Introduction

Engaging in regular exercise lowers the risk of coronary heart disease (CHD), and most recommendations suggest at least 30 minutes of moderate intensity physical activity on most (and preferably all) days as a primary-prevention strategy for CHD in the general population (1). However, much has also been made of the higher transient risk of sudden death from myocardial infarction during or shortly after exercise, particularly in sedentary individuals who are not accustomed to regular strenuous physical stress (1). Indeed, recent data from the Physicians’ Health Study suggests that vigorous exercise (defined as 30 minutes of 6 MET or more) could simultaneously increase the short-term risk of sudden death during and up to 30 minutes after vigorous exertion [a relative risk of sudden death of 16.9 (95% CI 10.5–27.0; P<0.001)] and also offer protection from this risk in those who habitually engage in vigorous exercise (2); however, the absolute risk of sudden death during any particular episode of vigorous exertion was extremely low (1 sudden death per 1.51 million episodes of exertion). Reassuringly, habitual vigorous exercise did attenuate the relative risk of sudden death that was associated with an episode of vigorous exertion.

What might be the underlying mechanisms responsible for this ‘paradox’ of vigorous versus habitual exercise? Albert et al (2) postulated that episodes of vigorous exertion activate the sympathetic nervous system and promote rupture of vulnerable atherosclerotic plaques, whereas habitual exercise could enhance the electrical stability of the myocardium by increasing vagal tone, thereby protecting against fatal ventricular arrhythmias. However, the possibility also arises that the ‘two-edged sword’ of vigorous exercise may relate to activation of the haemostatic system, leading to enhanced thrombogenesis.

The ‘two-edged sword’ of the exercise-haemostatic equilibrium

A number of haemostatic changes involving platelets, coagulation and fibrinolysis have been reported after acute physical exercise (3). Indeed, the available evidence from the intervention or randomised controlled trials would suggest that exercise or physical training evokes multiple effects on blood haemostasis in normal healthy individuals and in patients with cardiovascular disease. While bearing in mind the considerable inconsistency of the results of various exercise studies due to methodological variations, there are also important differences between the effects of moderate (chronic) endurance physical training and acute strenuous exercise on both the haemostatic and fibrinolytic variables.

By and large, regular (or habitual) physical activities of moderate intensity reduces thrombogenesis, presumably by enhancing fibrinolytic capacity and possibly, by reducing the blood coagulation tendency. Conversely, both coagulation and fibrinolytic cascades are stimulated by acute strenuous exercise. This increase in fibrinolysis is partly due to a rise in tissue-type plasminogen activator (tPA) and a decrease in plasminogen activator inhibitor-1 (PAI-1) levels; indeed, the rise in tPA activity is most apparent and appears to be directly proportional to the level of exercise intensity (4, 5). However, the increased level of fibrinolytic activity falls sharply during the recovery period, whilst activation of the coagulation cascade is persistent (6, 7).
Such a temporal unbalance between the two critical systems has been thought to precipitate acute coronary thrombosis, leading to sudden cardiac death in susceptible sedentary individuals or in patients with pre-existing atherosclerotic vascular disease who may not sustain their fibrinolytic capacity (perhaps due to some endothelial dysfunction), when they are exposed to unaccustomed strenuous physical exertion. Indeed, patients with atherosclerotic disease have high basal levels of PAI-1 levels and lack a similar degree of increase in the tPA activity after exercise, when compared with healthy subjects (8).

**Acute exercise and platelet reactivity**

The effect of acute exercise on platelet reactivity has been studied extensively, but with contradictory results, most likely due to methodological problems in the measurements of platelet aggregation and activation during and immediately after exercise (3). A variety of methods in assessing platelet reactivity has been used in these earlier studies. In particular, the in vitro or ex vivo agonist-induced aggregability assays or in vivo platelet secretory products (mainly β-thromboglobulin, platelet factor 4 or P-selectin) measurements are associated with considerable methodological differences. In addition, the differences in exercise protocol used, as well as the selection of subjects may account for the discrepancies of results reported in the literature.

However, the evidence available would again suggest that short-term or acute strenuous, or maximal (but not moderate) exercise induces a transient increase in agonist-induced platelet aggregation both in vitro and ex vivo, as well as increases in platelet counts, adhesiveness and in vivo platelet secretory activity. Overall, these effects seem to be more pronounced in sedentary than active healthy subjects (9, 10). In contrast, long-term endurance physical training (preconditioned) in men and in women at moderate intensity (50–55% of maximal oxygen consumption [VO2max]) appears to suppress platelet adhesiveness and aggregation both at rest and after acute strenuous exercise. However, the effects reverse back to the pretraining state after a period of deconditioning, thus emphasising the importance of regular moderate exercise in order to maintain such potential benefits (11, 12).

