Blood Fibrinolytic Activity in Man

DIURNAL VARIATION AND THE RESPONSE TO VARYING INTENSITIES OF EXERCISE

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ABSTRACT

This investigation was undertaken in normal subjects to define the relationship between the intensity of exercise and magnitude of fibrinolytic response and to examine the effect of diurnal variations on the exercise response. Fibrinolytic activity was measured on fibrin plates and expressed as mm². Diurnal variations occurred with lowest activity at 8:00 AM (mean, 66 mm²), and peak activity between 5:00 and 8:00 PM (mean, 266 mm², \( P < 0.001 \)). Five minutes of maximal treadmill exercise caused a marked increase in mean activity from 90 to 658 mm² (\( P < 0.001 \)). Five minutes of 70% maximal exercise produced no significant increase, but 30 minutes increased activity to 626 mm² (\( P < 0.005 \)). In contrast, 30 minutes of 40% maximal exercise produced a small elevation from 80 to 173 mm² (\( P < 0.005 \)).

Maximal and 40% maximal exercise evoked greater responses at 4:00 PM than at 8:00 AM. Exercise produces increases in fibrinolytic activity which are related to the relative intensity of exercise, its duration, and the time of day it is performed. Short bursts of intense exercise cause marked increases, but more prolonged bouts of moderate exercise are required to produce similar increases. The increases with prolonged mild exercise are small and comparable to those observed during resting diurnal variations.

ADDITIONAL KEY WORDS: plasminogen activators, oxygen uptake, maximal exercise, fibrinolytic inhibitors

Although various investigators (1-7) have confirmed the observation by Biggs et al. (8) that fibrinolytic activity in human blood increases in response to exercise, anxiety, and several other forms of stress, the responsiveness of the fibrinolytic system in blood to normal physiologic stress is still incompletely understood. In particular, the relationship between intensity of exercise and magnitude of fibrinolytic response (8a), and the possible effects of diurnal variation in fibrinolytic activity (9) on exercise-induced fibrinolysis, need to be clarified. Such relationships may be relevant to the recent observation that certain subjects manifest a reduction or absence of the fibrinolytic response to exercise (3-5). As a result of these considerations, and because of the role attributed to the fibrinolytic system in the regulation of tissue repair as well as its possible involvement in the pathogenesis of arteriosclerosis (10-12), the present investigation was undertaken: (1) to define the relationship between intensity of exercise and magnitude of the fibrinolytic response in normal subjects, and (2) to define the diurnal pattern of blood fibrinolytic activity and to determine whether or not such a pattern...
influences the responsiveness of the fibrinolytic system to exercise.

Methods

Seventeen normal subjects, 19 to 30 years of age, were initially selected for the study. After preliminary screening, three subjects were excluded: one because of inability to comply with the protocol; another because we could not determine the subject's maximal exercise level; and the third because of a high plasma level of inhibitors to tissue plasminogen activator. Of the 14 subjects included in this report, 12 were males and 2 females. All were in good physical condition, but none was a trained athlete. Studies were begun at 8:00 AM after a minimum of 8-hours bed rest, and with the subjects in the fasting state.

EXPERIMENTAL STUDIES

Diurnal Variation.—Blood samples were drawn serially, beginning at 8:00 AM, for periods lasting 7 to 24 hours. All subjects remained in bed; the nine subjects who participated in the 24-hour studies received regular meals, while the five in the shorter investigations fasted. In most studies blood samples were taken every 2 to 3 hours. To evaluate the influences of repeated venipunctures and awakening on fibrinolytic activity, studies were repeated in five of the subjects with sampling frequency reduced to every 12 hours.

Exercise.—After a subject had practiced running on a treadmill for several days, the intensity of exercise was determined which consistently produced exhaustion after 5 minutes. This intensity of exercise will be referred to as "maximal exercise" and was found to vary considerably between subjects. Oxygen uptake (\( V_{O_2} \)) was recorded during exercise using a continuous-flow system (12). In each subject \( V_{O_2} \) at maximal exercise was equivalent to the maximal \( V_{O_2} \) as conventionally determined (14). Once the maximal level of exercise and maximal \( V_{O_2} \) were defined, we determined levels of exercise that resulted in a \( V_{O_2} \) of 40% and 70% of that achieved during maximal exercise. These levels will subsequently be termed "40% maximal" and "70% maximal." The effects of 40% and 70% maximal exercise on fibrinolytic activity were also assessed, with the subjects again resting 1 hour between each bout of exercise. All blood samples were obtained within 30 seconds of the cessation of exercise.

