Are Hemostatic Factors Responsible for the Paradoxical Risk Factors for Coronary Heart Disease and Stroke?

Michael Gliksman, FAFPHM, and Andrew Wilson, FRACP

Background: The paradoxical occurrence of a high risk of stroke in some populations at low risk for coronary heart disease has long been known. Recently, evidence has appeared linking the paradoxical risk to population-based differences in diet, serum cholesterol, and alcohol intake. However, the pathophysiological mechanism of action that would explain this paradox is unlikely to be atherosclerosis alone.

Summary of Comment: Several recent cross-sectional and prospective population studies have shown that hemostatic factors vary between populations in a manner consistent with the paradox. Studies have also shown that certain hemostatic factors are independent predictors of risk of coronary heart disease, ischemic stroke, and, probably, hemorrhagic stroke.

Conclusions: Risk factors that enhance thrombosis and reduce fibrinolysis are capable of explaining the paradoxical occurrence of the incidence of coronary heart disease and stroke in certain populations. (Stroke 1992;23:607-610)

KEY WORDS • blood coagulation • cardiovascular diseases • risk factors

It is usually assumed that, because atherosclerosis at different sites is the underlying pathology for several different cardiovascular diseases (coronary heart disease [CHD], stroke, peripheral vascular disease), the risk factors for each disease will be the same. Recently it has become apparent that this is not the case.

The paradoxical differences in incidence density of CHD and stroke between different populations has long been known\(^1\) and has been confirmed in subsequent studies.\(^3\) Japanese men in Japan have high stroke and low CHD mortality rates, whereas those living in California show the reverse pattern. Those living in Hawaii show an intermediate pattern.\(^4\) Although the comparatively high rates of stroke mortality in Japan are due to both thromboembolic and hemorrhagic stroke,\(^5\) twice as high a proportion of strokes in Japan as in the United States are cerebral hemorrhages.\(^6\)

To identify differences in risk factors that could explain this paradox, the Honolulu Heart Study\(^4\) followed two cohorts of Japanese men for 20 years, one residents of Hawaii and the other Japan. The study results showed that three variables had opposing patterns of association for stroke and CHD. Serum cholesterol level was positively associated with the risk of CHD and negatively associated with the risk of hemorrhagic stroke; it was not significantly associated with thromboembolic stroke. Alcohol intake was negatively associated with the risk of CHD and positively associated with the risk of hemorrhagic stroke; it, too, was not significantly associated with thromboembolic stroke. A western diet, when characterized primarily by total fat and animal protein intake, was positively associated with CHD and negatively associated with thromboembolic stroke; it was not significantly associated with hemorrhagic stroke. Age-adjusted levels of serum total cholesterol, dietary fat, and animal protein intake were significantly higher in Japanese men living in Hawaii, whereas alcohol consumption was significantly higher in those living in Japan.

Systolic blood pressure and cigarette smoking were positively associated with the risk of CHD, thromboembolic stroke, and hemorrhagic stroke; these two variables are unlikely to explain the paradox despite the fact that the prevalence of smoking was significantly higher in Japan. Interest therefore centers on the role of diet, serum cholesterol, and alcohol intake in explaining the paradox, but what might their mechanism of action be?

Supporting the hypothesis proposed by Kuller and Reisler\(^7\) that risk factors for atherosclerosis differ in different arterial beds, autopsy findings in the Honolulu Heart Study\(^4\) showed that systolic blood pressure and cigarette smoking were positively correlated with atherosclerosis in the coronary, large, and small cerebral arteries, whereas total cholesterol was positively correlated with atherosclerosis only in the coronary and large cerebral arteries.

When viewed as a whole, these findings are consistent with the hypothesis that low serum cholesterol, high alcohol consumption, and a nonwestern diet (all of which characterized the Japanese men living in Japan when compared with those living in Hawaii) may explain...
the paradoxical occurrence of a high risk of stroke in a population at low risk for CHD. However, autopsy findings in that study showed that none of these variables operating in those directions were associated with an increased level of atherosclerosis in the large or small cerebral arteries. The implication of this finding is that the paradox cannot be explained only by atherosclerotic processes in the relevant vasculature, nor can it be explained by differences in blood pressure, as group mean levels were identical at baseline in both cohorts.

Ischemic vascular events consist not only of atherosclerosis but also of thrombosis and vessel spasm. Additional, in stroke there may be hemorrhage from vessel rupture. The degree of rupture will depend on the size and location of rupture and the rapidity with which hemostasis is achieved through vessel spasm and clotting. It could be hypothesized that factors decreasing clotting potential would benefit vascular conditions involving thrombosis and worsen those involving hemorrhage. Could the paradox be due to differences in hemostatic factors? For this hypothesis to be plausible, the following three conditions would need to be satisfied:

1. The differences found in lipids, diet, and alcohol consumption would need to be associated with differences in hemostatic factors in a way consistent with the differences in cardiovascular disease outcomes already noted. More specifically, serum cholesterol and dietary fat intake should be positively associated with hemostatic factors. Conversely, alcohol intake should be negatively associated with those factors.

