Association of Recurrent Myocardial Infarction with Hemostatic Factors*
A Prospective Study

John B. Kostis, M.D., F.C.C.P.; D. Joseph Baughman, M.D.; and Peter T. Kuo, M.D., F.C.C.P.

In a perspective blind study of 147 survivors of myocardial infarction, the 13 patients who had definite recurrent infarction during 38.1 ± 7.2 months (minimum, 34 months) of follow-up had higher plasma fibrinogen levels (334.4 ± 13.1 mg/dl vs 291.5 ± 4.7 mg/dl; P=0.0055), and higher maximum rate of fibrin growth (generation of turbidity) when measuring prothrombin time (PT Vmax, 7.76 ± 0.31 units vs 6.48 ± 0.11 units; P=0.0003), thrombin time (TT Vmax, 5.24 ± 0.32 units vs 4.22 ± 0.11 units; P=0.0002), and activated partial thromboplastin time (APTT Vmax, 7.47 ± 0.29 units vs 6.20 ± 0.10 units; P=0.0001) than patients who did not have reinfarction. Eleven of the 13 reinfarctions occurred among the quartile (37 patients) with the highest PT Vmax, while only two reinfarctions occurred among the remaining 110 patients (risk ratio, 16.5). The quartile with highest APTT Vmax included nine reinfarctions (risk ratio, 6.7), and the quartiles with the most fibrinogen and largest TT Vmax included eight of the 13 reinfarctions (risk ratio, 4.8). Significant associations (P=0.018 to 0.005, risk ratios, 2.5 to 4.8) of reinfarction with the values of Vmax corrected for fibrinogen were also found. These findings support recent evidence that hemostatic function contributes to the pathogenesis of the complications of coronary artery disease.

Thrombotic coronary occlusion is frequently present in patients with acute localized transmural myocardial infarction. However, relatively little attention has been paid to hemostasis as it relates to coronary thrombosis. Retrospective studies of blood coagulation after myocardial infarction do not clearly distinguish between changes resulting from the infarction and preexisting hemostatic alterations that contribute to coronary thrombosis.

Recently, Meade and co-workers11 in a prospective study found associations between death from cardiovascular disease and high levels of factor 7c, factor 8c, and fibrinogen. This article reports an association of increased fibrinogen and increased maximum rate of fibrin growth with reinfarction in a prospective study of 147 survivors of acute myocardial infarction participating in the aspirin myocardial infarction study.12

Methods

One hundred sixty-two survivors of definite myocardial infarction (152 men and ten women, aged 32 to 68 years, mean 52 years) were enrolled in the study three to 58 (23.5 ± 15.6) months after the qualifying myocardial infarction. These patients were recruited by one clinical center (CMDNJ-Rutgers Medical School, Prof. P. T. Kuo, principal investigator) of the aspirin myocardial infarction study.12 The infarction was documented either by the presence of typical symptoms and the development of pathologic Q waves, or by typical symptoms, compatible ST-T changes and elevation above twice the upper normal limit of two of three myocardial enzymes (SGOT, LDH and CPK).

Patients with previous cardiovascular surgery, uncontrolled hypertension, severe peptic ulcer disease, and those receiving anticoagulants, aspirin, dipyridamole, or sulfinpyrazone were excluded. Each patient was followed up every four months for a minimum of 34 months (38.1 ± 7.2, range 34 to 54 months) for mortality and for the occurrence of a new myocardial infarction, stroke, peripheral arterial occlusion, and pulmonary embolism. A definite reinfarction was diagnosed, either by the development of new diagnostic Q waves or by appropriate symptoms accompanied by ST-T changes indicative of transient ischemia or injury, and greatly elevated myocardial enzymes. Details of the design of aspirin myocardial infarction study, eligibility criteria, definitions of endpoints and procedures for follow-up have been published elsewhere.12 The patients were randomized to aspirin, 50 mg twice a day (82 patients) or placebo (80 patients).

