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BRIEF REVIEWS

Interactions of exercise, coagulation, platelets, and fibrinolysis—a brief review

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ABSTRACT

BOUREY, R. E. and S. A. SANTORO. Interactions of exercise, coagulation, platelets, and fibrinolysis—a brief review. *Med. Sci. Sports Exerc.*, Vol. 20, No. 5, pp. 439–446, 1988. Relationships between exercise and various measures of hemostasis have been reported throughout the last 70 years. As hemostatic mechanisms have been implicated in disease and have been manipulated in therapy, the relationship to exercise and endurance training demands attention. Studies to date, however, have often been discordant and confusing. This review summarizes and analyzes the literature with regard to the effects of exercise and training on measures of coagulation, platelet function, and fibrinolysis in normal human subjects. Although platelet count, coagulation factor VIII activity, and some measures of coagulation activity of the blood may increase after exercise, fibrinolytic potential also increases and there is no convincing evidence of clot formation or change in the overall balance of hemostatic mechanisms with exercise. Relatively few data exist on the effects of endurance training on hemostatic mechanisms. Although platelet function and the response to exercise of some measures of fibrinolytic and coagulation mechanisms may be modified, more standardized, quantitative data obtained by state of the art methods are needed before definitive conclusions are possible. Future studies will benefit from application of more standardized techniques of exercise research as well as attention to closer control of factors known to affect hemostatic mechanisms.

HEMOSTASIS, EXERCISE, PLATELET, COAGULATION, FIBRINOLYSIS, AEROBIC TRAINING

John Hunter first brought attention to a relationship between exercise and hemostasis with the observation that blood from animals run to death did not clot (24). Seemingly conflicting information that blood drawn after exercise was hypercoagulable followed in the early part of this century (7). More recently, there have been numerous studies of the relationships between exercise and the mechanisms of hemostasis, the results of which have frequently been conflicting.

The need for understanding these relationships has expanded. Platelets and the coagulation system have been implicated in the pathogenesis and activity of vascular disease, and antiplatelet and fibrinolytic therapy are gaining widespread acceptance. Physical activity seems to modify the progression and activity of vascular disease. Some evidence, discussed below, suggests that regular exercise modifies the coagulation and fibrinolytic systems, but the data are sparse and discordant.

This paper attempts to clarify some of the confusing aspects of the extensive literature in this area and to stimulate further research regarding the mechanisms and significance of hemostatic changes caused by exercise. The acute effects of exercise and the effects of endurance training are considered separately. For reasons of clarity and space, this review is focussed on information derived from normal human subjects.

OVERVIEW OF THROMBOSIS AND THROMBOLYSIS

Injury of a vessel stimulates a rapid, localized hemostatic reaction mediated by interaction between platelets, the coagulation system (soluble clotting proteins), and the vascular endothelium. Injury of the vascular endothelium exposes platelet activating substances, such as collagen, to which platelets rapidly adhere, become activated, and release soluble proaggregatory substances, such as ADP and thromboxane A_2, which recruit other platelets into the forming platelet plug. Thromboxane A_2, one of the substances released, also promotes vasospasm. Surrounding intact endothelium serves to localize platelet aggregation, in part, through the release of prostacyclin (PGI_2), a vasodilator and potent inhibitor of platelet aggregation.

The platelet plug becomes fixed by local fibrin deposition. Fibrin is generated from its precursor, fibrinogen, upon the proteolytic cleavage of specific peptides

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by thrombin. Thrombin is formed through activation of the sequence of serine proteases in the coagulation cascade. Thrombin is also a potent stimulant of platelet activation. In turn, activated platelets provide cofactors and a surface essential to rapid fibrin deposition.

The fibrinolytic system controls local fibrin deposition through degradation of fibrin by plasmin. Plasmin is also a serine protease derived from its inactive zymogen form, plasminogen, by specific proteolytic enzymes known as plasminogen activators. The most important physiological plasminogen activator is known as extrinsic or tissue-type plasminogen activator (t-PA).

