

Review Article

The impact of acute and chronic exercise on thrombosis in cardiovascular disease

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Summary

There is now a large and impressive literature showing that people who engage in chronic aerobic exercise or who have better cardiovascular fitness levels, tend to live longer and have lower levels of cardiovascular disease (CVD). However, there is a paradox, as acute aerobic exercise has been associated with an increased risk of CVD events. There are now a number of review articles suggesting that the differential benefits of chronic, relative to acute, exercise might be due to thrombotic changes, though the majority of this data is derived from healthy individuals. However, acute exercise is of greater concern and chronic

exercise of greater benefit to patient populations. In addition, these higher risk groups tend to present with more complex profiles, e.g. they may be taking medications that influence thrombotic pathways. As such, the current review has focused on newer information relating to exercise, physical activity and thrombosis in patient populations, and highlights some of the growing areas in the field. For example, the impact of warm-up exercise, the interaction of medications, and issues surrounding the optimal volume and intensity of exercise.

Keywords

Exercise, fibrinolysis, coagulation, platelets

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Introduction

There is now a large and impressive literature showing that people who engage in chronic aerobic exercise or who have better cardiovascular fitness levels, tend to live longer and have lower levels of cardiovascular disease (CVD) (1). However, there is a paradox, as acute aerobic exercise has been associated with an increased risk of CVD events (2–5). Though the actual risk of an exercise-induced CVD event is quite low, there is clearly a different risk profile in those with and without CVD, the former of which tend to be at greater risk of exercise-induced cardiac events (6).

Since the early 1900s, it has been known that acute exercise can perturb thrombus formation (7), and there are now a number of review articles suggesting that the differential benefits of chronic, relative to acute, exercise might be due to thrombotic changes, which may occur through alterations in platelet function, coagulation, and fibrinolysis (8–10). It would appear that the majority of this data has focused on healthy individuals,

likely due to the challenges associated with studying these phenomena in patients with, or at high risk for, CVD. However, acute exercise is of greater concern and chronic exercise of greater benefit to patient populations (6, 9). In addition, these higher risk groups tend to present with more complex profiles, e.g. they may be taking medications that influence thrombotic pathways. As such, the current review has focused on newer information relating to exercise, physical activity and thrombosis in patient populations, and highlights some of the growing areas in the field.

Acute exercise

Thrombotic changes to maximal exercise (Table 1)

A consistent pattern that has emerged across the literature is that both patients with CVD and non-diseased matched controls tend to demonstrate increased platelet activation, coagulation, and fibrinolysis in response to maximal exercise. This pattern of responses has been observed across several patient populations, e.g. stroke (11), heart failure (12), and intermittent claudication (13),

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Table 1: Details of studies reporting thrombotic changes to maximal exercise.

