Factors Affecting Fibrinolytic Potential: Cardiovascular Fitness, Body Composition, and Lipoprotein(a)

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The purpose of the study was to determine the factors that affect basal (resting) and poststressor fibrinolytic activity or potential. Variables of interest included cardiovascular fitness (maximal oxygen consumption [$\dot{V}O_2$max]), body fat, body mass index (BMI), and lipids/lipoproteins, including lipoprotein(a) [Lp(a)]. Blood was collected from 46 middle-aged men before and after a maximal exercise test. Pearson and Spearman correlation coefficients were calculated to determine associations between the variables of interest and tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) activities in the basal state and after stimulation with maximal exercise. Multiple regression analyses were also conducted to determine independent predictors of the fibrinolytic variables. Maximal exercise produced significant increases in t-PA activity and decreases in PAI-1 activity. Postexercise t-PA activity was inversely related to basal PAI-1 activity ($r = -.34$). $\dot{V}O_2$max was positively correlated with t-PA activity (basal, $r = .39$; postexercise, $r = .67$) and inversely related to PAI-1 activity (basal, $r = -.41$; postexercise, $r = -.42$). Body fat was correlated with postexercise t-PA activity ($r = -.60$) and both basal and postexercise PAI-1 activity ($r = .42$), but the correlation with basal t-PA activity was not significant ($P = .058$). Postexercise t-PA activity was positively correlated ($r = .37$) with high-density lipoprotein cholesterol (HDL-C) and negatively correlated ($r = -.42$) with low-density lipoprotein cholesterol (LDL-C). Basal PAI-1 activity was negatively correlated with HDL-C ($r = -.37$). Lp(a) was not correlated with any fibrinolytic variable or fitness. Multiple regression analyses showed that $\dot{V}O_2$max was an independent predictor of both basal and postexercise t-PA activity ($R^2 = .16$ and .34, respectively). Triglyceride (TG) levels and $\dot{V}O_2$max were significant independent predictors of PAI-1 activity ($R^2 = .31$). In conclusion, cardiovascular fitness was a strong independent predictor of fibrinolytic potential. In addition, poststressor measures of fibrinolytic potential may provide more information about the fibrinolytic system than basal values.

THE LINK BETWEEN impaired fibrinolytic activity and thromboembolic complications, both arterial and venous, has been well documented.[1-4] Recent results from the Northwick Park Heart Study[3] demonstrate a strong and independent relationship between low fibrinolytic activity, measured globally by dilute blood clot lysis, and the incidence of ischemic heart disease in men aged 40 to 54 years. Low fibrinolytic activity may have both short- and long-term effects on coronary heart disease (CHD) risk. For instance, the interval between the measurement of fibrinolytic activity and the ischemic event was approximately 9 years in the Northwick Park Heart Study, suggesting that low fibrinolytic activity exerts a long-term effect.

Components of the fibrinolytic system, primarily tissue plasminogen activator (t-PA), an important stimulator of fibrinolysis, and plasminogen activator inhibitor-1 (PAI-1), the primary fibrinolytic inhibitor, are often measured to assess fibrinolytic activity. t-PA antigen, which refers to the mass concentration of t-PA, is the sum of all t-PA molecules present in a sample, both active and bound to PAI-1, whereas t-PA activity refers to the enzymatically active amount of t-PA present. Similarly, PAI-1 antigen refers to total PAI-1, and PAI-1 activity is a functional measure of PAI-1. Defective fibrinolysis can be manifest as either low t-PA activity or elevated PAI-1 activity.[5] Interestingly, high levels of t-PA antigen often reflect high levels of inhibition, since most t-PA is in complex with PAI-1.[6] Low levels of t-PA activity and high levels of both t-PA antigen and PAI-1 antigen have been positively associated with myocardial infarction,[1] reinfarction,[2] stroke,[7] and deep vein thrombosis.[5]

A number of life-style factors have been identified as potentially affecting these fibrinolytic variables, including physical activity and fitness. Although cross-sectional data consistently show enhanced fibrinolytic activity in physically active individuals,[8-10] longitudinal data are sparse and have not included control groups.[11] Furthermore, whereas a number of the studies examining the relationship between physical activity and fibrinolytic activity have evaluated basal measures, available evidence suggests that poststressor fibrinolytic activity, often referred to as fibrinolytic potential or capacity, may be a better measure of the fibrinolytic system.[12,13]