EFFECTS OF ACUTE EXERCISE

Coagulation

When placed in a glass tube, blood sampled after exercise tends to clot faster than blood sampled at rest (whole blood clotting time) (16,20,26). A tendency toward *in vitro* hypercoagulability is also reflected in a decrease (7–38%) in activated partial thromboplastin time (APTT) observed after exercise to maximum effort (1,2,11,16–18,25) or after a marathon run (46%) (39), but not after submaximal treadmill tests to 85% of predicted maximum heart rate (63). In determination of APTT, decalcified plasma is recalcified in the presence of a surface activator and the time to clot formation is measured. The effect of a maximal bout of exercise persists for at least an hour (17,18). Most workers have not observed a detectable concomitant decrease in the prothrombin time (PT) (17,39,56), i.e., the time to clot formation in recalcified plasma activated by tissue factor. Ferguson et al. (18), however, recently described a transient, small decrease of less than 3% in prothrombin time in 60 subjects after an exhausting incremental treadmill test.

The mechanism underlying the measurable postexercise shortening of the APTT but not PT is unclear. Changes in plasma volume, white blood cell count, hemoconcentration, and platelet count (*vide infra*) are found following even short exercise, and all could affect *in vitro* tests of coagulation, but none could easily explain a decrease in the APTT but not the PT. The increase of factor VIII (FVIII) following exercise might account for these findings, at least in part. FVIII is a component of the "intrinsic" coagulation pathway tested by the APTT, but not common to the tissue factor-activated pathway tested by the PT.

The FVIII complex is composed of two distinct polypeptides, factor VIII:C, which manifests procoagulant activity (deficient in patients with classic hemophilia), and von Willebrand factor (a platelet-adhesive protein deficient in patients with von Willebrand's disease). The molar concentration of von Willebrand factor is approximately 100 times that of FVIII:C. Virtually all of FVIII:C in plasma exists in a noncovalent complex with von Willebrand factor. Until recently, the exact source of factor VIII:C was uncertain, but recent data suggest it originates from the liver, kidneys, spleen, and vascular endothelium. Von Willebrand factor is a product of the vascular endothelium.

The activities of the FVIII complex measured in plasma *in vitro* rise 200–400% with heavy exercise (1,5,10–12,17,21,26,27,32,45,50,56,61,62–64,66). This increased activity persists for at least an hour (17). Release of FVIII activity is also stimulated by epinephrine or desmopressin (a vasopressin analogue), and prior desmopressin administration blunts the activity released in response to exercise (64). The rise in FVIII activity can be eliminated or reduced with beta blockers (10,61). Increases in FVIII activity may occur only above a threshold of exercise intensity. Davis et al. noted that the rise in FVIII activity did not occur until oxygen uptake reached 95 to 100% of $\dot{V}O_{2max}$ on the treadmill (12). Hawkey et al. also noted that increases in FVIII activity occurred only at cycle ergometer work rates above 1500 kpm (250 W) (21).

Three assays for the two components of the FVIII complex are routinely employed. Functional assays exist for procoagulant activity (FVIII:C) and the ristocetin-cofactor activity of von Willebrand factor. Von Willebrand factor is also quantitated immunochemically as FVIII-related antigen (FVIII:RAg). All three determinants appear to increase after exercise.

Most data suggest that equivalent increases occur in FVIII:C and FVIII:RAg (11,17,61,64). There are, however, reports of a disproportional increase in FVIII:C over both FVIII:VWF and FVIII:RAg (42,62,66). Differences in exercise protocols do not easily explain the differences in results. Differences in laboratory methods, however, may be partly responsible. FVIII:C activity in a subject's plasma is determined by an expanded APTT, in which the subject's diluted plasma is added to a substrate plasma deficient in FVIII:C and the concentration is determined by comparing the time to clot formation with a standard curve. Brown et al. (5) demonstrated that the one-stage APTT, in which subject and substrate plasma are initially mixed, gives a higher level of FVIII:C than the two-stage assay, in which the subject's plasma is first activated and then added to the substrate plasma. All studies demonstrating a disproportionate increase in FVIII:C over FVIII:RAg used the one-stage assay, and all but one study demonstrating a proportionate increase (17) used the two-stage assay. There exists, however, no clear reason why this subtle difference in technique should produce a difference in FVIII:C activity. Furthermore, Kopitsky et al. (32) showed a disproportional increase in FVIII:C activity with exercise using either a one- or two-stage assay and also observed the well-established

increased activity of FVIII:C with thrombin activation. Their studies suggest that a disproportionate increase in FVIII:C after exercise could be due to increased *in vivo* activation of FVIII:C by thrombin (32). In recent years, it has become possible to quantitate plasma levels of FVIII:C antigen (as opposed to functional activity) by use of monoclonal antibody-based immunoassays. Application of this technology to the problem of exercise-induced elevations of FVIII:C would likely clarify the issue.