Reference	Participants	Exercise	Novel finding
Acil et al. 2007 (20)	19 patients with confirmed CAD 25 sex and age matched healthy controls	Peak treadmill test	<ul style="list-style-type: none"> – Exercise increased coagulation (F1+2) and fibrinolysis (Global Fibrinolytic Capacity), with no difference between the two groups – Two hours post exercise, F1+2 returned to baseline levels for controls, but was elevated in the CAD group
Pasupathy et al. 2005 (21)	8 patients with claudication 8 age matched healthy controls	2 peak exercise treadmill test, 1 without a warm-up and 1 with a warm-up	<ul style="list-style-type: none"> – Exercise increased platelet activation and aggregation for both patients and controls – Platelet aggregation was elevated 1 hour post-exercise when patients did not complete a warm-up. When patients completed a warm-up aggregation returned to baseline levels – Platelet aggregation returned to baseline 1 hour post-exercise in controls for both exercise conditions
Wang et al. 2006 (22)	23 healthy, sedentary men	3 exercise sessions 1 low intensity (40% VO ₂ max for 40 min) 1 high intensity (80% VO ₂ max for 40 min) without a warm-up 1 high intensity but with a warm-up (40% VO ₂ max for 20 min)	<ul style="list-style-type: none"> – High intensity exercise without a warm-up induced platelet aggregation and platelet-induced reactive oxygen species production – High intensity exercise with a warm-up platelet aggregation was suppressed, but not reactive oxygen species production – Light exercise was associated with suppression of aggregation and reactive oxygen species production
Kobusiak-Prokopowicz et al. 2006 (23)	35 patients with CAD taking aspirin 10 age and sex matched healthy controls who were not taking aspirin	Peak treadmill test	<ul style="list-style-type: none"> – Exercise-induced platelet aggregation was elevated in the controls but not in the patients – P-selectin expression was up-regulated one hour post-exercise in the patients and not the controls
Collins et al. 2006 (13)	20 patients with intermittent claudication taking aspirin 20 healthy controls	Peak treadmill test	<ul style="list-style-type: none"> – Exercise-induced D-dimer levels were elevated in the both controls and patients – 1 hour post exercise D-dimer levels were still elevated in patients but not in controls
Perneby et al. 2007 (24)	31 men with CAD taking aspirin Randomised to 2 weeks of placebo or clopidogrel	Peak treadmill test	<ul style="list-style-type: none"> – Clopidogrel inhibited platelet activation at rest, compared to placebo – No difference in exercise-induced platelet activation between the 2 groups
Lossnitzer et al. 2008 (25)	10 patients with dilated cardiomyopathy 10 matched healthy controls	Peak cycle test for all participants Controls also completed a sub-maximal test that matched the patients in time and absolute oxygen consumption	<ul style="list-style-type: none"> – Maximal exercise induced similar changes in total platelet count, TAT, and PAP for both groups – Submaximal exercise in controls produced a diminished response for PAP – Maximal exercise response of FPA was higher in controls than in patients, but the sub-maximal increase in controls was equivalent to the maximal increase in patients

though not all studies have reported this pattern of responses (14). It would also seem that coagulation and fibrinolysis are equally activated, and that there may be a null-balance for thrombus formation through these pathways (9, 10). If these processes seem to respond similarly for patients and controls, and if there seems to be no net increase in the prothrombotic state, how might acute exercise increase the risk of thrombotic events? Data from ambulatory studies suggests that there is a critical time window for acute exercise to actually trigger a CVD event, and it would appear that this time window is up to 2 hours (h) (4). This indicates that the recovery period following exercise might be the point at which acute physical activity becomes a risk factor for CVD events.

There are a few studies that have documented fluctuations in coagulation and fibrinolysis during recovery in healthy individuals, with a predominant pro-coagulation state being displayed during recovery (persistence of increased coagulation but diminished fibrinolysis) (15–19). However, these studies have focused on extreme exercise levels or were conducted in highly fit individuals. In contrast, there is less evidence in patients with CVD. However, one study comparing maximal aerobic exercise in 19 patients with angiographically confirmed coronary artery disease (CAD) and 25 sex- and age-matched healthy controls, found that at peak exercise, there was no difference in exercise-induced increases in coagulation (as measured by Prothrombin

Fragment 1+2 [F1+2]) or fibrinolysis (as measured by the Global Fibrinolytic Capacity) between the two groups (20). However, 2 h following the end of acute exercise, the control group had returned to baseline levels, whereas the CAD group still had elevated F1+2 levels. This suggests that in the 2-h post-exercise recovery phase, patients with underlying disease may have a greater potential for clot formation.

Further research has also expanded on this theme and explored potential mediators of the recovery effect. For example, a study of eight patients with claudication and eight healthy controls who completed two bouts of maximal exercise (one with a warm-up of 15 minutes [min] of low intensity walking with breaks, and one without a warm-up) found, unsurprisingly, that the exercise bouts increased fibrinogen- and P-selectin-induced platelet activation, and platelet-leukocyte and platelet-neutrophil aggregation for both patients and controls (21). However, it is noteworthy that 1 h after the cessation of exercise, platelet aggregation returned to baseline levels only when patients had completed the warm-up. When patients did not complete the warm-up, elevated aggregation levels persisted during the recovery. In contrast, aggregation returned to baseline 1 h post-exercise in controls, irrespective of whether they completed the warm-up or not. This study suggests that warm-up exercise may negate the prothrombotic milieu observed during the recovery period of patients. Further evidence to support the beneficial effects of a warm-up comes from a study of 23 healthy sedentary men who completed three exercise sessions: one at low intensity (40% VO_2max for 40 min), one at high intensity (80% VO_2max for 40 min) without a warm-up, and one at high intensity but with a warm-up (40% VO_2max for 20 min) (22). The authors found that high intensity exercise induced platelet aggregation and platelet-induced reactive oxygen species (ROS) production, but that when a warm-up was conducted prior to the exercise, there was a suppression of platelet aggregation (but not ROS generation). In contrast, light exercise was associated with suppression of aggregation and ROS production. These interesting findings generate future research questions. For example, what is the optimal amount of warm-up needed? Is there a positive role for active cool downs following exercise? Finally, what mechanisms are at play if there are truly beneficial effects of a pre-exercise warm-up?