As with the fibrinolytic response, platelet reactivity in response to acute strenuous exercise also appears to be both duration and intensity-dependent. However, the underlying mechanism(s) remain unclear. Increases in catecholamine concentrations and shear stress are probably important (13, 14). Indeed, at high concentrations, epinephrine promotes platelet aggregation, and at low concentrations, it potentiates platelet aggregation induced by other platelet agonists, such as ADP or collagen. The chronic platelet response, however, may be more related to nitric oxide release as a consequence of regular low to moderate exercise training (12).

In vitro, ex vivo and in vivo quantifications of platelet reactivity ... and strenuous versus moderate, acute exercise

Certainly, a great variety of methods are now available to determine the activity of platelets in experimental studies (15, 16). However, it is largely unknown, how much one could correlate the in vitro or ex vivo findings to the true in vivo biological activities in many of the human biological systems, and the differences between the venous side (where blood is normally sampled for studies) and arterial circulation (where atherothrombotic complications occur) are not fully understood. Thus, the in vivo significance of examining only one ‘portion’ (eg. platelet aggregation in vitro) of a complex system is unclear. Indeed, accumulating evidence suggests that recently developed in vitro and ex vivo platelet reactivity tests that employ shear forces to activate and aggregate platelets are more relevant to the in vivo situation than the conventional platelet aggregometry (in whole blood or platelet-rich plasma) which measures platelet reactivity to different agonists (17-21). Indeed, platelets, activated by shear forces at the site of a stenosis or fissure of an atherosclerotic plaque, play a pivotal role in arterial thrombus formation. Blood flow and wall shear forces also affect the haemodynamic interaction between the blood components and the vessel wall, whilst blood perfusion models allow exposure of various agonists (such as arterial subendothelium, collagen, and extracellular endothelial matrix) to flowing blood – but under (artificial) well-controlled and reproducible conditions. Such ex vivo models simulate a deep arterial wall injury exposed to shear forces typical of flow at sites of stenosed arteries, reflecting the in vivo situation of coronary thrombosis (19-21). More recent interests have focussed on molecular mechanisms of platelet–surface adhesion, platelet–platelet interaction, platelet-leukocytes interaction and the interplay between coagulation and platelet function in the growing thrombi (20-26). In addition, a variety of flow cytometry techniques are in use to evaluate in vivo blood platelet activation (15, 27, 28). By combining an ex vivo model of thrombogenesis with flow cytometry at an arterial shear rate, new flow cytometric techniques have made it possible to detect low levels of activation. These tests appear to be most sensitive and specific and may include determination of platelet glycoprotein IIb/IIIa receptors, platelet surface P-selectin, circulating platelet-leukocyte aggregates, and platelet microparticles (16, 20-28). Nonetheless, no experimental method or test tube can fully and precisely reproduce the biological scenario.

Using these newer methods for the assessment of platelet reactivity, several recent studies have found significant increase in platelet reactivity of one sort or another in vitro or ex vivo after acute exercise at strenuous, but not at moderate intensity

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However, an earlier study by Wang et al demonstrated that moderate exercise at the level of 50-55% of VO₂max apparently has an inhibitory effect, at least in sedentary subjects, whereas strenuous physical exercise in young healthy subjects increased platelet adhesion and aggregation in sedentary as well as in physically active subjects (10). Thus, all these data would suggest that acute strenuous exercise might increase the risk of cardiac arrest whilst acute exercise at moderate intensity may protect us from cardiovascular diseases.

More recently, Wang et al (20) investigated the effects of strenuous, acute exercise on a bicycle ergometer at 80%VO₂max for 40 min in 18 sedentary men. Shear-induced platelet adhesion/aggregation/activation, polymorphonuclear leucocyte (PMN) interaction with surface-adherent platelets under various shear flow conditions with a tapered, parallel-plate chamber (i.e. a linear shear stress flow chamber) were measured both before and immediately after exercise: not unsurprisingly, shear- and agonist-induced platelet activation increased immediately after strenuous exercise. Strenuous exercise also increased the mean velocity and percentage of rolling PMN and decreased the numbers of PMN remaining bound to surface-adherent platelets under shear flow. In addition, strenuous exercise is also associated with greater PMN-dependent inhibition of platelet [Ca²⁺]i elevation and soluble P-selectin release. More importantly, PMN-derived NO metabolites increased whilst oxidized LDL-promoted interaction between platelets and PMN decreased after acute strenuous exercise. Thus, acute strenuous exercise promoted platelet reactivity and also simultaneously enhanced the PMN-dependent antiplatelet function.

