHD, a matched case-control study was conducted on Japanese male white-collar workers. In the present study, positive relationships between hematological parameters such as Hct, Hb and the onset of IHD were observed. The results of the multivariate analysis suggest that these hematological parameters may act as independent risk factors for IHD in Japanese male white-collar workers aged 35–60 yr.

In this study measurements of hematological parameters were carried out as part of the last periodic health examination before the occurrence of IHD so that the results of the health examination were thus not biased by the presence of disease itself. Enhanced reliability in the diagnosis of IHD was maintained by the use of medical records judged by two physicians.

Although many studies have been conducted on the...
The study of males of Japanese ancestry in Honolulu14, 15) revealed that the mean Hct value among the cases was greater than that in the controls combined. In the Occupational Health examination in 1997 (n=3,405) was 46.8%. In the average Hct of all the male workers who received hematological examination remains on the list of mandatory health check-up items, the target population was middle and older aged males, the hematological examination should be performed in older workers. As far as we know, only one population-based study was conducted more than 15 yr ago18), and no independent contribution of Hct to IHD risk was found. On the other hand, in the occupational health care setting in the Netherlands19), a case-control study similar to the present study was conducted and likewise revealed that high Hct or Hb was independently associated with a high incidence of myocardial infarction in men aged 50–60 yr. As for the Japanese population, studies on the relationship between Hct or Hb and IHD are very limited. Few recent studies have suggested that high iron intake or high Hct value is associated with an increase in blood viscosity, which may lead to vascular occlusion6, 21, 22). It has also been reported that the Hct level and the severity of the coronary artery stenosis are positively associated in IHD patients25). Another report indicated that cerebral blood flow was inversely related to RBC or Hct25). In addition, recent studies have suggested that high iron intake or high stored body iron might be related to an increased risk of coronary heart disease24, 25). Apart from the high viscosity associated with high Hct, a high iron level per se may play a role in the pathogenesis of IHD through metabolic effects of iron such as free radical production26, 27).

There is much evidence to support the relationship between Hct or Hb and other well-known cardiovascular risk factors such as smoking, hypertension and high T-chol28–33). For example, Gaisböck34) found a positive relation between stress polycythemia and hypertension. Our recent report on Japanese male office workers also showed a positive relationship between Hct and blood pressure15). Hypoxia caused by increased carboxyhemoglobin in the circulating blood of smokers is believed to induce compensatory polycythemia19, 20). Even after matching for smoking and age in the present study, both crude and multivariate adjusted OR for Hct and Hb were significant. Although the effects of smoking might not be completely adjusted by matching, these results suggest that increased hematological parameters are independent risk factors for IHD.

In Japan, the hematological test is a mandatory part of the workplace periodic health examination. Although the prevalence of anemia has decreased, the above-normal range values in the hematological test can be utilized to identify subjects at high-risk for IHD. When hematological examination remains on the list of mandatory health check-up items, the target population is to be selected and specified. Because the prevalent anemia group among workers used to be young females whereas those with high risk for cardiovascular diseases are middle and older aged males, the hematological examination should be performed in older workers.

References
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