Effects of strenuous exercise on haemostasis

J E Smith

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Methods: The search strategy included articles from 1966 to August 2002 using Medline and SportDiscus databases, and cross referencing the bibliographies of relevant papers.

Results: Exercise results in activation of both the coagulation and fibrinolytic cascades, as shown by a reduction in whole blood clotting time and activated partial thromboplastin time, an increase in the activity of several components of the cascades, and an increase in fibrin degradation products. Studies of fibrinogen level have given conflicting results, with some showing no difference after exercise, although some have shown a significant shortening of thrombin time. Changes in individual components of the coagulation cascade as a result of exercise have also been shown. Factor VIII activity has been shown to increase by 200–400%, and the degree of increase in factor VIII activity is dependent on volume and intensity of exercise. Studies of fibrinogen level have given conflicting results, with some showing no difference after exercise, some showing an increase, and some showing a decrease. A recent study has postulated that fibrinogen levels are decreased after maximal and submaximal exercise, suggesting consumption during the coagulation cascade, but this is only evident when the reduction in plasma volume after exercise is taken into account. There is little convincing evidence of alterations in other components of the coagulation cascade. The cascade also has its own regulatory proteins that inhibit coagulation at various stages, such as antithrombin III and protein C. These inhibitors of coagulation are also affected by exercise, although the results of studies looking at this are not so conclusive. Antithrombin III has been shown to fall in one study, although little change was seen in others. Ferguson et al describe a rise in absolute antithrombin III concentration, but a fall in concentration once corrections were made for plasma volume, suggesting consumption of the factors. In two studies, the level of thrombin-antithrombin III complexes rose significantly with exercise, suggesting that there had been in vivo formation of thrombin that had been neutralised by the antithrombin III. This was confirmed in later studies which found that thrombin-antithrombin III complexes increased after maximal exercise, and this was more pronounced after prolonged exercise.

Fibrinolysis
Fibrinolysis is the process by which fibrin is broken down and made soluble. It is stimulated by plasmin, which is derived from its inactive precursor, plasminogen, as a result of the action of plasminogen activating factors. The most important of these is tissue-type plasminogen activator (t-PA). As a result of fibrinolysis, fibrin degradation products are produced. Plasminogen activator inhibitor (PAI-1) inhibits the action of t-PA,
and plasmin is inhibited by antithrombin III. Fibrinolysis can be measured in various ways, the most common being a measurement of the time taken for the test sample to break down a standardised clot, as shown by the euglobulin lysis time.

Fibrinolysis is activated in response to exercise. This is usually attributed to an increase in t-PA, which is released by the vascular endothelium.40 41 Significant rises in t-PA have been found in various exercise protocols.13 14 16 17 21 22 30 39 41 42 This increase is positively related to exercise intensity and duration, such that the higher the intensity and duration of exercise, the more exaggerated the effect.15 16 21 22 30 41 There is also some evidence that aerobic training enhances the activation of fibrinolysis after exercise.42 43 Fibrinolysis is controlled not only by the activators, but also by inhibitors such as PAI-1, another substance released by damaged endothelial cells. Circulating t-PA is either in its active form or, when combined with PAI-1, it is inactivated. The activity of PAI-1 can be measured (by combining the test sample with a standard solution containing one chain t-PA, and measuring residual t-PA level after the reaction), and has been shown to fall after both endurance and resistance exercise.21 30 40 41 42 Rocker et al41 found that PAI-1 activity was undetectable after a marathon, suggesting that it had all been consumed in bound form with plasminogen activator.

The end products of fibrinolysis, fibrin degradation products, have been shown to increase after endurance exercise of different types.13 14 15 16 22 31 34 44 d-dimers, which are products of the breakdown of activated factor XIII (fibrin stabilising factor) and fibrin, are often used as a marker of fibrin degradation, and have also been shown to increase.13 15 17 20 22 31 This would suggest that the activation of fibrinolysis is not simply an in vitro response to exercise, but does actually occur in vivo.45 It has been suggested that subjects have a fibrinolytic capacity relating to their risk of developing thromboembolic or atherosclerotic disease, and this capacity is impaired in patients with some forms of illness.46

**Platelet aggregation**

As a result of vessel wall injury, substances that activate platelets are exposed, such as collagen. Platelets adhere to these and become activated, releasing substances that promote platelet adherence and vasoconstriction, such as thromboxane A2, and ADP as well as platelet specific proteins such as β-thromboglobulin and platelet factor 4. Counteracting substances such as prostacyclin (which acts as a vasodilator) regulate this process. Platelet activation can be estimated in several ways, one of which being estimation of the level of platelet specific proteins such as platelet factor 4 or β-thromboglobulin, which are both in vivo indicators of platelet activation and degranulation.