Much attention has also focused on the potential link between lipoprotein(a) [Lp(a)] and fibrinolysis. Lp(a), similar in composition to the low-density lipoprotein cholesterol (LDL-C) molecule but distinguished by the presence of apoprotein(a),[14] has been identified as a risk factor for CHD,[15] restenosis,[16] peripheral vascular disease,[17] and stroke.[18] One proposed mechanism explaining the link between Lp(a) and the fibrinolytic system is the homology between Lp(a) and plasminogen, the precursor to the fibrinolytic enzyme, plasmin. Because of this similarity, it is hypothesized that both molecules compete for receptor sites on fibrin and fibrinogen.[14,19] Consequently, by binding to the receptor sites, Lp(a) could prevent plasminogen from binding, thus decreasing fibrinolysis and possibly promoting thrombotic events. However, it is important to note that the existing data regarding the relationship between Lp(a) and fibrinolytic activity are controversial.[20-25]

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The purpose of this investigation was to determine the factors that affect fibrinolytic potential. The variables of primary interest were cardiovascular fitness, body composition, and lipids and lipoproteins, including Lp(a). The fibrinolytic variables measured included t-PA and PAI-1 activities in the resting (basal) state and after stimulation with maximal exercise.

SUBJECTS AND METHODS

The subjects included 46 apparently healthy white men. Habitual physical activity status ranged from sedentary to highly active. Fifteen subjects were defined as sedentary (≤ 1 day of exercise per week), 16 were noncompetitive runners who exercised a minimum of 3 days per week, and 15 were highly competitive runners. All subjects were nonsmokers and were not currently taking any medications, including aspirin and nonsteroidal antiinflammatory agents. Exclusion criteria also included the diagnosis of diabetes or triglyceride (TG) levels of 400 mg/dL or greater. All subjects volunteered to take part in the study, and written informed consent was obtained before participation. The study was approved by the University's Institutional Review Board.

All subjects underwent a maximal graded treadmill exercise test between 6:30 AM and 10:00 AM. Subjects were instructed to report to the testing session in a fasted state (12 hours), not to engage in physical activity at least 24 hours before the testing session, and to refrain from ingesting aspirin and nonsteroidal antiinflammatory drugs 14 days before the testing session. A modified Balke protocol[26] was used. Treadmill speed and grade were individualized for each subject to ensure that the duration of the test was 11 to 15 minutes, to minimize the potential effects of exercise duration on fibrinolytic variables. Oxygen consumption was continuously monitored with an automated system using an Applied Electrochemistry S-3A O_2 analyzer (Ametek, Pittsburgh, PA), an LB-2 carbon dioxide analyzer (Beckman Instruments, Irvine, CA), and a Parkinson-Cowan gasometer. Maximal oxygen consumption ($\dot{V}O_2max$) was defined as the greatest oxygen consumption observed during any full minute of the exercise test. The criteria used for attaining $\dot{V}O_2max$ included a plateau in oxygen consumption with an increasing work rate, a respiratory exchange ratio of 1.05 or greater, and/or a maximum heart rate within 5 bpm of the age-predicted maximum.

Blood Collection

Basal blood samples were obtained after 15 minutes of rest, and postexercise blood samples were collected within 1 minute of exercise termination. Blood samples were collected while subjects were in the seated position by venipuncture from an antecubital vein with little or no stasis into tubes containing 50 μL 15% K_3-EDTA as an anticoagulant. Blood from the second tube was used for t-PA and PAI-1 determinations. Anticoagulated blood was combined 2:1 with 0.5 mol · L^{-1} sodium acetate (pH 4.2) within 60 seconds of being drawn, to stabilize t-PA activity. Blood was centrifuged at 1,000 × *g* for 10 minutes, and plasma was separated and stored at −80°C until analyzed.