Another potential mediator of the negative effects of acute exercise in patient populations is the impact of medication use, especially aspirin. A recent study assessed platelet aggregation responses to maximal treadmill testing in 35 patients with CAD taking aspirin and 10 age- and sex-matched healthy controls who were not taking aspirin (23). Results of this study showed that post-exercise levels of ADP-induced platelet aggregation were elevated in the controls but not in the patients. In contrast, collagen-induced aggregation tended to increase in both patients and controls. Furthermore, platelet membrane P-selectin expression did not change following peak-exercise, but was up-regulated 1 h post-exercise in the patients only. This study suggests that there is a protective effect of aspirin immediately post-exercise, that provides no benefit in the recovery period. Using a similar protocol, but assessing 20 patients with intermittent claudication who were taking aspirin and 20 healthy controls, Collins et al. (13) found that D-dimer levels significantly in-

creased following exercise for both patients and controls, with no group differences in the magnitude of the exercise-induced change in D-dimer. However, D-dimer levels remained elevated 1 h following the test in patients only. Patients also showed a post-exercise increase in thrombin-antithrombin (TAT) complex, which persisted at 1 h post-exercise. Controls, on the other hand, had no immediate post-exercise surge in TAT levels, but did have elevated levels 1 h post-exercise, which were comparable to those observed in patients. These data support those of Kobusiak-Prokopowicz et al. (23), indicating a protective aspirin effect post-exercise that is not maintained during recovery. Finally, a recent study assessed the impact of combination therapies on exercise-induced platelet activation. Perneby et al. (24) randomized 31 men with documented CAD and taking aspirin to either two weeks of placebo or clopidogrel. Before randomization and post-treatment, all participants underwent maximal treadmill testing. Although the addition of clopidogrel inhibited ADP-induced platelet activation, compared to placebo, this inhibition was similar for resting and exercise-induced activation. As such, exercise-induced platelet activation was not different in the two groups. It should be noted that whilst the level of clopidogrel treatment was constant (75 mg/day), patients were on varying levels of aspirin treatment (75–160 mg/day). This raises issues of optimal treatment levels for the two medications, an issue which could not be explored with such a small sample size. Whilst these studies provide us with exciting insights into possible ways of minimizing the potential negative impacts of acute exercise (i.e. via aspirin administration), study limitations (e.g. failure to compare patients taking and not taking aspirin) suggest that future studies are needed. In addition, given the positive impact of a warm-up on thrombotic changes during the recovery period, and the benefits of aspirin on exercise-induced changes, would the combination of the two provide multiplicative or additive benefit?

Of course, one of the issues involved in comparing maximal exercise between patients with CVD and healthy controls is that patients tend to have lower fitness levels, and thus exercise to lower absolute levels. In an attempt to address this, Lossnitzer et al. (25) assessed changes in haemostatic markers in response to maximal cycle testing in 10 patients with dilated cardiomyopathy and 10 matched healthy control participants. The 10 control participants then completed a sub-maximal test that matched the patients in time and absolute oxygen consumption (this averaged out to be approximately 60% of peak VO_2 for the controls). The authors found that maximal exercise induced similar changes in total platelet count, TAT, and plasmin-antiplasmin complexes (PAP) for both patients and controls. Submaximal exercise in controls tended to elicit similar magnitude changes in total platelets and TAT. However, submaximal exercise in controls produced a diminished response for PAP, compared to the maximal response for both groups. In contrast, the maximal exercise response of fibrinopeptide A (FPA) was much higher in controls than in patients, but the sub-maximal increase in controls was equivalent to the maximal increase in patients. A tentative interpretation of these results could be that plasmin formation is related to the relative intensity of exercise, whereas fibrin formation is related to the absolute intensity of exercise. However, further research is needed to clarify this issue.

