Effects of Dietary and Pharmacologic Alteration of Serum Lipids on Platelet Survival Time

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SUMMARY Platelet survival time (SURV) (autologous labelling with 51Chromium) was shortened (3 ± 0.03 days; average t 1/2 ± SEM; normal t 1/2 3.7 ± 0.03 days) in 88 out of 128 (69%) men with coronary disease. In 35 out of 47 men with hyperprebetalipoproteinemia, SURV was shortened (3 ± 0.09 days) (74%). Of 30 men with hyperbetalipoproteinemia, SURV was shortened (2.5 ± 0.10 days) in 26 (87%). Of 51 men without hyperlipoproteinemia, SURV was normal (3.3 ± 0.10 days) in 24 (47%). Dietary alteration of serum triglyceride was undertaken in 12 men with hyperprebetalipoproteinemia, and in eight a decrease of triglyceride of more than 75 mg% was achieved (324 ± 21-219 ± 18 mg%; P < 0.001) with an increase of SURV (2.2 ± 0.11-2.8 ± 0.13 days; P < 0.001). In four, serum triglyceride increased by more than 75 mg% (279 ± 14-451 ± 28 mg%) and SURV decreased (2.7 ± 0.16-2.3 ± 0.21 days). Cholestyramine (16 g.d.) and diet decreased serum cholesterol (348 ± 7.6-319 ± 6.3 mg%; P < 0.001) in 15 men with hyperbetalipoproteinemia and SURV increased (2.3 ± 0.08-2.7 ± 0.07 days; P < 0.001). Results suggest that SURV is shortened in men with coronary disease, particularly in those with hyperlipoproteinemia, and that alteration of triglyceride and cholesterol are associated with alteration of SURV.

INCREASED LEVELS OF SERUM CHOLESTEROL and triglyceride are generally regarded as one of several predisposing factors in the development of atherosclerotic vascular disease.1 Platelets contribute to thrombosis and may play an important role in atherosclerosis.2,3 Platelet survival time is shortened in patients with prosthetic cardiac valves4,5 and correlates with thromboembolism in these patients.6 Platelet survival time is shortened in patients with coronary artery disease.6,7 There may be a relationship between platelet reactivity and serum lipids.8 Carvalho and associates observed increased platelet sensitivity to aggregating agents in patients with hypercholesterolemia,9 and Shattil and associates have shown that this increased sensitivity to aggregation was associated with increased cholesterol content of the platelet membrane.10 It is interesting to consider that the mechanism of increased risk of atherosclerosis in hyperlipemia is due to an associated increase in platelet reactivity. In the present study, platelet survival time was measured before and after alteration of serum lipids in men with coronary artery disease.

Patients

Platelet survival time was measured in 128 men with arteriographically defined coronary disease. All men had been in a stable clinical state for at least three months. Of these 128 men, 47 had hyperprebetalipoproteinemia, 30 had hyperbetalipoproteinemia and 51 had normal serum cholesterol and triglyceride. Twenty of the men with hyperprebetalipoproteinemia attempted dietary therapy of their hyperlipidemia. Cholestyramine in association with dietary restriction of saturated fats and carbohydrates was undertaken in 15 men with shortened platelet survival and hyperbetalipoproteinemia. All men gave their informed consent to participate in this study which was approved by the Human Subject Committee, University of Colorado Medical Center. Sixty-eight of these men were the subjects of a previous report.6

Methods

Platelet survival time was measured by labelling the platelets from about 400 ml of the patients venous blood with 100-150 μCi of 51Chromium.11 Following reinfusion of labelled platelets, blood was obtained for seven days, and using computer-assisted least-squares analysis, a single exponent was fitted to the platelet count-rate data for determination of the half-time. In 26 normal men, platelet survival half-time averaged 3.7 days, and all had a half-time greater than 3.3 days. Although the platelet count-rates tended to be lower for men with hyperlipidemia, statistical differences were not observed. All patients had normal platelet counts.

In the men subjected to pharmacologic and dietary treatment, platelet survival was repeated after a three month treatment period. Serum cholesterol,12 triglyceride,13 and lipoprotein electrophoresis on paper14 were measured during the performance of platelet survival. Blood for lipid analysis was obtained after an overnight fast.

All men classified as hyperbetalipoproteinemia had serum triglyceride 200 mg%, or without an increase in cholesterol, and all had increased prebeta staining on paper. All men classified as hyperbeta-lipoproteinemia had serum cholesterol in excess of 300 mg% with triglyceride < 200 mg%. Lipoproteins were not measured in these men. The men treated with cholestyramine received 16 g/day in divided doses for three months and then 24 g/day in divided doses for another three months.
Results

Platelet survival time was shortened (< 3.3 days) in 88 of the 128 men (69%) with coronary disease (3 ± 0.03 days; average ± SEM; normal 3.7 ± 0.03; P < 0.001). Platelet survival was shortened in 35 of 47 men (74%) with hyperprebetalipoproteinemia (3 ± 0.09 days) and in 26 of 30 men (87%) with hyperbetalipoproteinemia (2.5 ± 0.10 days). In the men with normal levels of serum cholesterol and triglyceride, platelet survival was shortened in 27 of 51 men (53%) (3.3 ± 0.10 days). The average platelet survival was significantly shorter for men with hyperbetalipoproteinemia (P < 0.001), and the average value for men without lipidemia was significantly increased compared to the average for those with either lipid abnormality. Thus, men with coronary disease and lipidemia had an increased frequency of shortened platelet survival and a more abnormal average value than men with coronary disease who did not have hyperlipidemia.