Blood Analyses

Hematocrit and hemoglobin. The hematocrit was measured in triplicate using the standard microhematocrit technique. Hemoglobin was assayed in duplicate using the cyanmethemoglobin method.[27] Percent changes in plasma volumes were estimated from hematocrit and hemoglobin values.[28]

t-PA activity. t-PA activity, expressed in international units (IU), was measured in triplicate by chromogenic assay under the optimum conditions described by Chandler et al.[29] Briefly, 5 μL anticoagulated, acidified plasma was added to 250 μL plasminogen-chromogenic substrate reagent consisting of 75 mmol · L^{-1} Tris-acetic acid (pH 8.15 at 37°C), 0.1% Triton X-100, 0.50 μmol · L^{-1} human glu-plasminogen (American Diagnostica Inc, Greenwich, CT), 0.65 mmol · L^{-1} S-2251 substrate (Pharmacia, Franklin, OH), and 80 μg · mL^{-1} CNBr-cleaved fibrinogen, and incubated at 37°C for 90 minutes. After incubation, the reaction was stopped by adding 25% acetic acid to the solution. Absorbance was measured at 405 nm. A standard curve made with one-chain melanoma-derived t-PA (American Diagnostica) was developed to determine t-PA activity. Results were multiplied by 1.5 to correct for acetate buffer dilution, and were also corrected for changes in plasma volume.

PAI-1 activity. PAI-1 activity, expressed in arbitrary units (AU), was measured in duplicate by chromogenic assay according to the standardized method of Chandler et al.[30] Briefly, plasma was diluted 1:2, 1:5, 1:10, and 1:20 with phosphate-buffered saline–Triton X-100 buffer containing 1 g bovine albumin and 0.6 mmol · L^{-1} sodium azide. Then, 200 μL diluted plasma was mixed with 200 μL 10-IU · mL^{-1} one-chain t-PA reagent (diluted in phosphate-buffered saline–Triton X-100 buffer) and incubated for 15 minutes at 37°C to allow t-PA and PAI-1 to react. The reaction was stopped, and any α_2-plasmin inhibitor was destroyed by adding 200 μL 0.5-mol · L^{-1} sodium acetate buffer (pH 4.2) to the solution. Residual t-PA content was measured as already described. Since plasma dilutions that inhibit less than 8% and more than 50% of the original t-PA have produced inaccurate results,[30] only dilutions that inhibited between 8% and 50% of the original t-PA were used to determine residual t-PA activity. One AU of PAI-1 activity was defined as the amount of PAI-1 that inhibited 1 IU t-PA under the specified conditions. Results were corrected for changes in plasma volume.

Samples from each subject were analyzed at one time to control for interassay variations. To determine interassay variation for the fibrinolytic variables, blood drawn from a single individual was stored in aliquots and assayed with each batch. Intraassay and interassay coefficients of variation for t-PA activity were 4.4% and 5.5%, respectively, and for PAI-1 activity 4.2% and 5.8%, respectively.

Lipids and lipoproteins. Separation of high-density lipoprotein cholesterol (HDL-C) from very–low-density lipoprotein cholesterol and LDL-C was accomplished by precipitation with manganese chloride and sodium heparin.[31] Total cholesterol (TC) and HDL-C levels were measured spectrophotometrically using a stable Liebermann-Burchard reagent.[32] TG concentration was measured enzymatically using a kit from Sigma Diagnostics (St Louis, MO). LDL-C was calculated according to the Friedewald equation.[33] Lp(a) concentrations were determined using the Macra Lp(a) enzyme immunoassay kit (Strategic Diagnostics, Newark, DE). Interassay coefficients of variation for TG, TC, and Lp(a) were 2.7%, 2.1%, and 4.6%, respectively.

Other Measures

Height, weight, and skinfold thicknesses were measured on all subjects. Body fat was determined using four sites (abdomen, ilium, tricep, and thigh) according to equations reported by Jackson and Pollock.[34] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Statistical Analysis

Descriptive statistical analyses were conducted for all variables. All variables were tested for normality using the Kolmogorov-Smirnov statistic. Variables that did not meet the assumption of

normality were analyzed with nonparametric statistics. Differences between basal and post–maximal exercise t-PA activity and PAI-1 activity were analyzed using *t* tests for paired samples or the nonparametric Wilcoxon matched-pairs signed-rank test. Pearson correlation coefficients and Spearman correlations (nonparametric) were calculated to determine if statistically significant relationships existed between the fibrinolytic variables, both basal and postexercise values, and physical fitness, body composition, lipids/lipoproteins, and Lp(a). To determine whether selected basal and postexercise correlation coefficients were statistically different, the values were converted to *z* scores and analyzed.[35] Stepwise multiple regression analyses were conducted to determine which variables were significant independent predictors of the fibrinolytic variables. Variables included in the regression models were those that showed significant Spearman or Pearson correlations, or those that would be expected to be important predictors. Thus, variables included in the analyses to predict t-PA activity included $\dot{V}O_2$max, body fat, LDL-C, and HDL-C. Variables included in the analyses to predict PAI-1 activity included $\dot{V}O_2$max, TG, and body fat. HDL-C was not included, to avoid colinearity problems due to the strong relationship with TG. Statistical significance was reached at *P* less than .05.