There is little change in the activity of other coagulation proteins upon exercise (5,10,11,17,23,26,27, 39,47,56,63). Iatridis and Ferguson (26) described an isolated increase in FXII of 318% after a run to exhaustion. Their exercise protocol is distinctive only in that maximal effort was reached as late as 32 min after the test began. On the other hand, Mandalaki et al. (39) saw no increase in FXII after a marathon run of much longer duration. There have been some conflicting reports suggesting that a slight increase or decrease occurs in levels of protease inhibitors (18,21,23,25,42,63), but the significance of these subtle differences is difficult to assess. In addition, measures of hemoconcentration have generally been absent or ignored. Both intensity and duration of exercise influence this parameter, but in only two studies have protein levels been corrected for plasma volume changes during exercise (18,23). These two studies showed slight decreases in protease inhibitors and factor XII.

Summary. A single bout of exercise is associated with an observed shortening of APTT of 7–38%. The shortening of the APTT is associated with a 200–400% increase in FVIII coagulant activity. The increase in FVIII:C is directly proportional to an increase in FVIII:Ag. Although reports of a disproportionate increase in FVIII:C over FVIII:Ag seem to be related to the use of a one-stage instead of a two-stage assay for FVIII:C, recent evidence suggests that a disproportionate increase in FVIII:C may occur as the result of *in vivo* activation by thrombin. There seems to be little evidence for change in the activity of other proteins of the coagulation cascade or protease inhibitors which might affect coagulation.

Fibrinolysis

A 5–10-fold rise in fibrinolytic activity of plasma sampled after exercise has been well established by a number of studies (1–3,8–12,17,18,21,23,26,28–30, 39,42,43,50,54–57,64,66,69). In spite of the use of many different assays based on techniques of clot lysis, fibrin plate degradation, or immunoassay, the results obtained in these studies are similar. For a review of the different methods used, see the review by Prowse and Cash (51). The rise in fibrinolytic activity takes place early in exercise, is related to both intensity and duration (12,42,43,57), and, unlike the rise in FVIII:C, is not blocked by propranolol (3,10,61). Unlike the rise in FVIII, the rise in fibrinolytic activity occurs with an effort of only 50–60% of $\dot{V}O_{2max}$ (12). The fibrinolytic activity can remain elevated for up to an hour but has a half-life of approximately 2–5 min (10,30). There is a diurnal variation in resting nonfasted subjects with the lowest levels of fibrinolytic activity seen in the morning and highest levels (4-fold in basal) noted in the early evening (57). More pronounced responses to exercise are also seen in the early evening. There is a great variation between individuals, but, for each individual, basal levels and responses tend to be similar from day to day. Women seem to have similar basal levels to men, and these results seem unaffected by the menstrual cycle (8). Cash (8) reported a greater rise in fibrinolytic activity in women than men after an 8-min treadmill walk at 3.4 mph and 5 degrees elevation, but this difference was also associated with a greater increase in pulse rate in the women, signifying a greater work rate relative to capacity. The use of birth control pills does not seem to affect total fibrinolytic activity in trained women either at rest or after exercise, though differences between groups in some components of the fibrinolytic system have been noted (23). One study using a 90-s step exercise suggested a decreased response in elderly compared to young subjects, but the exercise was not standardized for relative intensity (2).

The increase in fibrinolytic activity is attributed to increased levels of t-PA. This enzyme is synthesized and stored in the vascular endothelium and is released in response to a number of stimuli including fear, surgical stress, venous occlusion, hypoglycemia, desmopressin, microwave radiation of the hypothalamus, and various medications (51). Increased venous blood flow may represent a mechanism common to some of these stimuli. A simple study by Rennie et al. (54) revealed that fibrinolytic activity induced by local exercise (wrist flexion) is prevented if arterial blood flow is occluded during the exercise. Furthermore, like FVIII:C, the response of fibrinolytic activity to exercise may be blunted after prior stimulation by tourniquet (28), desmopressin (64), or exercise (29). The increased fibrinolytic activity of t-PA is attributed to an actual increase in free t-PA (55).