Dietary treatment of hyperprebetalipoproteinemia was attempted for three months in 20 men. All men were at least 20% overweight and were encouraged to restrict dietary carbohydrates, saturated fats and total calories. Eight men were able to decrease serum triglyceride by at least 75 mg% (324 ± 21-219 ± 18 mg%; P < 0.001) and in these men, platelet survival time increased (2.2 ± 0.11-2.8 ± 0.13 days; P < 0.001). In four men, an acutal increase in triglyceride by at least 75 mg% was observed (279 ± 14-451 ± 28 mg%) and platelet survival decreased (2.7 ± 0.16-2.3 ± 0.21 days). In the eight men who did not alter their serum triglycerides (± 50 mg%), platelet survival was not changed (2.5 ± 0.12-2.4 ± 0.11 days; NS). In these men, dietary alteration of cholesterol was modest, with no change greater than 5% of control. Thus, in men with shortened platelet survival time, a substantial alteration of serum triglyceride was associated with an alteration of platelet survival time.

Fifteen men with hyperbetalipoproteinemia were treated with cholestyramine and encouraged to restrict dietary carbohydrates and saturated fats. Cholestyramine, in a dosage of 16 g/day, decreased serum cholesterol (348 ± 7.6-319 ± 6.3 mg%; P < 0.001) in association with an increase in platelet survival time (2.3 ± 0.08-2.7 ± 0.07 days; P < 0.001) (fig. 1). These 15 men received 24 g/day of cholestyramine and only small additional changes in serum cholesterol (310 ± 6.5 mg%; NS) and platelet survival (2.9 ± 0.07 days; NS) were observed (fig. 1). Cholestyramine treatment was associated with increases in serum triglyceride,15 16 but this increase did not exceed 50 mg%. Thus, a decrease in serum cholesterol in men with hypercholesterolemia was associated with an increase in platelet survival time.

Discussion

The results of the present study suggest a relationship between serum lipids and platelet survival time in men with coronary disease. Men with coronary disease and increased serum levels of cholesterol (hyperbetalipoproteinemia) or triglyceride (hyperprebetalipoproteinemia) have more abnormal average values for platelet survival and a greater frequency of shortened platelet survival time than men with coronary disease who do not have hyperlipidemia. Dietary-induced decreases in serum triglyceride were associated with increases in platelet survival. Increases in serum triglyceride were associated with decreases in platelet survival time. Pharmacologic decreases in

![Figure 1. Relationship between platelet survival time (open bars: average ± SEM) and serum cholesterol (closed bars: average ± SEM) in 15 men with coronary disease and hyperbetalipoproteinemia. Average platelet survival and serum cholesterol were altered by cholestyramine (chstyr 16 g q.d. and 24 g q.d.). CAD = coronary artery disease.](http://circ.ahajournals.org/doi/figure/1)
serum cholesterol increased platelet survival in men with hypercholesterolemia. The increases in average platelet survival induced by decreases in serum triglyceride or cholesterol were quantitatively similar to the increase in platelet survival time observed with the administration of the platelet suppressant drugs, sulfinpyrazone and dipyridamole, drugs which do not alter serum lipids.6, 17

Ross and Harker observed a decrease in platelet survival time and loss of endothelium in association with an increase in serum cholesterol in monkeys.18 Balloon injury also resulted in endothelial loss and shortening of platelet survival time.19 O’Brien and associates measured the heparin thrombin clotting time in normals after a large meal of saturated and a large meal of unsaturated fats.19 The clotting time was shortened after ingestion of saturated fats and prolonged after ingestion of unsaturated fats.19 The heparin thrombin clotting time may measure platelet antiheparin activity (platelet factor four),19 and this activity has correlated with platelet survival time in men with coronary disease.20

It is unclear whether platelet survival time is altered by a change in serum lipids because of a decrease in arterial endothelial injury or because of a decrease in platelet responsiveness to a constant level of endothelial injury, or both mechanisms in combination. Platelet survival time should measure either situation, and certainly measures endothelial injury as shown by the balloon-induced and homocysteinemic endothelial cell injury experiments in monkeys.18, 21

It is likely that platelet aggregation and release play a part in the development of atherosclerotic vascular disease and its complications. The atherosclerotic process could result in shortened platelet survival time both in patients with and without elevated serum lipid levels. This increased platelet turnover could result in an increased number of younger, more reactive platelets.22 The reactivity of these younger platelets could then be easily altered by changes in the lipid levels in the blood and platelet membranes so that further alteration of platelet survival could occur.

Carvalho and associates observed increased platelet sensitivity to aggregating agents in patients with hyperbetalipoproteinemia.9 Shattil and associates have shown that the sensitivity of platelets to aggregating agents correlated with the cholesterol-phospholipid ratio of platelets, and that aggregation sensitivity can be increased by incubation of platelets with cholesterol.10 These data suggest that the alteration of platelet survival time induced by alteration of serum lipids might be due to decreased platelet responsiveness to endothelial injury. The results of our study of platelet survival do not exclude the notion that alteration of serum lipids alters platelet survival time by changing the intensity of lipid-induced endothelial injury.

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