RESULTS

Subject characteristics are shown in Table 1. As expected, there were wide ranges in body composition and $\dot{V}O_2$max, emphasizing differences in cardiovascular fitness among the subjects. Lipid/lipoprotein and Lp(a) values are shown in Table 2. Highly skewed values were observed for Lp(a). The median value was 2.25 mg/dL. Only three subjects had an Lp(a) value of 25 mg/dL or more. Basal and postexercise results for t-PA activity and PAI-1 activity corrected for changes in plasma volume are shown in Table 3. Both variables significantly changed with maximal exercise ($P < .0001$).

Correlations

Lp(a), TG, postexercise t-PA activity, and basal and postexercise PAI-1 activities were not normally distributed, and Spearman correlation coefficients were therefore calculated for these variables. Basal PAI-1 activity was inversely related to postexercise t-PA activity ($r = -.34$, $P = .023$). Correlation coefficients between the variables of interest and basal and postexercise PAI-1 activity were similar, whereas correlation coefficients between the variables of interest and basal and postexercise t-PA activity tended to be less similar. Because previous research from our laboratory[10] demonstrated large differences in postexercise t-PA activity among men of varying habitual physical activity even when basal levels were similar, whereas significant differences in basal PAI-1 activity were detected among the groups, we have chosen to highlight the correlation results between the variables of interest and postexercise t-PA and basal PAI-1 activities.

Table 1. Subject Characteristics

Variable	Mean ± SD	Range
Age (yr)	34.1 ± 4.0	26-43
Height (in)	71.0 ± 3.0	61-76
Weight (kg)	81.7 ± 13.1	56.6-107.7
BMI (kg/m^2)	25.1 ± 3.5	19.7-34.3
Body fat (%)	17.2 ± 6.6	4.3-28.6
$\dot{V}O_2$max (mL/kg/min)	49.7 ± 10.9	27.3-70.7

Table 2. Lipid and Lipoprotein Concentrations

Variable (mg/dL)	Mean ± SD	Range
TC	170.1 ± 36.3	109-258
HDL-C	47.6 ± 13.0	25-88
LDL-C	102.0 ± 34.7	48-186
TG	102.5 ± 66.7	38-353
Lp(a)	8.6 ± 10.6	0-38

Cardiovascular fitness (determined by $\dot{V}O_2$max). $\dot{V}O_2$max was positively correlated with t-PA activity, both basal ($r = .39$, $P = .008$) and postexercise ($r = .67$, $P = .0001$) values. The statistical analysis to determine whether these two correlation coefficients were different did not reach significance ($P = .07$). $\dot{V}O_2$max was inversely related to PAI-1 activity (basal, $r = -.41$, $P = .005$; postexercise, $r = -.42$, $P = .003$). Relationships between $\dot{V}O_2$max and the fibrinolytic variables, postexercise t-PA activity and basal PAI-1 activity, are shown in Fig 1.

Body composition. Graphic representations of the relationships between body composition and fibrinolytic potential are shown in Fig 2. There were significant correlations between body fat percentage and postexercise t-PA activity ($r = -.60$, $P = .0001$) and basal and postexercise PAI-1 activity ($r = .42$, $P = .005$). The correlation between body fat and basal t-PA activity approached but did not reach statistical significance ($r = -.29$, $P = .058$). BMI was not significantly correlated with either fibrinolytic variable.

Lipids/lipoproteins. Correlations between lipids/lipoproteins and fibrinolytic potential are shown in Fig 3. Postexercise t-PA activity was positively correlated with HDL-C ($r = .37$, $P = .012$) and negatively correlated with LDL-C ($r = -.42$, $P = .004$). The correlation between basal t-PA and LDL-C did not reach statistical significance ($r = -.28$, $P = .061$). PAI-1 activity was negatively correlated with HDL-C ($r = -.37$, $P = .011$), but was not correlated with TG ($r = .13$, $P = .406$). Again, similar correlation coefficients were observed for both basal and postexercise PAI-1 activities.