2. Population mean levels of hemostatic factors should be lower in Japan than in the United States. It should also be lower in Japanese living in Japan compared with those living in the USA.

3. Hemostatic factors should be positively associated with risk of CHD and thromboembolic stroke but negatively associated with risk of hemorrhagic stroke, independent of other risk factors. Because hemostatic factors are themselves altered by cardiovascular disease events, these associations should be demonstrated in prospective studies.

Recent large-scale population-based studies have shown significant associations between lifestyle factors, serum lipid levels, and hemostatic factors. Table 1 shows that serum lipids are mainly positively correlated with fibrinogen and factor VII but alcohol is negatively associated with fibrinogen.

Positive associations have also been found in the Northwick Park Heart Survey between dietary fat intake and factor VIIc. In ex-smokers, factor VIIc increased only in those whose body mass index, possibly a marker of dietary fat intake, rose after cessation of smoking. Serum triglyceride level, which is positively associated with recent dietary saturated fat intake, has also been found to be positively associated with factor VII and factor VII phospholipid complex (VIIpl). The same study found a negative association between high density lipoprotein-cholesterol (which is negatively associated with dietary saturated fat intake) and factors VII and VIIpl.

One study reported that hyperlipidemia partially activates factor VII in humans, suggesting a mechanism linking diet, hyperlipidemia, and increased thrombotic tendency. Other studies have shown an association between diet and thrombolytic tendency that is the reverse of that seen between diet and thrombotic tendency. The Northwick Park Heart Survey found a significant positive association between alcohol consumption and fibrinolytic activity. The same study found fibrinolytic activity was lower in the obese. A later Northwick Park paper reported a negative association between alcohol intake and platelet aggregability.

In addition to the results reported in the table, the Caerphilly and Speedwell studies reported a negative association between alcohol intake and antithrombin III levels in a multivariate analysis of the same data. Positive associations were also reported between dietary fiber, dietary polysaturated fat intake, and antithrombin III levels. The polysaturated/saturated fatty acid ratio of the diet, fatty fish consumption, and alcohol intake have all been found to be negatively associated with platelet aggregation in this collaborative study.

These studies show that the first condition is supported by the relevant literature. Is the same true for the second condition? A recent transnational survey compared levels of plasma fibrinogen, factors VIIc and VIIIc, and von Willebrand's factor in men aged 34-55 years in four different samples: rural Japanese, urban Japanese, Japanese Americans, and Caucasian Americans. This study found that mean fibrinogen, factor VIIc, and factor VIIIc levels were highest in Japanese Americans and Caucasian Americans; von Willebrand's factor did not

### Table 1. Associations Between Hemostatic Factors and Known Cardiovascular Disease Risk Factors

<table>
<thead>
<tr>
<th>Factor/study</th>
<th>Cholesterol</th>
<th>Blood Pressure</th>
<th>Smoking</th>
<th>Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northwick Park</td>
<td>0.06</td>
<td>NR</td>
<td>(p&lt;0.0001)</td>
<td>~ve (p=0.02)</td>
</tr>
<tr>
<td>Göteborg</td>
<td>0.10</td>
<td>0.08</td>
<td>0.18</td>
<td>NM</td>
</tr>
<tr>
<td>Framingham</td>
<td>NS</td>
<td>(p&lt;0.05)</td>
<td>(p&lt;0.05)</td>
<td>NR</td>
</tr>
<tr>
<td>Leigh</td>
<td>0.13</td>
<td>0.21</td>
<td></td>
<td>NM</td>
</tr>
<tr>
<td>Caerphilly/Speedwell</td>
<td>0.15</td>
<td>NR</td>
<td>(p&lt;0.001)</td>
<td>-0.03</td>
</tr>
<tr>
<td>Factor VII</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northwick Park</td>
<td>0.24</td>
<td>NR</td>
<td>(p&lt;0.05)</td>
<td>NS</td>
</tr>
<tr>
<td>Göteborg</td>
<td>0.18</td>
<td>0.10</td>
<td>-0.05</td>
<td>NM</td>
</tr>
</tbody>
</table>

Values are correlation coefficients, or probability values for positive associations between variables. Correlation coefficients are significant at p<0.05 or less unless otherwise stated. NR, not reported; NM, not measured; NS, not significant, no p value reported.

*Significant positive relationship stated but no p or r value reported.
differ between the four groups. Plasma fibrinogen was significantly higher in smokers within each group, and factors VIIc and VIIIc were positively correlated with serum total cholesterol and serum triglyceride levels. The significant differences in fibrinogen and factor VIIc remained between the groups after controlling for differences in covariates (smoking, serum total cholesterol and triglycerides, age, blood pressure, body mass index, and alcohol intake).