In addition to secretion of t-PA by endothelial cells, exercise may also induce changes in its substrate, plasminogen. An increased amount of modified plasminogen has been reported in post-exercise plasma (69). This form of plasminogen has a greater affinity for fibrin and is more easily activated by plasminogen activator.

Reports have occasionally noted the existence of "poor responders" among groups of otherwise healthy subjects. These individuals demonstrate little increase in fibrinolytic activity with exercise (8,9,12,29). In a recent study of a group of "poor responders," which

included one healthy individual, and selected patients with hyperlipoproteinemia or a history of spontaneous thromboembolism, Brommer et al. (4) noted that endothelial release of t-PA as assessed by immunologic methods was normal, but the expected increase in fibrinolytic activity was masked by high levels of a free, fast-acting t-PA inhibitor. Follow-up studies of otherwise normal "poor responders" have not been provided to date.

The significance of increased *in vitro* fibrinolytic activity of plasma following exercise is not clear. With few exceptions (11,39), *in vivo* fibrinolysis has not been observed (1,3,17,18,43,50,61). Ferguson has consistently reported a significant increase in fibrin split products (evidence for fibrinolysis) after a Bruce treadmill protocol to exhaustion (17,18). The source of these degradation products has not yet been elucidated, but pre-existent clots *in vivo*, clots formed in response to exercise-induced trauma, or *ex vivo* fibrin generation during venipuncture are all possibilities.

Summary. Exercise induces a 5- to 10-fold increase in plasma fibrinolytic activity which is related to both intensity and duration of exercise. The increase in fibrinolytic activity is attributed primarily to t-PA release from the vascular endothelium. "Poor responders" may have abnormal levels of a t-PA inhibitor. The physiological significance of an increase in fibrinolytic activity remains unknown.

Platelet Function

Various studies cite an 18–80% increase in platelet number (12,18,25,40,47,49) and a small increase in platelet size (49) immediately after treadmill or bicycle exercise to at least 85% of maximum heart rate. The increase in platelet count occurs early, is out of proportion to the rise in hematocrit, and is not blocked by propranolol (12,40). The slight increase in mean platelet volume may represent the release of larger, younger platelets from the spleen or marrow (19,59). The pulmonary vasculature is also a likely reservoir for the exercise-induced increase in platelets (19). In spite of the increase in platelet number, most studies have shown little change in platelet function in normal individuals following acute exercise.

Attempts to assess *in vivo* platelet activation by measurement of platelet-specific products in plasma have tended to support the hypothesis that platelets are not activated by exercise (15,40,41,44,-46,61), but some conflicting results do exist (22,35,46,58). The differences in results are not easily explained by variation in intensity of exercise or methods of assay. Patrono et al. (48) have elegantly demonstrated the effect of venous sampling on platelet products by estimating basal thromboxane B_2 production on the basis of urinary metabolite concentrations. Their maximal estimate of endogenous thromboxane B_2 concentration is 2.0 pg/ml. This value contrasts markedly with the plasma values of 20–500 pg/ml in the studies cited above and suggests that *ex vivo* platelet activation severely limits conclusions based on studies of venous samples.

Many studies have attempted to assess platelet function *in vitro*. Older methods included the relatively nonspecific whole-blood clotting time and the highly variable platelet retention test. These methods are now primarily of historical interest. They have been supplanted by tests in which an aggregating agent such as ADP, epinephrine, or collagen is added to a sample of platelet-rich plasma and aggregation is assessed by increased light transmission or scattering, impedance, or, rarely, the disappearance of single platelets.

Older *in vitro* studies demonstrated a variable increase in the extent of platelet aggregation after exercise (13,50,65), but these studies failed to use a uniform platelet count and did not correct for the post-exercise increase in platelets. Their conclusions are erroneous. Subsequent studies have used a standardized platelet count and have shown no change in the extent of platelet aggregation after exercise (6,45,60,61,63), although Ohri et al. (47) estimated a 28% increase in aggregation rate in response to a small dose of ADP.