Lp(a). Lp(a) was not significantly correlated with any fibrinolytic variable or any other variable. As expected, $\dot{V}O_2$max was significantly correlated with other lipoproteins (HDL-C, $r = .71$, $P = .0001$; LDL-C, $r = -.47$, $P = .001$; TC, $r = -.36$, $P = .014$; and TG, $r = -.41$, $P = .005$), but not with Lp(a) ($r = .16$, $P = .337$).

Multiple Regressions

Predictors of t-PA activity. Of the variables included in the stepwise multiple regression analysis for t-PA activity,

Table 3. Fibrinolytic Variables: Basal and Postmaximal Exercise

Variable	Basal	Postexercise
t-PA activity (IU/mL)	4.1 ± 2.2	13.0 ± 9.4*
PAI-1 activity (AU/mL)	17.7 ± 10.6	12.1 ± 11.2*

NOTE. Values are the mean ± SD.
*Significantly different from basal value ($P < .0001$).

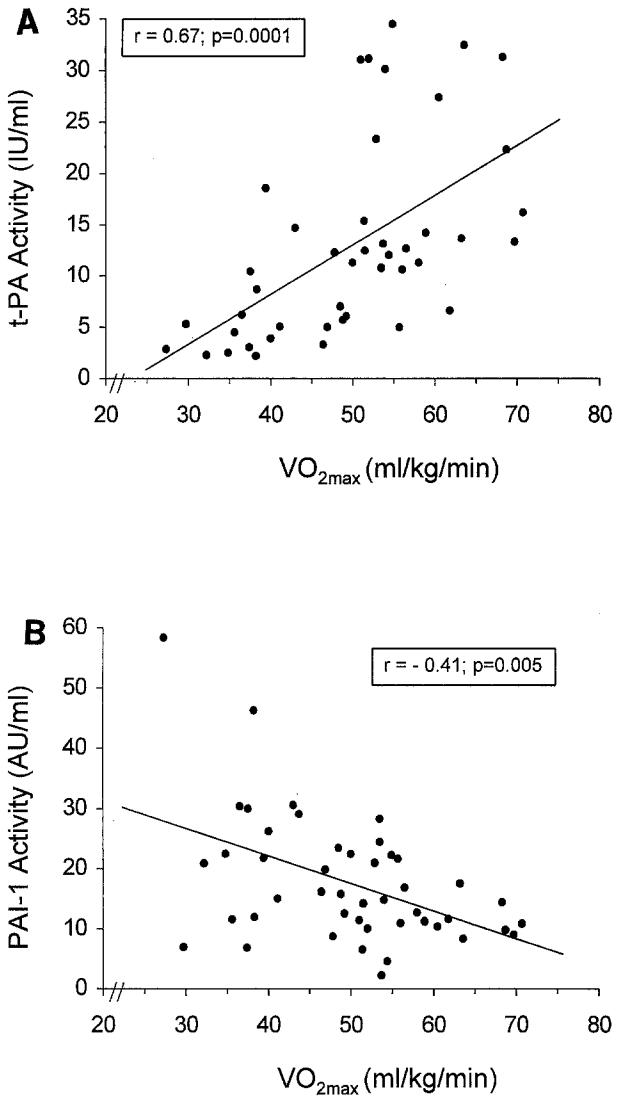

Fig 1. Scatterplots depicting relationships between cardiovascular fitness ($\dot{V}O_2$max) and fibrinolytic potential. (A) Relationship between $\dot{V}O_2$max and postexercise t-PA activity. (B) Relationship between $\dot{V}O_2$max and basal PAI-1 activity.

$\dot{V}O_2$max, body fat, HDL-C, and LDL-C, $\dot{V}O_2$max was the only variable that independently predicted basal t-PA activity ($R^2 = .16$, $P = .008$). In other words, 16% of the variance in basal t-PA activity could be explained by the positive relationship with $\dot{V}O_2$max. $\dot{V}O_2$max was also the only variable that was a significant predictor of postexercise t-PA activity ($R^2 = .34$, $P < .0001$). Thus, an even greater percentage of the variance in postexercise t-PA activity, 34%, could be explained by $\dot{V}O_2$max.

Predictors of PAI-1 activity. Of the variables included in the stepwise multiple regression analysis for PAI-1 activity, $\dot{V}O_2$max, TG, and body fat, TG and $\dot{V}O_2$max were significant independent predictors of basal PAI-1 ($R^2 = .31$, $P = .0005$). The results for postexercise PAI-1 activity indicate that $\dot{V}O_2$max was the only significant predictor ($R^2 = .23$, $P = .0009$).