Combination of Exercise and Diurnal Variation.—To determine if the diurnal variation influenced the fibrinolytic response to exercise, in two of the subjects identical exercise was performed on one day at 8:00 AM and on another day at 4:00 PM. On the day they exercised at 4:00 PM, the subjects remained at bed rest until the beginning of the study.

Blood Aways.—Blood samples were obtained from an antecubital vein in such a manner that blood flowed freely from an 18-gauge needle into a chilled glass centrifuge tube containing 3.2% trisodium citrate dihydrate (one part citrate; nine parts blood). In three individuals simultaneous arterial and venous samples were obtained at rest and after maximal exercise; brachial arterial blood was withdrawn through an indwelling, 4-inch, 18-gauge siliconized Teflon catheter while venous samples were obtained from an antecubital vein in two of the subjects and from a catheter in the pulmonary artery in the third. Samples were refrigerated and brought to the laboratory in an ice-cooled container. Platelet-poor plasma, prepared in a refrigerated centrifuge and kept in small aliquots at −20°C, was used for the assays. Immediate freezing of the platelet-poor plasma prevents the loss of fibrinolytic activity, which occurs during storage in the refrigerator (unpublished observation).

The fibrinolytic activity was assayed by the Astrup fibrin plate method (15). Fibrin plates were prepared with ammonium sulfate precipitated bovine fibrinogen (0.1%) clotted with bovine thrombin (Leo Pharmaceuticals, Copenhagen). Plasma fibrinolytic activity was measured in an euglobulin fraction isoelectrically precipitated at pH 5.9 from 1-ml plasma diluted to 10 ml with cold distilled water. Addition of acetic acid (0.25% solution) was by an automatic titrator (Radiometer, Copenhagen). Precipitation of euglobulins at pH 5.9 gives optimal recovery of fibrinolytic activity (16); an observation confirmed in the present study for plasma obtained immediately after exercise. The separated euglobulin precipitate was dissolved to the original plasma volume in saline barbitur buffer containing 1 g EDTA and 2.5 g gelatin/liter. The reconstituted solution was applied to normal fibrin plates, which were incubated for 17 hours at 37°C. Fibrinolytic activity was expressed as the diameter product in square millimeters of the lysed zone, each being the mean of a triple determination.

Plasminogen was assayed after treatment of plasma with acetone to remove inhibitors followed by activation of plasminogen with 2 Ploug

1Ploug unit is approximately 1.34 C.T.A. units as established by the Committee on Thrombolytic Agents of the National Heart and Lung Institute.
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units/ml of human urine activator (urokinase, Leo Pharmaceuticals) (15). After activation plasma samples were serially diluted and assayed on fibrin plates prepared with plasminogen-free fibrinogen. Results were expressed as concentrations in percents of a pooled control plasma simultaneously assayed.

Fibrinogen was estimated by a modified Ratnoff and Menzie method (17, 18) and reported in milligrams per 100 ml plasma as the mean of two determinations.

Screening of inhibition of tissue plasminogen activator, urokinase, and plasmin was performed as previously described (19) by determining the fibrinolytic activity of serially diluted plasma samples mixed with an equal volume of active compound. To avoid total inhibition by undiluted plasma, higher concentrations of active compounds than previously employed were used: (1) porcine tissue activator, 50 A and A units/ml, product I (20); (2) urokinase (Leo Pharmaceuticals, 24 Ploug units/ml); and (3) human plasmin (Michigan Department of Health, 8 MDH units/ml). Regular plasminogen-rich fibrin plates were used but incubation was for only 6 hours (21).

The statistical significance of differences was evaluated by Student's t-test for paired data. Correlation analysis was used to compare fibrinolytic activity with VO2 and resting fibrinolytic activity with increments and absolute levels of activity achieved during diurnal variations and exercise. Linear regression analysis was used to compare fibrinolytic activity and exercise duration and intensity.