A coagulation profile consisting of prothrombin time (PT), prothrombin time Vmax (the maximum rate of fibrin growth during clot formation when measuring PT, PT Vmax), activated partial thromboplastin time (APTT), APTT Vmax, thrombin time (TT) Vmax, fibrinogen, antithrombin 3, and lysis time was performed on the first visit after randomization on 147 patients (139 men and eight women, aged 32 to 68 years, mean 52.3 years; 77 randomized to placebo, 70 to aspirin; three to 58, mean 23.4 ± 15.6 months after the qualifying infarction). Blood was collected into citrated (3.8 percent) vacuum tubes and centrifuged at 2,000 g. The PT, TT, and APTT assays were performed on the same day, using reagents manufactured by Ortho Diag-

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*From the Department of Medicine, CMDNJ-Rutgers Medical School, Piscataway, New Jersey. Reprint requests: Dr. Kostis, Cardiology, Middlesex General Hospital, New Brunswick, New Jersey 08903

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nagnostics Systems, Inc, on a Bio Data Profiler CP-7 (Bio Data Corp). The maximum rate of fibrin growth was measured as the maximum rate of turbidity generation. The turbidity was obtained from the Profiler CA-7 recording, while clotting assays were performed (Vmax from PT, APTT, and TT). Fibrinogen was measured the next day by the method of Blomback and Blomback harvesting the clot by centrifugation at 27,700 g for 20 minutes. Antithrombin 3 was assayed on frozen-thawed samples within seven days using the Ortho Antithrombin 3 kit. Lysis times were performed according to the CLUE procedure using urokinase (200 μg/ml) and a Biodata PAP-2A instrument.

The coefficient of variation for replicate measurements of the same sample (N=304) was 1.5 percent for fibrinogen, 4.4 percent for APTT Vmax, 4.7 percent for PT Vmax, and 5.4 percent for TT Vmax. The coefficient of variation for blood samples drawn on the same patient three months apart (N=145) were 1.7 percent for fibrinogen, 12.4 percent for APTT Vmax, 11.8 percent for PT Vmax, and 11.0 percent for TT Vmax. Analysis using the values obtained at the first or second measurements yielded similar results. The results of clotting assays were not revealed to the investigators until the end of the study and the completion of classification of all reinfarctions by an independent committee.

RESULTS

During follow-up, 13 patients had definite reinfarction, three had definite stroke, and nine died. Of the seven deaths due to cardiovascular causes, six occurred within 24 hours of the onset of symptoms (three within one hour) and were classified as sudden deaths. In only one patient was a definite recurrent myocardial infarction diagnosed before death. Definite pulmonary embolism was not diagnosed in any patient. Patients who had reinfarction had higher fibrinogen levels (334.4 ± 13.1 mg/dl vs 291.5 ± 4.7 mg/dl; P = 0.0055), PT Vmax (7.76 ± 0.31 units vs 6.48 ± 0.11 units; P = 0.0003), TT Vmax (5.24 units ± 0.32 units vs 4.22 ± 0.11 units; P = 0.0002), and APTT Vmax (7.47 ± 0.29 units vs 6.20 ± 0.10 units; P = 0.0001) than patients who did not have reinfarction. These differences remained statistically significant when the placebo group was analyzed alone (seven reinfarctions among 77 patients; P<0.05), when all thrombotic complications (definite reinfarction plus definite stroke) were included in the analysis (P<0.001), and when the occurrence of either cardiovascular mortality or reinfarction was considered as the dependent variable (P<0.01). Since the distribution of fibrinogen, PT Vmax, APTT Vmax, and TT Vmax