DISCUSSION

The major finding of this investigation is the strong independent association between cardiovascular fitness and fibrinolytic potential. Both fibrinolytic variables exhibited significant correlations with $\dot{V}O_2$max. Positive relationships were present between $\dot{V}O_2$max and basal ($r = .39$) and postexercise ($r = .60$) t-PA activity. Furthermore, these significant relationships were maintained with multiple regression analysis, suggesting independent relationships. On the other hand, there was a significant negative correlation between $\dot{V}O_2$max and PAI-1 activity that was similar for basal and postexercise values ($r = -.41$ and $-.42$). This was not surprising, considering that differences in PAI-1 activity among individuals of varying fitness levels have been shown to be evident when examining basal levels.[9,10] This association between cardiovascular fitness and PAI-1 activity also maintained its significance with multiple regression analysis, suggesting an independent relationship.

Fibrinolytic activity appears to be related to a number of

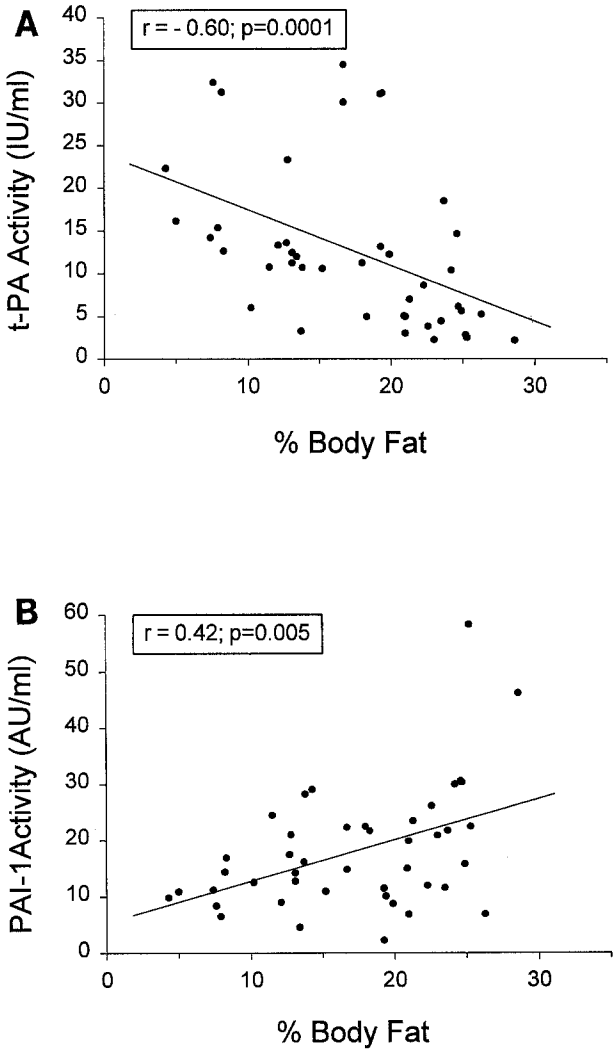

Fig 2. Scatterplots depicting relationships between body composition and fibrinolytic potential. (A) Percent body fat *v* postexercise t-PA activity. (B) Percent body fat *v* basal PAI-1 activity.

