The exercise paradox may be solved by measuring the overall thrombotic state using native blood

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Summary While exercise is widely believed to prevent atherothrombotic diseases, it occasionally causes sudden death. This exercise paradox may be due to the inadequate testing of the thrombotic and thrombolytic status. A recently developed shear-induced thrombosis/endogenous fibrinolysis test performed with non-anticoagulated blood samples allows the assessment of the thrombotic state of an individual both at rest and after exercise. This sensitive and physiologically relevant test may help to solve the aforementioned exercise paradox.

**Keywords:** Exercise, platelet reactivity, platelet aggregation, coagulation, fibrinolysis, non-anticoagulated blood

1. Introduction

Prevention of atherothrombotic diseases such as coronary artery disease and stroke is an important social issue. Evidence from epidemiological and clinical studies suggests that regular exercise is an efficient way to prevent such diseases. However, the benefit of exercise is still a subject of debate that is referred to as the "exercise paradox" or the "double-edged sword in exercise" (1-5).

Findings from studies that have sought to explain that paradox are a subject of debate (6-10). The intensity of exercise of endurance training may be responsible for this paradox according to the American College of Sports Medicine (Table 1) (11). Inconsistent evidence might be partly due to differences between the laboratory tests used to study the thrombotic status. Hemostasis tests in common use are performed on anticoagulated blood (12-14). Anticoagulants interfere with the mechanism of hemostasis and render the obtained results unphysiological. To overcome this limitation, some tests (shear-induced platelet-rich thrombosis and thrombolysis tests) use non-anticoagulated whole blood (15-20). The aim of the present review was to compare the effects of short-term and long-term exercise on the thrombotic state. These effects were measured with two types of tests using either anticoagulated or non-anticoagulated blood in order to understand the exercise paradox.

2. Measurement of the effects of acute and long-term exercise on the thrombotic/fibrinolytic state using anticoagulated blood

2.1. Effect of acute exercise on platelet function

Only a few studies have examined the effect of low-intensity exercise (< 49% maximal oxygen consumption, %VO₂max) on platelet reactivity. However, the effect of moderate-intensity exercise (50-74% VO₂max) and heavy-intensity or strenuous exercise (> 75% VO₂max) on platelet reactivity have been extensively studied. Studies using conventional tests have measured agonist-induced platelet aggregation, release of markers of platelet activation, such as β-thromboglobulin, platelet factor 4, and P-selectin, and an increase in metabolites such as thromboxane B₂ after moderate-intensity exercise (21-24). Those studies failed to yield conclusive results regarding the effect of moderate-intensity exercise on platelet reactivity.

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Heavy-intensity exercise (> 75% VO₂max) seems to enhance platelet reactivity.

2.2. Effect of acute exercise on coagulation and fibrinolytic activity

Moderate-intensity exercise is known to increase fibrinolytic activity without raising levels of coagulation activation markers, while heavy-intensity exercise concurrently activates both the fibrinolytic and coagulation system (25). Fibrinolytic activity is enhanced by exercise and the extent of that enhancement mainly depends on the intensity of exercise (7, 10, 25-27). In healthy volunteers and patients with peripheral arterial disease, coronary artery disease, metabolic syndrome, or hypertension, moderate-intensity exercise consistently increased tissue plasminogen activator (t-PA) activity (28-33) but not plasminogen activator inhibitor-1 (PAI-1) activity (31,34). Heavy-intensity exercise seems to enhance fibrinolytic activity along with coagulation (25,35-37).

2.3. Effect of long-term exercise on coagulation and fibrinolytic activity

Antithrombotic effects of regular or long-term exercise have been measured in healthy volunteers and patients of various ages. Studies have found that long-term exercise inhibited thrombin generation, reduced platelet reactivity and fibrin formation, and increased fibrinolytic activity (28,38-41). These results suggest that long-term exercise may help to prevent sudden death.

Because of individual variation, the thrombotic state of individuals needs to be measured before and during long-term exercise training. Since the thrombotic state is governed by a balance of and overall interaction between coagulation, fibrinolysis, platelet reactivity, and flow, the overall thrombotic state needs to be measured in individuals.

3. Effects of exercise on the thrombotic state assessed using non-anticoagulated blood

A wide variety of tests are used to measure the individual components of the hemostasis system, but their results are difficult to interpret. An overall test of hemostasis is greatly needed to assess the actual thrombotic state of an individual (12-14). Kovacs and her colleagues have focused on creating tests that can simultaneously measure platelet reactivity, coagulation, and endogenous thrombolytic (fibrinolytic) activity using one blood sample. Such a test, named the Global Thrombosis Test (GTT), is now commercially available. This test induces platelet-rich thrombus formation in non-anticoagulated (native) blood solely by shear forces, as opposed to conventional tests that use chemical agonists. Further, this test detects the spontaneous lysis of formed autologous thrombi in the same blood sample (15-20).

3.1. Effect of acute exercise

In a study by the current authors, results from a thrombotic status analyser indicated that low-intensity exercise (50% VO₂max, 40 min) does not affect platelet reactivity (42). In contrast, moderate-intensity exercise (60% VO₂max, 20 min) significantly increased platelet reactivity but did not affect fibrinolytic activity (Figure 1) (43).

In another study by the current authors, results from a haemostatometer verified that the effects of exercise at different levels of intensity on the thrombotic status depended on the individual's anaerobic threshold (AT), platelet reactivity, and coagulation not only during exercise but also during the recovery period after exercise (44). A significant increase in platelet reactivity (H1) and coagulation (CT1) was observed immediately and
In conclusion, using the GTT and a non-anticoagulated blood sample to measure the thrombotic state at rest and immediately after exercise may help to solve the exercise paradox.

References


9. Ex-VT 130% (approximately 55% VO₂max), 30 minutes after heavy-intensity exercise (corresponding to approximately 80% VO₂max), but such changes were not observed after moderate-intensity exercise (corresponding to approximately 55% VO₂max) (Figure 2).

3.2. Effect of long-term exercise

Research used the GTT to measure the thrombotic state in patients with metabolic syndrome before and after three months' exercise (45). Results of that research are shown in Figure 3. A thrombotic state indicated by hyper-platelet reactivity before long-term exercise abated after exercise, but long-term exercise did not appear to affect endogenous fibrinolytic activity.

The thrombotic state was measured in healthy volunteers and patients under various conditions. The shear-induced thrombosis and thrombolysis tests were performed on non-anticoagulated blood (haemostatometer, thrombotic status analyser, and GTT). The thrombotic state was influenced by age (46), smoking (46-48), gender (47), and race (49). These findings corroborate the results of clinical studies indicating that physical exercise or sports helped to prevent a prothrombotic state and increased an individual's quality of life (3,38,41,50).


40. Baba Y. Effects of exercise and diet interventions modeled on Healthy Japan 21 on thrombus formation.


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