The use of linear regression analysis represents only a technique of internal statistical comparison, which is justified by the empirically observed linearity of the data. This does not imply or require that measured fibrinolytic activity bears a linear relationship to concentrations of plasminogen activator or to in-vivo thrombolysis.

Results

DIURNAL VARIATION IN FIBRINOLYTIC ACTIVITY

Bed Rest, Fasting.—A progressive increase in fibrinolytic activity occurred during the course of the day in each of the five subjects studied at bed rest while fasting (Fig. 1). Fibrinolytic activity increased from a mean of 92 mm² at 8:00 AM to a mean of 255 mm² at 3:00 PM (SEMD = ±24, P < 0.005).

Bed Rest, Eating.—A similar increase in fibrinolytic activity occurred during the course of the day in each of nine subjects studied at bed rest but eating regular meals (Fig. 2). Activity increased from a mean of 66 mm² at 8:00 AM to a peak averaging 266 mm² reached between 5:00 and 8:00 PM (SEMD = ±18, P < 0.001). Although fibrinolytic activity decreased after the peak was attained, at the conclusion of the 24-hour study it had not returned to values comparable to those at the beginning of the study.

To determine whether or not the stresses of repeated venipunctures and of awakening subjects in the middle of the night contributed to these diurnal changes, five of the subjects repeated the studies during which fewer samples were taken and the subjects were not awakened (Table 1). Although significant increases in fibrinolytic activity occurred (from a mean of 117 mm² at 8:00 AM to a mean of 244 mm² at 8:00 PM, SEMD = ±24, P < 0.01), the increases were smaller than those obtained during studies with more frequent sampling. In addition, fibrinolytic activity of the 24-hour samples returned to a mean of 124 mm² at 8:00 AM (SEMD = ±24, NS).

EFFECT OF EXERCISE ON FIBRINOLYTIC ACTIVITY

Maximal Exercise.—A typical response to maximal exercise is depicted in Figure 3. Marked elevation of fibrinolytic activity was
seen after 5 minutes of exercise. Similar levels of fibrinolytic activity were found in simultaneously obtained samples of venous and arterial blood in this individual and also in the two other subjects studied in this manner (Table 2), suggesting that after exercise arterial-venous differences in fibrinolytic activity do not occur. The heart rate, $V_{O_2}$, and fibrinolytic responses to 5 minutes of maximal treadmill exercise in each of 10 subjects studied are shown in Figure 4 and Table 3. Fibrinolytic activity increased from a control mean of 90 mm$^2$ to 658 mm$^2$ at the conclusion of exercise (mean $\pm$ SEM, 23, $P < 0.001$). In all subjects the activity returned to resting levels within 60 minutes of the termination of exercise.

The fibrinolytic response to successive 5-minute bouts of maximal exercise in each of the four subjects studied is illustrated in Figure 5. The second bout of exercise evoked less of a response than the first bout. Two subjects performed four serial bouts of exercise each. Although fibrinolytic activity increased to a greater extent during the third and fourth bouts than it did during the second, the increases still did not equal that observed during the initial exercise.

70% Maximal Exercise.—Table 3 and Figure 6 show the heart rate, $V_{O_2}$, and fibrinolytic responses to 30 minutes of 70% maximal exercise in each of the five subjects studied. This level of exercise required subjects to jog at a rate of 4.4 to 7 mph and resulted in an average peak heart rate of 176 (range 160 to 198) beats/min. Five minutes of jogging produced a small and statistically insignificant increase in fibrinolytic activity.
from a mean of 129 mm$^2$ to 206 mm$^2$ ($\text{SEM} = \pm 48$, NS). However, 15 minutes of exercise increased the response to a mean of 421 mm$^2$ ($\text{SEM} = \pm 44$, $P < 0.005$), and 30 minutes increased it to 626 mm$^2$ ($\text{SEM} = \pm 62$, $P < 0.005$).

40% Maximal Exercise—The heart rate, $V_{O_2}$, and fibrinolytic responses to 30 minutes of 40% maximal exercise in each of the eight subjects studied is shown in Figure 7 and Table 3. This level of exercise required most subjects to walk briskly and resulted in an average peak heart rate of 131 (range 110 to 160) beats/min. Fibrinolytic activity increased only minimally during the first 15 minutes of exercise from a mean of 80 mm$^2$ to 144 mm$^2$ ($\text{SEM} = \pm 12$, $P < 0.005$). Moreover, 30 minutes of brisk walking covering a distance of 1.8 to 2.6 miles increased the mean fibrinolytic activity to only 173 mm$^2$ ($\text{SEM} = \pm 19$, $P < 0.005$).