![Figure 1. Number of reinfarctions by quartiles for fibrinogen, APTT Vmax, PT Vmax, and TT Vmax.](http://journal.publications.chestnet.org/pd/access.asu?url=/data/journals/chest/21288/ on 06/05/2017)
were symmetric, statistical analysis was performed assuming normal distributions. When log-transformed values were used, nearly identical results were obtained. Eleven (29.7 percent) of the 37 patients with the highest PT Vmax (the 25 percent of patients with highest PT Vmax) had reinfarction, while only two (1.8 percent) of the remaining 110 patients had this complication (risk ratio, 16.5). In a similar fashion, the quartile with highest APTT Vmax included nine of the 13 reinfarctions (risk ratio, 6.7) and the quartiles of largest TT Vmax and highest fibrinogen had eight of the 13 reinfarctions (risk ratio, 4.8; Fig 1).

There were no significant differences in APTT, PT, TT, antithrombin 3, or lysis time between patients who had reinfarction and those who did not. There was no significant association between coagulation parameters and sudden coronary death. A relationship was not observed between coagulation parameters and age, sex, blood pressure, hematocrit, history of angina, use of coffee or alcohol, signs or symptoms of congestive heart failure, presence of Q waves or ST depression on the ECGs, or the number, age, site, or severity of previous infarctions. Serum cholesterol values were positively associated with fibrinogen \( (r = 0.31, P = 0.005) \), APTT Vmax \( (r = 0.24, P = 0.007) \), and PT Vmax \( (r = 0.22, P = 0.01) \) and was negatively associated with antithrombin 3 \( (r = -0.19, P = 0.04) \). Serum triglyceride levels were positively associated with fibrinogen \( (r = 0.19, P = 0.04) \); smoking was negatively associated with PT Vmax \( (r = -0.22, P = 0.008) \), APTT Vmax \( (r = -0.15, P = 0.07) \), and TT Vmax \( (r = -0.31, P = 0.0002) \).

There were no significant differences in fibrinogen, TT Vmax, APTT Vmax, and PT Vmax between the aspirin and the placebo groups. Serum cholesterol and triglyceride levels, systolic blood pressure, and smoking habits were similar \( (P > 0.15) \) in the patients who had reinfarction and those who did not.

Strong, positive correlations of fibrinogen with APTT Vmax \( (r = 0.83, P = 0.0001) \), PT Vmax \( (r = 0.85, P = 0.0001) \), and TT Vmax \( (r = 0.53, P = 0.0001) \) were observed. Since fibrinogen is a major determinant of Vmax, scatter plots of fibrinogen vs PT Vmax (Fig 2), APTT Vmax, and TT Vmax were constructed, and the corresponding regression equations estimated. For each patient (one point in Fig 2) the difference between the value of Vmax predicted from fibrinogen using the regression line and the actual value of Vmax was calculated. These differences (Vmax residuals) had a positive value \( (eg, R_1 \text{ in Fig 2}) \) when the actual Vmax was higher than that predicted by fibrinogen for a given patient and a negative value \( (eg, R_2 \text{ in Fig 2}) \) when the

![Figure 2. Scatter plot of PT Vmax vs fibrinogen. PT Vmax residuals \( (R_1, R_2) \) defined as actual PT Vmax minus PT Vmax predicted by fibrinogen for each patient using regression line. Note that reinfarctions (large circles) and strokes (squares) cluster above regression line, ie, have positive PT Vmax residuals.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21288/ on 06/05/2017)
actual $V_{\text{max}}$ was less than that predicted by fibrinogen. Patients who had reinfarction had larger positive PT $V_{\text{max}}$ residuals ($P = 0.018$), APTT $V_{\text{max}}$ residuals ($P = 0.006$), and TT $V_{\text{max}}$ residuals ($P = 0.05$). Eight of 13 reinfarctions occurred in the quartile with the most positive APTT $V_{\text{max}}$ residuals (risk ratio, 4.8), seven in the quartile with most positive PT $V_{\text{max}}$ residuals (risk ratio, 3.4), and six in the quartile with the highest positive TT $V_{\text{max}}$ residuals (risk ratio, 2.5). Consequently, patients with reinfarction tended to cluster above the regression line in the scatter plots (Fig 2). Strong, positive, correlations among $V_{\text{max}}$ residuals were observed ($r = 0.45$ to 0.75; $P < 0.0001$).