Thrombotic changes to non-maximal exercise and comparisons with maximal exercise (Table 2)

Whilst the maximal exercise paradigm provides some interesting information on potential mechanisms and intervention options, it does not really reflect clinical reality. Most people, particularly patient populations, rarely, if ever, exercise maximally (2, 26). As such, understanding the impact of sub-maximal levels of exercise on thrombosis may provide greater information regarding the potential impact of daily physical activity on CVD event risk.

In general, it is believed that submaximal exercise leads to activation of fibrinolysis, coagulation, and platelets (17, 18, 27). For example, a recent study of 20 patients with untreated hypertension who completed 45 min of exercise at 65–70% of maximum predicted heart rate found evidence that the acute-submaximal exercise increased coagulation (decrease in partial thromboplastin time and an increase in factor VIII [FVIII]), increased fibrinolysis (increase in PAP), increased platelet activation (increase in platelet count), and increased endothelial function (increase in von Willebrand factor [VWF]) (28). It has also been suggested that this response is different in patient populations, compared to controls (27, 29). However, this is not consistently found, and where there are equivalent responses in the two groups, understanding why is a critical issue. For example, building upon work that had previously shown 30 min of submaximal exercise (50% maximal wattage) induced similar increases in fibrinogen, tissue plasminogen activator [tPA] activity, tPA antigen, and VWF, as well as decreases in PAI-1 in 25 older women with CVD and 25 healthy older women (30), Walter et al. (31) explored potential explanations for these findings. In an experiment assessing the haemostatic response to 60 min of exercise at 75–80% of maximal VO_2 in 22 young healthy women who were ($n=10$) and were not ($n=11$) taking oral contraceptives, these investigators found that the submaximal exercise

induced increases in F1+2, TAT, FPA, and D-dimer (31). However, those taking oral contraceptives showed an exaggerated prothrombotic response in comparison to those who were not taking oral contraceptives. As aspirin was shown to be potentially beneficial for exercise-induced thrombotic changes, there may be other medications that derive negative effects. For example, what are the impacts of hormone therapy or pain medications?

It has been argued that the extent to which fibrinolysis and coagulation are activated may be dependent upon exercise intensity (32, 33). Few studies of patients with or at risk of CVD have assessed maximal and submaximal exercise within the same study. In addition, the focus of previous studies has been on fibrinolysis and coagulation, with little attention devoted to the assessment of other prothrombotic markers. Recent studies have tried to address these issues. For example, Goette et al. (34) assessed 26 participants (13 with atrial fibrillation and 13 sinus rhythm controls) using a protocol which began with 20 min of exercise at 33% of their predicted maximum workload, and then progressed to volitional fatigue. The authors found that submaximal exercise did not alter platelet factor 4 or β -thromboglobulin and only tended to increase VWF in patients with atrial fibrillation, whereas maximal exercise increased all three markers. In comparison, sinus rhythm participants only demonstrated increases in VWF to maximal exercise. These data suggest that exercising at 33% of predicted maximum is not sufficient to perturb platelet or endothelial function, but maximal exercise is. This result needs to be interpreted with caution as there is clearly no distinction between time and intensity, with the maximal exercise test being a prolongation of the submaximal test. As such, are the effects observed at maximal exercise due to the intensity of the activity or the longer duration? This point is further illustrated by the fact that a previous study (35) found that

Table 2: Details of studies reporting thrombotic changes to non-maximal exercise and comparisons with maximal exercise.