Plasma levels of the endothelial anti-aggregating agent PGI_2 appear to rise after a treadmill test using the Bruce protocol to at least 85% of maximum predicted heart rate (45,46), but not after an 8-min treadmill walk at an average work rate of 150 W (61). On the other hand, the sensitivity of platelets to the anti-aggregating effects of PGI_2 *in vitro* has been observed to decrease after exhausting bicycle exercise (34), treadmill exercise (63), or squash (6), but not in submaximal exercise (6,60). One could hypothesize that PGI_2 stimulation of platelet cAMP production during exercise makes the platelets less sensitive to further inhibition by PGI_2 *in vitro*. The findings of increased platelet cAMP and decreased PGI_2 sensitivity in some racers after a marathon run (13) support this hypothesis. An increase in platelet cAMP should result in an observed decrease in platelet aggregability, but the fact that this decrease is not seen suggests that the effects of increased cAMP may be negated *in vivo* by increases in epinephrine or other proaggregatory factors associated with exercise.

Summary. An 18–80% increase in platelet count and a small increase in platelet size occur after exercise. These increases probably represent the release of platelets from the vascular beds of the spleen, marrow, and lungs. Measurement of plasma concentrations of platelet activation products tend to support the hypothesis that platelets are not activated by exercise, but recent studies by Patrono et al. have demonstrated that *ex vivo* platelet activation during venous sampling of blood limits the usefulness of this approach. Studies of platelet aggregation show no increase in aggregability after ex-

ercise if uniform platelet counts are used. Strenuous exercise is associated with increases in the anti-aggregating agent PGI_2, but its effects on aggregation may be negated by a concomitant increase in proaggregatory factors such as epinephrine.

EFFECTS OF ENDURANCE TRAINING

Coagulation

Although the concept of exercise-induced hypercoagulability is nearly 70 years old, information regarding the effects of endurance training on coagulation is almost nonexistent. In a recent cross-sectional study which compared relatively lean marathon runners with more sedentary individuals, Ferguson et al. (18) found no difference between groups in the PT or APTT at rest or after a maximal Bruce treadmill test. In a study of 54-year-old men whose levels of physical activity were evaluated by questionnaire, Korsan-Bengtsen et al. (33) found a decreased APTT at rest in more active individuals, but no difference in FVIII levels or PT. In the only prospective study to date, Ferguson and Guest (16) showed that 14 subjects had less decrease in whole blood clotting time and APTT in response to a standard workload after 1 month of aerobic training (running or cycling 30 min/day, 3 times/wk) when compared to pre-training responses.

Summary. Obviously, no significant conclusions can be advanced on the basis of reported studies.

Fibrinolysis

The above studies also examined fibrinolytic activity. The recent cross-sectional study of Ferguson et al. (18) demonstrated that marathon runners had a level of fibrinolytic activity at rest which did not differ from that of less active individuals. In contrast, an earlier, prospective study of Ferguson and Guest (16) revealed a decrease, after training, in fibrinolytic activity at rest. Williams et al. (68) also demonstrated a small decrease, after 10 wk of training (walking or jogging at 70–85% of maximum heart rate for 30–45 min, 3 times/wk), in fibrinolytic activity at rest.

In the recent work of Ferguson et al., the fibrinolytic activity increased more in response to maximal exercise in the highly trained group (18). This additional fibrinolytic activity may have reflected the higher absolute work rate achieved by the trained individuals, as the earlier study by Ferguson and Guest (16) showed no difference before or after training in exercise-stimulated fibrinolytic activity using a standard 10-min treadmill walk at 3 miles/h and a 10° grade. Using the more potent technique of venous occlusion instead of exercise, Williams et al. (67) showed a 50% greater fibrinolytic response after as compared to before training.

Summary. These studies suggest that training individuals may have a lower level of plasma fibrinolytic activity at rest and no change in fibrinolytic response to a fixed, submaximal work rate. The training individuals may, however, have a greater fibrinolytic reserve as demonstrated by venous occlusion.