Relationship of Fibrinolytic Activity to $V_{O_2}$—The correlation coefficients for the fibrinolytic response to the absolute intensity of exercise (expressed as $V_{O_2}$ in ml·min$^{-1}$·kg$^{-1}$), and for the fibrinolytic response to the relative intensity of exercise (expressed as $V_{O_2}$ divided by the individual's maximal $V_{O_2}$) were calculated. A higher correlation was found when fibrinolytic activity was related to relative intensity of exercise ($r = 0.91$) than to absolute intensity ($r = 0.71$).

RELATION OF EXERCISE AND DIURNAL FIBRINOLYTIC RESPONSES TO RESTING FIBRINOLYTIC ACTIVITY

An attempt was made to determine if resting levels of fibrinolytic activity influenced the increments and absolute levels of fibrinolytic activity achieved during diurnal variations and during the varying intensities of exercise. None of the correlation coefficients achieved statistical significance except when resting activity was compared to peak fibrinolytic activity after 40% maximal exercise ($r = 0.87$).

CONTRIBUTION OF DIURNAL VARIATION TO THE FIBRINOLYTIC RESPONSE TO EXERCISE

In the two subjects studied, higher levels of fibrinolytic activity were attained immediately after 5 minutes of maximal exercise performed...
at 4:00 PM compared to 8:00 AM (Fig. 8). Similar results were demonstrated when 30 minutes of 40% maximal exercise performed at 4:00 PM was compared to the same exercise performed at 8:00 AM (Fig. 8).

**Table 2**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sample</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
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<td>E.D.</td>
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<td>134</td>
<td>656</td>
</tr>
<tr>
<td></td>
<td>Venous</td>
<td>102</td>
<td>543</td>
</tr>
<tr>
<td>P.F.</td>
<td>Arterial</td>
<td>240</td>
<td>427*</td>
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<tr>
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<td>Venous</td>
<td>191</td>
<td>400*</td>
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<tr>
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<td>90</td>
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<tr>
<td></td>
<td>Venous</td>
<td>119</td>
<td>788</td>
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**Discussion**

Many previous studies have shown that fibrinolytic activity in blood increases in response to exercise (1-8), a change that appears to be caused by an increase in plasminogen activators (1-3). In addition,
several of these reports have emphasized that the magnitude of the fibrinolytic response varies considerably between subjects (1-4, 8). It also has been suggested that the fibrinolytic system of a certain proportion of an otherwise normal population responds inadequately to exercise (3-5). These assertions are difficult to evaluate, however, since all previous studies but one (of) have used either nonstandardized levels of exercise or a level of stress that was the same for each subject. The present investigation demonstrates that the magnitude of the fibrinolytic response to exercise depends on the intensity of exercise and the duration of time it is performed. Moreover, several observations suggest that it is not the absolute intensity of exercise that determines the magnitude of the fibrinolytic response but rather the intensity of exercise relative to the subject's maximal exercise capacity.

Running at 5 mph at a 5% grade was a maximal effort for G.M., and exercising for 5 minutes at this intensity caused an activity of 700 mm². When R.T. exercised at this same level, however, no increase occurred in fibrinolytic activity after 5 minutes, and after 30 minutes lytic activity had risen to only 125 mm². If only absolute levels of exercise were utilized to evaluate the fibrinolytic response without regard to the individuals' maximal capacity to exercise, R.T.'s response might have been considered inadequate. This intensity of exercise, however, produced a VO₂ of only 40% of R.T.'s maximal VO₂; in contrast, his
maximal effort caused lytic activity to increase to 615 mm$^2$. Further evidence emphasizing the importance of maximal exercise capacity in assessing adequacy of the fibrinolytic response was inadvertently obtained when one individual was exercised repeatedly over several weeks. When he was initially tested, maximal exercise produced a large increase in fibrinolytic activity (from 91 to 672 mm$^2$). Retesting after several weeks of daily exercise demonstrated that the same level of exercise resulted in an activity of only 269 mm$^2$. Additional testing revealed that the repeated daily bouts of exercise had exerted a conditioning effect and increased the subject's maximal exercise capacity. Exercise at his new maximal level was again associated with a large increase in fibrinolytic activity (from 95 to 683 mm$^2$).