Other studies have shown that transnational and national differences in plasma fibrinogen may be due in part to differences in genotype coding for fibrinogen protein. This may explain why the groups with the highest prevalence of cigarette smoking (rural and urban Japanese) had lower mean fibrinogen levels than did Caucasian Americans.

Overall, these findings support the second condition.

Do the relevant studies support the third condition?

Several prospective studies conducted among men have found serum fibrinogen is a risk factor for stroke. The Göteborg Study found that blood pressure was the strongest risk factor, followed (in order) by central obesity, fibrinogen, and maternal history of stroke.

The Framingham Study was conducted among women as well as men. For both men and women, fibrinogen had as powerful a positive association with risk of cardiovascular disease (as a whole) as age, blood pressure, cholesterol level, and glucose intolerance. For men, it was second only to blood pressure as a risk factor for stroke. Fibrinogen was positively associated with risk of cardiovascular disease in men at all ages, but in women the association decreased with age and disappeared in women over 70 years of age. In men, fibrinogen was significantly associated with risk of stroke, but this association was not seen in women.

In none of these prospective studies was stroke broken down into thromboembolic and hemorrhagic categories, but, because thromboembolic stroke is much more common than hemorrhagic stroke in western societies, it is reasonable to assume that the association refers primarily to risk of the former.

Several studies have also shown fibrinogen to be an independent risk factor for CHD. In a prospective study of 297 men aged 40–69 years at entry who were observed for a mean observation period of 7.3 years, fibrinogen was found to be an independent risk factor for CHD. It was at least as important as serum total cholesterol, blood pressure, and smoking in predicting risk. That smoking and fibrinogen were both independent predictors of risk suggests that the effect of smoking is in part independent of its effect on fibrinogen. Cigarette smoking is associated with atherosclerosis in all arterial beds, and it is likely that the interaction of its effects on hemostasis and atherosclerosis is of importance in assessing its contribution to the risk of cardiovascular disease.

The prospective component of the Northwick Park Heart Survey found that for men aged 40–64 years at recruitment, factors VIIc and VIIIc and fibrinogen were significantly positively associated with the risk of death due to CHD. The independent association of factor VIIc and fibrinogen with risk of death due to CHD equaled that for serum total cholesterol. Later Northwick Park results (for men) also found a significant positive association between factor VIIc, fibrinogen, and the risk of first CHD events, especially those occurring within the first 5 years of recruitment. This latter analysis also showed that within the 5-year period, serum total cholesterol was not a risk factor for first CHD events. For follow-up periods longer than 5 years (mean follow-up period <10 years at that stage), serum total cholesterol became marginally significant. Considered together, these results indicate that, in the shorter term at least, blood coagulability is a stronger independent risk factor for CHD than is serum total cholesterol or cigarette smoking.

The latest results from the Caerphilly/Speedwell study confirm the importance of fibrinogen in predicting the incidence and prevalence of CHD in men. Fibrinogen and plasma viscosity were stronger predictors of incident CHD than was cholesterol. Cigarette smoking was the most powerful positive predictor of hemostatic and rheological factors, but it did not account for their full predictive power, as the relationship of hemostatic factors with incident ischemic heart disease was also seen in nonsmokers.

Another study found that plasma fibrinogen was the most important variable in predicting femoropopliteal vein graft occlusion, followed by cigarette smoking and serum cholesterol. Antiplatelet therapy, while associated with a significant reduction in nonfatal myocardial infarction and secondary ischemic stroke, was also associated with a small increase in risk of hemorrhagic stroke.

The fibrinolytic pathway may also be of importance in predicting the risk of cardiovascular disease. In a prospective study, 109 men who had a first myocardial infarction at less than 45 years of age were observed for 3 years. High plasma levels of fast-acting plasminogen activator inhibitor, high serum levels of very low density lipoprotein–cholesterol, and lower levels of high density lipoprotein–cholesterol were independently related to risk of reinfarction.

These results lend weight to the belief that thrombogenesis as well as atheroma formation is important in the pathophysiology of cardiovascular disease and provide support for the third condition.

Several conclusions emerge from this review. Cross-sectional studies show that hemostatic factors vary in a way consistent with the paradox noted and with population-based risk of various forms of cardiovascular disease. Further, some prospective studies (conducted mainly in men) show that a variety of hemostatic factors are independent risk factors for CHD and thromboembolic stroke. Risk factors that affect thrombotic tendency and fibrinolysis are associated with risk of CHD, ischemic stroke, and, probably, hemorrhagic stroke.

The importance of this observation is that intervention aimed at reducing the susceptibility to thrombosis may be a more effective way to reduce the risk of CHD and thromboembolic stroke than is manipulation of serum cholesterol, at least in the short term. However, before this observation can form the basis of preventive programs, further prospective research is needed to clarify certain aspects of the relationship of hemostatic factors to the risk of cardiovascular disease. In particular, it is unclear whether such action might increase the risk of hemorrhagic stroke, especially in populations at increased risk for stroke.
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