Reference	Participants	Exercise	Novel finding
Lekakis et al. 2008 (28)	20 patients with untreated hypertension	45 minutes of cycling at 65–70% of mean predicted heart rate	– Exercise increased coagulation, fibrinolysis, platelet activation, and endothelial function
Walter et al. 2006 (31)	22 young healthy women who were ($n=10$) and were not ($n=11$) taking oral contraceptives	60 minutes of treadmill exercise at 75–80% of maximal VO_2	– Exercise induced increases in F1+2, TAT, FPA, and D-dimer – This increase was greater in those taking oral contraceptives
Goette et al. 2004 (34)	13 patients with atrial fibrillation 13 sinus rhythm controls	20 minutes of cycling at 33% of predicted max workload, progressing to volitional fatigue	– Sub-maximal exercise did not alter platelet factor 4, β -thromboglobulin, or VWF in patients, whereas maximal exercise increased all three markers – Maximal exercise only increased VWF in controls, with no changes to sub-maximal exercise
Hilberg et al. 2004 (36)	16 moderately trained male patients with insulin-dependent diabetes 16 matched control	Maximal cycle test and 45 min submaximal cycle test at 90% of anaerobic threshold	– Maximal exercise increased platelet reactivity but not platelet activity. – Submaximal exercise showed an attenuated response to maximal – No group differences
Hilberg et al. 2008 (37)	20 healthy men	60 min cycling at 80% anaerobic threshold 45–60 min cycling at 100% of anaerobic threshold	– Both exercise bouts caused increased platelet reactivity and no change in platelet activity, with no differences between the exercise bouts – Platelet conjugate formation was higher at 100% vs 80% of anaerobic threshold

maximal exercise did not increase VWF in patients with atrial fibrillation, though their average exercise length was 5 min, compared to 24 min in the Goette et al study.

Another limiting factor of this literature is the variable levels of submaximal exercise employed across protocols. In contrast to the Goette et al. study (34), which used a submaximal level of 33% of predicted maximum workload, a study of 16 moderately trained male patients with insulin-dependent diabetes and 16 matched control participants used a maximal cycle test and a 45 min submaximal cycle test at 90% of anaerobic threshold (ca. 55–60% maximum) (36). The authors found that platelet reactivity was increased following exercise, but that platelet activity was not altered. Also, there seemed to be a dampened, yet significant response to the submaximal test compared to the maximal test. In addition, there were no group differences reported between those patients with diabetes and the control participants. These results suggest that exercising at 55% of maximum, rather than at 33%, is sufficient to disrupt platelets. A recent study by the same authors provides additional support for these findings. A population of 20 healthy males exercising at 80% (57% maximum) and then 100% (69% maximum) of their anaerobic threshold (37) were found to have increased platelet reactivity, independent of exercise intensity, but not platelet activity. However, exercise-induced platelet conjugate formation was higher at 69% maximum compared to 57% maximum. These results collectively suggest that there is a band of submaximal intensity where platelet reactivity is triggered, but is offset by a positive fibrinolytic/coagulation balance, though we do not know at what exact intensity this band begins and ends.

Chronic exercise

As highlighted above, whilst acute exercise is a serious potential trigger of CVD events, engaging in a programme of chronic exercise has been shown to be beneficial to individuals with a history of CVD or CVD risk factors. For example, longitudinal

studies have shown that increased levels of physical activity reduce thrombotic related cardiovascular events, e.g. non-fatal myocardial infarctions, strokes, and mortality, in those free of CVD (38–40) and those with a history of CVD (41–43). In addition, a recent study suggested that a large part of this relationship was mediated by physiological risk factors, especially blood pressure and haemostatic factors (44). Clearly, the primary ways of assessing the chronic effects of exercise on thrombosis is through epidemiological cohort studies and intervention trials. Given the complexity of such designs, it is unsurprising that over the last few years, there have been few published studies.

Cohort studies (Table 3)

Some recent analyses from cohort studies have provided new information and potential areas for future research. For example, what is the relative importance of physical activity in comparison to other risk factors? In a sample of 109 patients with well controlled essential hypertension, self-reported physical activity levels were associated with F1+2 (45). Those participants who engaged in physical activity for more than 30 min per day or who had manual labor jobs, had lower levels of F1+2 compared to those who were sedentary. The significant impact of physical activity even seemed to mitigate the negative impacts of smoking, as those who smoked but who were active, had similar levels of F1+2 as those who exercised but did not smoke. In contrast, data from a trial of 177 sedentary, overweight men with essential hypertension (46) found VWF to be negatively, and tPA antigen to be positively, correlated with self-reported physical activity levels but not physical fitness (time to exhaustion on a cycle ergometer). However, when covariates were adjusted for (age, body mass index [BMI], smoking, lipid levels), these relationships were no longer significant, suggesting that other health behaviour indicators, i.e. smoking and BMI, may be more important to the prothrombotic state. As such, what is the true relative impact of exercise? For there to be a benefit of chronic exercise, do other individual factors need to be at recommended levels, e.g. calorie intake? Another issue raised

Table 3: Details of studies reporting data from cohort studies.