The hypothesis that the magnitude of the fibrinolytic response is determined by the intensity of exercise relative to each subject's maximal effort is also supported by the finding that fibrinolytic activity is more highly correlated to $V_o_2$ expressed as a function of maximal $V_o_2$ than to the absolute level of $V_o_2$.

The importance of the relative intensity and the duration of exercise on the magnitude of the fibrinolytic response to exercise is seen in Figure 9. After 5 minutes of exertion, fibrinolytic activity is significantly higher during maximal exercise than during 70% maximal, and significantly higher during 70% maximal than 40%. Although fibrinolytic activity in-
Fibrinolytic Responses to Varying Levels of Exercise

<table>
<thead>
<tr>
<th>Subject (gender)</th>
<th>% figurine (kg • m • s^{-1})</th>
<th>Exercise level</th>
<th>Peak HR (bpm/min)</th>
<th>Fibrinolytic activity (30 min)</th>
<th>Exercise level</th>
<th>Peak HR (bpm/min)</th>
<th>Fibrinolytic activity (30 min)</th>
<th>Exercise level</th>
<th>Peak HR (bpm/min)</th>
<th>Fibrinolytic activity (30 min)</th>
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<td>H.B. (19/M)</td>
<td>56.5</td>
<td>8 mph</td>
<td>210</td>
<td>568</td>
<td>4.0</td>
<td>160</td>
<td>85</td>
<td>391</td>
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<tr>
<td>E.D. (20/M)</td>
<td>50.4</td>
<td>6 mph</td>
<td>185</td>
<td>543</td>
<td>6 mph</td>
<td>180</td>
<td>401</td>
<td>6 mph</td>
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<tr>
<td>C.G. (20/M)</td>
<td>49.7</td>
<td>5 mph</td>
<td>175</td>
<td>693</td>
<td>0%</td>
<td>160</td>
<td>401</td>
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<tr>
<td>M.J. (20/M)</td>
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<td>5%</td>
<td>220</td>
<td>0%</td>
<td>3.5 mph</td>
<td>110</td>
<td>0%</td>
<td>25 mph</td>
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<td>T.L. (35/M)</td>
<td>50.2</td>
<td>10 mph</td>
<td>185</td>
<td>0%</td>
<td>4.4 mph</td>
<td>125</td>
<td>0%</td>
<td>125 mph</td>
<td></td>
<td></td>
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<tr>
<td>G.M. (20/F)</td>
<td>33</td>
<td>5%</td>
<td>185</td>
<td>780</td>
<td>5%</td>
<td>174</td>
<td>552</td>
<td>3.5 mph</td>
<td></td>
<td></td>
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<tr>
<td>B.M. (20/M)</td>
<td>52.1</td>
<td>10%</td>
<td>190</td>
<td>766</td>
<td>0%</td>
<td>129</td>
<td>163</td>
<td>240 mph</td>
<td></td>
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<tr>
<td>P.R. (20/M)</td>
<td>44.5</td>
<td>8%</td>
<td>187</td>
<td>742</td>
<td>0%</td>
<td>135</td>
<td>294</td>
<td>&gt;300 mph</td>
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<td></td>
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<tr>
<td>B.S. (19/M)</td>
<td>54.6</td>
<td>5%</td>
<td>200</td>
<td>0%</td>
<td>4.5 mph</td>
<td>125</td>
<td>0%</td>
<td>25 mph</td>
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<td>R.T. (19/M)</td>
<td>51.1</td>
<td>15%</td>
<td>185</td>
<td>615</td>
<td>5.2 mph</td>
<td>129</td>
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<td>D.W. (20/M)</td>
<td>41.2</td>
<td>7 mph</td>
<td>200</td>
<td>&gt;450 mph</td>
<td>7.6%</td>
<td>174</td>
<td>774</td>
<td>0%</td>
<td></td>
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</tr>
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</table>

Table 3

Abbreviations: HR = heart rate; M = male; F = female.