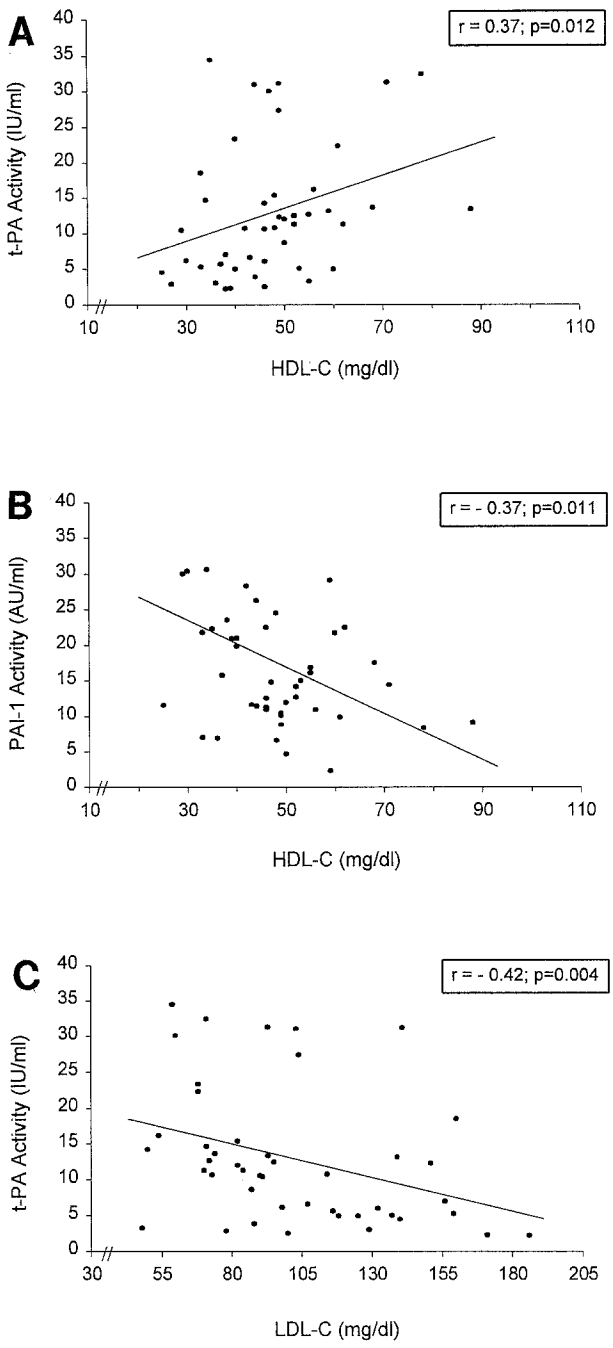

Fig 3. Scatterplots depicting relationships between various lipid measures and fibrinolytic potential (A) HDL-C *v* postexercise t-PA activity. (B) HDL-C *v* basal PAI-1 activity. (C) LDL-C *v* postexercise t-PA activity.

body composition measures. In the present study, we report significant correlations between body fat percentage and the fibrinolytic variables. Percent body fat was negatively correlated with postexercise t-PA activity ($r = -.60$) and positively correlated with PAI-1 activity ($r = .42$). Thus, the higher the body fat, the lower the fibrinolytic potential. This is in agreement with the research by Sundell et al,[20] who observed positive correlations between skinfold thicknesses, a measure of body fat, and both PAI-1 activity ($r = .27$) and t-PA antigen ($r = .32$). Although we did not find a significant correlation between BMI and PAI-1 activity, several other investigations have reported significant relationships.[20,21,36,37] This lack of a correlation between PAI-1 activity and BMI in the present study may be because two thirds of our subjects were runners with lower relative amounts of body fat. Thus, body fat percentage is a more accurate measure of body composition in these subjects, and stronger correlations would be expected with body fat compared with BMI. Additional evidence linking fibrinolytic activity to body composition includes observations of a positive correlation between the waist to hip ratio, another important body composition measure that has been linked to CHD risk, and PAI-1 activity.[20,38] Furthermore, cross-sectional analyses have found higher PAI-1 activity in obese versus non-obese women.[36] Finally, weight reduction appears to decrease PAI-1 activity and antigen levels.[39,40] Consequently, these results have led researchers to hypothesize that impaired fibrinolytic activity may be an important mechanism mediating the increased CHD risk observed in obese individuals.

Our results also indicate relationships between lipids and lipoproteins and fibrinolytic potential. Although Spearman correlations between TG level and PAI-1 activity were not statistically significant, results from the multiple regression analysis indicated that TG concentration was a significant independent predictor of PAI-1 activity, which has been previously documented.[36,38,41] Associations between TG and PAI-1 have been reported in population studies,[20] in patients with CHD,[1,42] and in patients with hypertriglyceridemia.[43] Postexercise t-PA activity was positively correlated with the cardioprotective HDL-C ($r = .37$) and negatively correlated with the atherogenic LDL-C ($r = -.42$). These lipoproteins were not significantly correlated with basal t-PA activity. Additionally, PAI-1 activity was negatively related to HDL-C ($r = -.37$). Glueck et al[21] have also reported significant correlations between lipids and fibrinolytic variables. Basal levels of t-PA were positively associated with HDL-C ($r = .19$) and negatively associated with TG ($r = -.26$), whereas PAI-1 activity was significantly correlated with TG ($r = .43$), HDL-C ($r = -.31$), and TC ($r = .19$). Sundell et al[20] also reported a significant relationship between HDL-C and PAI-1 ($r = -.27$).