The platelet count has repeatedly been shown to rise after acute exercise.24 30 42 43 This is presumed to be due to mobilisation of platelets from the spleen, bone marrow, and other reticuloendothelial organs, in response to stimulation by catecholamines released during exercise.44 However, the effect of exercise on platelet function is less clear cut, with some reports of increased aggregation, and some of decreased aggregation.45 β-Thromboglobulin was found to be increased after graded exercise, with higher values after more strenuous exercise46 and in less trained individuals.47 Both platelet factor 4 and β-thromboglobulin were found to be increased after a marathon.21 25 However, in one marathon study, despite increased levels of β-thromboglobulin, platelet aggregation was found to be decreased after exercise,47 suggesting that the platelets had been activated, had released β-thromboglobulin, and then reverted to a less reactive state. The mechanisms behind platelet activation during exercise are not fully understood, but may be related to shear stress causing endothelial damage, increases in plasma catecholamines, thrombin generation, and mobilisation of more active platelets from the reticuloendothelial system.25

**DISCUSSION**

The findings of this report support the hypothesis that both coagulation and fibrinolysis are stimulated by strenuous exercise, and these effects are summarised in table 1. The activation of these systems is less pronounced in athletes than untrained runners.14 In healthy subjects, the activation of the cascades should work to maintain the balance between the two systems,13 14 21 42 but if the activation of these systems is not in balance, a predisposition to thrombus formation may be the result. In a group of patients followed up for one hour after exercise, Hegde et al41 found that, although t-PA antigen level declined gradually over the hour, activated partial thromboplastin time remained shortened, suggesting continued activation of coagulation. These findings were similar to those of Lin et al,10 who found that clotting activity (factor VIII activity) remained elevated for some hours, while fibrinolytic activity fell sharply. In a field study of marathon runners, Siegel et al16 found that markers of coagulation remained activated the day after the race, whereas fibrinolytic activity had returned to baseline. In theory, this could predispose some subjects to a dangerous tendency to form intravascular thrombus, although other effects of exercise such as vasodilatation and increased blood flow should work to counteract this. There is general agreement that exercise is beneficial to health, and has many positive effects on various aspects of physiology such as blood lipid profile, cardiovascular disease, bone health, and psychological wellbeing. However, how much exercise is good for which patients is a more difficult question. Very strenuous physical activity such as marathon running may not be beneficial to some people, and one of the mechanisms behind this may be an unequal activation of the coagulation and fibrinolytic cascades.

Many of the conclusions drawn from these studies have limitations. There is no standardised protocol for defining exercise intensity or duration, uniformity of sampling, and populations studied. Studies have varied from laboratory based treadmill protocols at a given percentage of maximum oxygen consumption to field based protocols in events as diverse as running, cycling, and triathlon. Subjects used for these studies have tended to be young and healthy, and so it is difficult to extrapolate their results to patients with abnormal or diseased cardiovascular systems, such as the elderly and those with atherosclerosis, or those with multiple risk factors for cardiac disease. It should be stressed that it is not clear how the changes in laboratory values of factors involved in coagulation and fibrinolysis relate to clinical disease processes, and many of the conclusions drawn in these studies are speculative.

Resistence exercise is promoted by the American College of Sports Medicine and the American Heart Association, especially in the older population, but studies into its effects on the balance of coagulation and fibrinolysis are limited.

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**Table 1** Summary of effects of exercise on markers of clotting and fibrinolysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting APTT PT</td>
<td>Decreased</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Factor VIII activity</td>
<td>Increased</td>
</tr>
<tr>
<td>Fibrinolysis</td>
<td>Increased</td>
</tr>
<tr>
<td>t-PA (activation)</td>
<td>Decreased</td>
</tr>
<tr>
<td>PAI-1 (inhibition)</td>
<td>Decreased</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Increased</td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

APTT, Activated partial thromboplastin time; PT, prothrombin time; t-PA, tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor.
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Take home message

Exercise has been shown to stimulate both coagulation and fibrinolysis, although whether this activation is balanced has yet to be clarified. If unbalanced, this could be responsible for adverse clinical events in susceptible people.

It would be of benefit to examine the temporal relation of alterations in the coagulation and fibrinolytic cascades in more detail, to look for further evidence of imbalance in the activation of these two systems. This should clarify whether suggestions that this may be the mechanism responsible for episodes of sudden death after exercise are justified. Opportunities to examine the effects of exercise on the clotting process using more sophisticated techniques such as thromboplastography, which gives a graphical representation of the clotting process and can accurately detect hypercoagulable states, may provide the solution to the debate.

Conclusion

Both the coagulation and fibrinolytic cascades are stimulated by strenuous exercise, but the temporal relation between the two and its clinical significance have yet to be clarified. Unfavourable haemostatic changes at the extremes of exercise intensity may predispose to the formation of intravascular thrombus and may contribute to the phenomenon of sudden cardiac death after exercise. Further work is suggested to investigate this possibility, especially in the older age group and those with coronary risk factors.

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REFERENCES


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