*Subjects who had only diurnal studies performed are not included in this table. 1Percent of incline. 1Peak exercise sample was collected. The sample taken 30 minutes after exercise  = 618 mni; ly. Diurnal study was terminated at 1 rpm. Diurnal study was terminated at 3 rpm.
FIGURE 6

Effect of 70% maximal exercise on fibrinolytic activity in five subjects.

FIGURE 7

Effect of 40% maximal exercise on fibrinolytic activity in eight subjects.

* Circulation Research, Vol. XXVII, August 1970
creases progressively as the moderate intensity of exercise continues, it requires 30 minutes to decrease to levels that are comparable to those achieved during 5 minutes of exhausting exercise. Fibrinolytic activity also increases with time during the mildest level of exercise, but the increase is so small that after 30 minutes it does not exceed the peak diurnal levels attained while subjects are at bed rest (Fig. 9). In contrast, peak fibrinolytic activity and increases in activity occurring at 70% of maximal and at maximal exercise bear no relationship to resting levels of fibrinolytic activity. The diurnal fluctuation in fibrinolytic activity first observed by Fearnley and co-workers (9) led us to evaluate the fibrinolytic response to exercise performed at different times of the day. When maximal and 40% maximal exercise were performed by the same individual at both 8:00 AM (low fibrinolytic activity at rest) and 4:00 PM (maximum or near maximum fibrinolytic activity at rest), the increase in fibrinolytic activity was appreciably greater at 4:00 PM. Thus, the fibrinolytic response to exercise depends not only on the relative intensity and duration of exercise, but also on the time of day the exercise is performed. Alterations in response of the fibrinolytic system to repeated bouts of maximal exercise may also influence interpretation of studies in which the fibrinolytic response to exercise is evaluated. Thus, the fibrinolytic response to a second bout of maximal exercise was reduced in comparison to the initial response. During third and fourth bouts of maximal exercise performed by two subjects, fibrinolytic activity increased to a greater extent than it did during the second bout of exercise, but the increment was still less than that attained initially. The effects of mental stress on fibrinolytic activity are well-known (2, 22). Since experimental interventions often evoke an emotional response from the subject, it is important to consider the possibility that the experimental intervention itself might significantly influence fibrinolytic activity, especially when relatively small changes are being evaluated. For example, although the diurnal variation meas-
Summary of the effects of varying intensities of exercise and diurnal variation on fibrinolytic activity. The broken lines are regression lines showing the mean group response to each intensity of exercise performed at 8:00 AM. The solid lines denote 95% confidence bands. The "peak diurnal" line represents the mean peak level of fibrinolytic activity attained during the diurnal studies.

The results of the present investigation, in which all subjects accepted for study responded in a similar and consistent manner when the fibrinolytic response was related to the relative intensity of exercise, to the duration of exercise, and to the time of day it was performed, explain to a large extent the variations of the fibrinolytic response reported by other workers. Inconsistent responses were observed, however, in a 20-year-old man previously excluded from the study because markedly elevated levels of inhibitors of tissue plasminogen activator were found during routine screening studies. Maximal exercise performed at 8:00 AM produced no increase in fibrinolytic activity, but the same exercise repeated at 4:00 PM on a different day provoked an increase to 820 mm$^2$. Consistently high levels of inhibitors of tissue activator were demonstrated on five different days; unfortunately, the diurnal pattern of the inhibitors was not assessed and their presence was not evaluated on the day the subject did demonstrate a marked increase in fibrinolytic activity in response to maximal exercise. The subject's physical examination and laboratory data were normal except for the presence of exogenous obesity (87 kg, 168 cm). It would
thus appear that this subject represents an individual whose fibrinolytic system does not consistently respond to the stimulus of maximal exercise. Because of the previously mentioned uncertainties relating to the concept of the "nonresponder," we suggest that this term be reserved solely for those in whom an augmentation in fibrinolytic activity does not occur in response to a maximal level of exercise.

Since the analyses of fibrinolytic activity are performed in vitro, the relationship of the findings of this investigation to processes occurring in vivo remains uncertain (23). Nevertheless, the present investigation clearly demonstrates that the increase in fibrinolytic activity occurring during exercise is a function of the relative intensity and duration of exercise, and of the time of day the exercise is performed. It remains to be seen if an aberration of these normal responses plays a role in the pathogenesis of human disease processes.

Acknowledgment

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