Reference	Participants	Exercise	Novel finding
Nagashima et al. 2007 (45)	109 patients with well controlled essential hypertension	Self-reported physical activity levels	<ul style="list-style-type: none"> Participants who engaged in physical activity for more than 30 minutes per day or who had manual labor jobs, had lower levels of F1+2 compared to those who were sedentary This was independent of smoking
Hjelstuen et al. 2006 (46)	177 sedentary, overweight men with essential hypertension	Self-reported physical activity levels Physical fitness – time to exhaustion on a cycle ergometer	<ul style="list-style-type: none"> VWF was negatively, and tPA antigen was positively correlated with physical activity levels, but not physical fitness When adjusted for age, body mass index, smoking, and lipid levels these relationships were no longer significant
Gardner et al. 2002 (48)	106 patients with peripheral arterial disease	48 hour accelerometry	<ul style="list-style-type: none"> The group with the lowest tertile of activity had significantly more tPA activity and less PAI-I activity, compared to the other two groups. Greater walking speed was associated with higher tPA activity A greater 6-min walking test distance was associated with lower PAI-I activity

Table 4: Details of studies reporting data from intervention studies.

Reference	Participants	Exercise	Novel finding
Killewich et al. 2004 (49)	41 men with intermittent claudication	6 months of supervised aerobic exercise pre-post analysis	<ul style="list-style-type: none"> - Exercise was associated with a decrease in PAI-1 activity and an increase in tPA activity - Patients with the lowest levels of baseline PAI-1 activity showed the least amount of decrease in PAI-1 post exercise
Lockard et al. 2007 (50)	47 sedentary healthy men and women	6 months of supervised aerobic exercise pre-post analysis	<ul style="list-style-type: none"> - Exercise reduced F1+2 levels and increased Factor VIII antigen levels - Patients with the lowest levels of baseline F1+2 showed the least amount of decrease post exercise - Patients with the lowest levels of baseline Factor VIII showed the greatest increase in post exercise levels
Bjornstad et al. 2008 (52)	15 heart failure patients	20 weeks of supervised aerobic and resistance exercise training pre-post analysis	<ul style="list-style-type: none"> - Exercise decreased soluble CD40 ligand and P-selectin - No change in tumor necrosis factor-alpha, monocyte chemoattractant protein-1, or vascular cell adhesion molecule-1 - After 1-year soluble CD40 ligand and P-selectin returned to baseline
Hobbs et al. 2007 (54)	34 patients with intermittent claudication	2 x 2 factorial trial of 3 months of cilostazol and supervised aerobic exercise	<ul style="list-style-type: none"> - There were no main or interaction effects of exercise on TAT, F1+2, PAI-1 antigen, or tPA antigen at 3 months (post intervention) or 6 months

by the Hjelstuen et al. study that requires further investigation is the comparison of fitness to activity. There is a diverse literature showing that both fitness and activity levels are independently associated with a decreased risk of CVD events (47). However, what is the impact of alterations in the thrombotic state on these relationships? The implications of the Hjelstuen et al. study is that activity level is more important than fitness, though more research is needed to confirm this conclusion.

Clearly, a recurrent issue in these kinds of studies is the objectivity of the measure of physical activity. A slightly older study addressed this issue, in which 106 patients with peripheral arterial disease had their physical activity measured objectively via 48-h accelerometry, which was found to be associated with tPA and plasminogen activator inhibitor-1 [PAI-1] activity (48). When split into tertiles, the lowest activity group (equivalent to less than 35 min of exercise per day) had significantly more tPA activity and less PAI-1 activity, compared to the other two groups. These results suggest that increased daily activity was associated with a decrease in the prothrombotic state. Other interesting sub-findings from this study were that walking speed was associated with tPA activity (greater speed; more tPA), and 6-min walk test distance was associated with PAI-1 activity (greater distance; less PAI-1). This once again raises issues about the optimal intensity of exercise (walking speed) and contrasts it with issues of fitness (walking test distance). These results thus beg the question: do different processes in the thrombotic chain respond differently to varying modes of exercise?