**Discussion**

An association of cardiovascular mortality and hemostasis was seen in the early results of the Northwick Park prospective heart study. Higher levels of factor 7, factor 8, and fibrinogen were measured in men who subsequently died from cardiovascular disease. The findings pertaining to nonfatal myocardial infarction have not been published. A strong association of recurrent nonfatal myocardial infarction with high levels of fibrinogen, and increased maximum rates of fibrin growth (turbidity production when measuring APTT, PT, or TT) was observed in this prospective study of survivors of a myocardial infarction. The lack of association between coronary mortality and coagulation parameters may be due to the fact that the majority of deaths in this study were sudden deaths. Different pathogenic mechanisms underlie sudden death and myocardial infarction, since occlusive coronary thrombi are rare in the former condition and common in the latter. In either instance, a decrease of coronary blood flow in areas of coronary stenosis may be initiated by platelet aggregation, coronary spasm, or other influences and may lead to angina, arrhythmia, or sudden death. If the decrease of coronary flow is of long duration and the hemostatic mechanisms are enhanced, a fibrin clot leading to a transmural infarction may be produced. In the absence of enhanced hemostasis or a prolonged decrease of coronary flow, the spasm or platelet aggregates are reversed, and a transmural myocardial infarction does not take place. It is, therefore, interesting that hemostatic factors associated with or describing the speed of clot formation (fibrinogen, $V_{\text{max}}$) were associated with reinfarction in this study.

It is unlikely that the changes in hemostatic function associated with reinfarction were due to the previous (qualifying) infarction, since the changes did not correlate with the age, number, and severity of previous infarctions and since the average age of the qualifying infarction at the beginning of the study was 23 months. Fibrinogen levels increase after myocardial infarction, but return to normal within a year. Elevated fibrinogen levels may predispose to infarction by enhancing thrombus formation, by increasing blood viscosity and probably by facilitating the growth of atherosclerotic lesions. However, reinfarction showed a stronger association with the maximum rate of fibrin growth ($V_{\text{max}}$) than with plasma fibrinogen. In addition, $V_{\text{max}}$ residuals, corrected for fibrinogen level, showed an independent association with recurrent infarction. These two findings suggest that, in addition to fibrinogen, other factors such as factor 7c and 8c (not measured in this study) may play a role by increasing the quantity and rate of thrombin production which affects $V_{\text{max}}$. It is, therefore, possible that increased $V_{\text{max}}$ may represent the common pathway whereby hemostatic function may predispose to coronary thrombosis.

The association of reinfarction with $V_{\text{max}}$ measured when testing either the extrinsic pathway (PT $V_{\text{max}}$) or the intrinsic pathway (APTT $V_{\text{max}}$) is in agreement with the observation of “clusters” of increased hemostatic factors (fibrinogen, factor 7c, factor 8c) in subjects who died due to cardiovascular disease reported by Meade. On the other hand, the high positive correlations among the residuals of APTT $V_{\text{max}}$, PT $V_{\text{max}}$, and TT $V_{\text{max}}$ and the association of recurrent infarction with TT $V_{\text{max}}$ (theoretically not affected by the intrinsic or extrinsic pathways) suggest that other factors—e.g., subtle qualitative differences in fibrinogen or changes in the interaction of fibrinogen with thrombin—may be important. Associations of cholesterol with $V_{\text{max}}$ and fibrinogen and between triglycerides and fibrinogen were found in this and other studies. However, these blood lipids did not show a strong association with reinfarction. Whatever the underlying mechanisms, this prospective study demonstrates a clear association between definite recurrent myocardial infarction and hemostasis and supports the theory that thrombosis is important in the pathogenesis of coronary artery disease.

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