Platelet Function

Dix et al. found the platelets of marathon runners to be marginally less sensitive to epinephrine than those of non-runners (14). He also noted an increased sensitivity of the runners' platelets to the anti-aggregating effects of PGI_2. His study, however, was performed 24 h after a marathon, and the role of persistent effects from that exercise in these observations cannot be discounted. Lehmann et al. (37) also found the platelets of eight endurance-trained athletes at rest to be less sensitive to epinephrine-induced aggregation than platelets of nine non-endurance-trained athletes. This decreased sensitivity was associated with decreased alpha-2 adrenoceptor number and affinity on the platelets of the endurance athletes. There was a significant negative correlation between adrenoceptor number and $\dot{V}O_{2max}$. Unfortunately, the issue remains muddled as Lockette et al. (38) recently reported an increased alpha-2 adrenoreceptor density with no change in affinity of platelets from 16 endurance-trained athletes when compared to platelets from sedentary individuals. The methods used were similar, but the control groups were different (athletes in the first case and sedentary individuals in the second case). There may be a further difference in levels of activity of subjects on the day of study. We know only that Lehmann and Keul studied their subjects between 8 and 9 a.m. and that Lockette et al. studied subjects who "... performed their normal daily activity pattern." The possibility of exercise preceding venipuncture in the latter study cannot be discounted.

Prospective studies on cardiac patients tend to support a training-related decrease in sensitivity of platelet aggregation to epinephrine. Both Williams et al. (68) and Lehmann and Keul (36) report a decrease in epinephrine-induced aggregation of platelets from cardiac rehabilitation patients after, respectively, 6 months and a year of training.

Rauramaa et al. (52) noted that regular mild-intensity exercise tended to lower the serum thromboxane levels of normal middle-aged men. The same group recently reported the effects of 12 wk of light training (walking or jogging at 45–59% of $\dot{V}O_{2max}$ for 45–60 min, 4 times/wk) on 19 hypertensive, overweight men (53). When compared to platelets of control subjects, those of trained subjects released 32% less ATP and exhibited 27% less second-phase response after challenge by small doses of ADP.

Summary. Training of middle-aged men with cardiac risk factors and cardiac patients has been associated with decreased *in vitro* aggregability in response to epinephrine or low doses of ADP. The mechanisms for this change at the cellular level are not clear.

CONCLUSIONS

Although some facets of the thrombotic and fibrinolytic system appear to be raised to a higher level of "readiness" following exercise, one should come away with the impression that the fine balance between thrombotic and fibrinolytic promoters and inhibitors is maintained in normal individuals. On the basis of this review, regular exercise offers no definite benefits with respect to favorably changing this balance. The significance of changes in the whole blood clotting time is unknown. The increase in recoverable fibrinolytic activity after exercise seems related primarily to the work rate achieved, but the demonstration by Williams et al. (68) of an increased response in fibrinolytic activity to venous occlusion after training suggests that some changes may occur at the cellular or molecular level. The findings of Lehmann and Keul (37) of decreased platelet sensitivity to aggregating agents with increased levels of aerobic fitness appears beneficial, but the recent contradictory study by Lockette et al. (38) suggests that more information is needed before a definitive statement can be made.

It is interesting and provocative that the fibrinolytic activity has a half-life of minutes, whereas the half-life of FVIII is measured in hours. One might expect an imbalance of coagulation and fibrinolytic activities after an hour of recovery from exercise. Attempts to apply this hypothesis in therapy have shown that exercise can induce variable increases in FVIII levels in patients with mild classic hemophilia (31,56), but at least one family exhibited a deterioration in hemostasis after exercise associated with increased levels of t-PA (20). The hemostatic systems are obviously complex and defy simple analysis.

Hyperlipoproteinemia may promote a loss of hemostatic balance by blunting the fibrinolytic response to exercise, increasing inhibitors of plasminogen activator, and increasing the susceptibility of platelets to aggregating agents (4,57). Catecholamines and metabolites of glycolysis may also modify hemostasis in exercise. The ability of aerobic endurance training to modify these factors is well established and should provide further impetus to future studies of exercise and hemostasis.

Obvious questions remain in regard to hemostatic changes with acute exercise at the molecular level and endurance exercise at the epidemiologic and physiological levels. Due to a lack of standardization in methodology, the existing literature can be confusing. For example, only four of the studies cited in this review include information on relative work rates or fitness based on $\dot{V}O_{2max}$. Other factors which need to be more closely controlled in the future are diet, lipoprotein levels, diurnal variation, interindividual variation, and shifts in plasma volume. The demonstration by Patrono et al. (48) of significant *ex vivo* platelet activation during venipuncture suggests that the design and interpretation of any study which involves blood sampling warrant exceptional caution. With improved techniques, the relationship of hemostasis to exercise should soon attain better definition.

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