In the current issue of Thrombosis and Haemostasis, Wang et al (21) extend their work by reporting that moderate, acute exercise (at 60% VO₂max for 40 min) not only suppresses surface-adherent platelets-PVN interaction under shear flow and the enhancement of platelet-PVN interaction by oxidized LDL, but also increases PMN-derived NO metabolites. In contrast to strenuous, acute exercise that sensitises platelet reactivity, exercise at moderate intensity seems to directly suppress platelet adhesion and aggregation induced by physical shear forces and chemical agonists, accompanied by a decrease in von Willebrand factor binding to platelets and glycoprotein IIB/IIIa activation, and P-selectin expression on platelet under high

Table 1: Recent studies of acute exercise on platelet reactivity.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Exercise</th>
<th>Method</th>
<th>Summary of results</th>
<th>Study and subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilberg et al (27)</td>
<td>Maximal BE for 90 s</td>
<td>Flow-cytometry</td>
<td>Increased platelet reactivity and platelet-leukocyte conjugates</td>
<td>15 healthy non-smokers</td>
</tr>
<tr>
<td>Hilberg et al (28)</td>
<td>Exercise treadmill at 90% individual anaerobic threshold for 1 ~ 2 hr</td>
<td>Flow-cytometry</td>
<td>Increased platelet reactivity and platelet-leukocyte conjugates.</td>
<td>17 healthy non-smoking males</td>
</tr>
<tr>
<td>Ikarugi et al (17)</td>
<td>60% VO₂max for 20 min on BE</td>
<td>Haemostatometry</td>
<td>Increased platelet reactivity and platelet-mediated enhanced coagulation.</td>
<td>13 healthy non-smoking sedentary males</td>
</tr>
<tr>
<td>Ikarugi et al (18)</td>
<td>50% VO₂max for 40 min on BE</td>
<td>Haemostatometry</td>
<td>No significant increase in platelet reactivity</td>
<td>18 healthy non-smoking premenopausal females</td>
</tr>
<tr>
<td>Wang et al (31)</td>
<td>Maximal BE until exhaustion</td>
<td>Tapered, parallel-plate chamber</td>
<td>Epinephrine release potentiates platelet activation via platelet α2-adreno-receptors</td>
<td>15 healthy sedentary males</td>
</tr>
<tr>
<td>Cadroy et al (19)</td>
<td>Strenuous (at 70% VO₂max) v/ moderate (at 50% VO₂max) for 30 min on BE</td>
<td>Parallel-plate perfusion chamber</td>
<td>Strenuous but not moderate exercise increases platelet thrombus formation</td>
<td>15 sedentary healthy males</td>
</tr>
<tr>
<td>Tozzi-Ciancarelli et al (29)</td>
<td>Strenuous (until exhaustion) v/ moderate (at 60% VO₂max) for 30 min on BE</td>
<td>ADP and collagen-induced aggregation</td>
<td>Strenuous but not moderate exercise increases oxidized LDL-mediated platelet activation and decreases plasma and platelet-derived NO bioactivity</td>
<td>15 sedentary healthy non-smoking males</td>
</tr>
</tbody>
</table>

BE, bicycle ergometer; ADP, adenosine diphosphate
shear stress. These results are therefore in agreement with their previously published studies that moderate-intensity exercise may have inhibitory effects on platelet activation (10).

As in many other exercise studies, one limitation of the current study by Wang et al is that subjects used tended to be young and healthy, and thus 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. Furthermore, as previously pointed out, it is not clear how the changes in vitro and ex vivo relate to clinical disease processes, and thus many of the conclusions drawn in these studies remain speculative. Nevertheless, the present study suggests that with moderate, acute exercise, the suppression of platelet reactivity (and platelet-PMN interactions, etc) may lower the risk of vascular thrombosis.

Taken the depth of the evidence available (3, 10-12, 20, 21, 30-33), the data may constitute a rational pathophysiological basis for recommending moderate-intensity but not strenuous exercise as a safe level of exercise. Although at present there is no clear direct clinical evidence that a haemostatic imbalance per se may trigger acute cardiac events after strenuous exercise, more consistent exercise at moderate intensity may blunt the transient risk of sudden death associated with intense or strenuous exertion. The question that will be asked is ‘to exercise or not to exercise?’ As with many things in life which require moderation and routine, we should undertake regular moderate intensity exercise with regular consistency, and keep our haemostatic system and platelets happy – and not make exercise a two-edged sword (3).

References