Since Lp(a) has been designated a risk factor for CHD, much interest has focused on its relationship to fibrinolysis and potential factors that may affect Lp(a) levels such as cardiovascular fitness. Because of its homology with plasminogen and its potential link with fibrinolysis, it has been hypothesized that Lp(a) may represent the "bridge" between atherosclerosis and thrombosis.[44] However, although its homology with plasminogen is thought to be an important link, studies examining the effects of Lp(a) on fibrinolytic activity have provided inconsistent results. In vitro studies[22,23] suggest that Lp(a) competes with plasminogen for fibrin binding sites, inhibiting the activation of plasminogen by t-PA and possibly leading to a decrease in fibrinolysis. However, in agreement with the results from the present study, other in vivo studies have not found significant correlations between Lp(a) and fibrinolytic vari-

ables.[20,21,24,25,41] Szczeklik et al[24] have compared fibrinolytic activity after venous occlusion in healthy male subjects with low (<5 mg/dL) and high (>30 mg/dL) Lp(a) levels and reported no differences in fibrinolytic parameters between the two groups. Similar to the present study, Glueck et al[21] have also examined relationships between Lp(a) and fibrinolytic variables, both basal and stimulated (post–venous occlusion) levels, and reported no significant correlations.

Although these inconclusive results regarding Lp(a) and fibrinolytic activity are difficult to explain, some investigators hypothesize that the observed inconsistencies among existing studies could be attributed to differences in functionality of the various Lp(a) isoforms.[22] However, subsequent research[45] has found no differences in fibrinolytic activity between the different apoprotein(a) isoforms in subjects with elevated Lp(a). Thus, firm conclusions regarding the relationship between Lp(a) and fibrinolytic activity cannot yet be made.

Because physical activity and cardiovascular fitness have been strongly linked to beneficial changes in other lipids and lipoproteins,[46] it seems plausible to examine their effects on Lp(a). However, the available data on the effects of cardiovascular fitness or physical activity on Lp(a) concentrations are inconclusive, with preliminary data primarily indicating little or no effect. Similar to the results from the present study, a cross-sectional study by Israel et al[47] showed no associations between Lp(a) and body composition, fat distribution, or cardiovascular fitness in healthy men and women. Similarly, Hubinger et al[48] found no differences in Lp(a) concentrations between male runners and inactive control subjects, even though the expected differences in other lipoproteins were present. Longitudinal data have also suggested that increases in fitness do not produce significant changes in Lp(a).[49] Thus, it appears that Lp(a) is determined primarily by genetic rather than life-style factors; however, more research is needed.

One reason we did not find any significant relationships between Lp(a) and fibrinolytic activity or cardiovascular fitness may be that the Lp(a) values in our subjects were highly skewed toward low concentrations, which is similar to findings by others.[47,48,50,51] According to Genest et al,[51] CHD risk increases when Lp(a) values exceed 25 mg/dL. In the present study, only three subjects had Lp(a) values of 25 mg/dL or greater. Consequently, perhaps findings would differ in a population with higher Lp(a) values. However, Glueck et al[21,41] and Szczeklik et al[24] did not observe relationships between fibrinolytic activity and Lp(a) in subjects with elevated Lp(a) concentrations.

In conclusion, the unique aspects of this study are the inclusion of cardiovascular fitness as a potential factor affecting fibrinolytic potential, as well as the post–maximal exercise measures of the fibrinolytic variables. A strong independent relationship between cardiovascular fitness and fibrinolytic potential was observed. This relationship may be an important mechanism mediating the documented cardioprotective effect of regular physical activity and fitness.[52] These data also provide more support for using post-stressor measures of fibrinolytic variables to evaluate the fibrinolytic system, rather than examining basal values only. Although several variables were not significantly correlated with basal t-PA activity, the correlations became significant after providing a fibrinolytic stressor (ie, maximal exercise). Additionally, even though $\dot{V}O_2max$ was a significant predictor of both basal and postexercise t-PA activity, R^2 was greater for postexercise t-PA activity. It is possible that previous studies that have reported no association between physical activity status and fibrinolytic activity[53,54] would have found relationships if post-stressor activity was evaluated. Finally, these results provide more evidence that Lp(a) is not related to fibrinolytic potential or cardiovascular fitness.

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