Interventions studies (Table 4)

While the general consensus is that exercise intervention studies have shown that patients who exercise improve their thrombotic profile (9), recent studies have attempted to refine some aspects

of our understanding of the benefits of exercise. For example, fibrinolytic changes were assessed in a pre-post intervention consisting of 6-months of supervised aerobic exercise in 41 men with intermittent claudication (49). The authors found that exercise was associated with a decrease in PAI-1 activity and an increase in tPA activity, suggesting an improvement in fibrinolysis. Whilst this finding is not surprising, the authors also found that there was a significant relationship between baseline PAI-1 and change in PAI-1, such that those with the lowest starting levels of PAI-1 showed the least amount of benefit. In support of this finding, are results of a pre-post analysis of 47 sedentary healthy men and women undergoing six months of supervised exercise (50), which revealed that exercise reduced F1+2 levels and increased FVIII antigen levels. A greater decrease in F1+2 levels with training was also associated with higher levels of F1+2 at baseline, and likewise, a greater increase in FVIII was associated with lower levels of FVIII at baseline. Whilst a regression to the mean effect cannot be discounted, these data suggest a threshold effect of exercise on fibrinolysis and coagulation. If this is true, this leads to questions about the exact threshold level? Once this can be identified, then the impacts of individual baseline levels can be taken into account and individualized exercise prescriptions might be possible.

Further issues which currently plague the exercise intervention literature are how much, how intense, and what kind of exercise is optimal for patients? For example, the question of strength training versus aerobic training is an evolving area in the field. A recent study of the impact of an acute bout of resistance exercise on tPA antigen, PAI activity, and VWF in 14 patients with CAD (51), found that resistance exercise to volitional fatigue increased tPA, decreased PAI, and had no effect on VWF. Following a 1-h recovery phase, all measures had returned to

baseline levels. These results suggest that acute resistance exercise increases fibrinolysis in a similar manner to aerobic exercise. However, what is the effect of a resistance exercise training intervention? Bjornstand et al. (52) recently assessed the impact of 20 weeks of supervised aerobic and resistance exercise training in 15 heart failure patients. Upon completion of the intervention, there was a significant decrease in soluble CD40 ligand and P-selectin, but no change in tumour necrosis factor- α , monocyte chemoattractant protein-1, or vascular cell adhesion molecule-1. One year after training, CD40 ligand and P-selectin levels returned to baseline. Although none of these changes correlated with individual changes in fitness (as assessed by distance on a 6-min walk test), fitness across the group did improve following the intervention and decreased at one year. In contrast, although resistance training was a part of the exercise training, strength was not assessed at any time point. It may be possible that the active component of the intervention was the resistance training and that changes in strength may have correlated with improvements in thrombotic markers. Further research is needed to clarify this. One issue raised by the Bjornstand et al. study is the link between training-induced fitness and thrombosis. An extension of this is the role of exercise-training and improved fitness on thrombotic changes in response to acute aerobic exercise. To our knowledge, there have been no studies that have assessed this in patients with, or at risk of, CVD. However, a recent cross-sectional study assessed the impact of training status on exercise-induced fibrinolysis in 40 young men (16 endurance-trained, 14 resistance-trained, and 10 untrained) (53). The authors found no group differences in post maximal-treadmill levels of t-PA antigen, t-PA activity, or PAI-1 activity, though pre-exercise PAI-1 activity was lower in the resistance-trained group. Clearly these data, suffer from a lack of control for the exercise training undertaken by the participants, and as such, should be interpreted with caution. However, they suggest a minimal benefit of exercise training on acute exercise response. An examination of this in patients with CVD is needed.

Finally, one other area of recent study that requires further exploration is the impact of combined therapeutic interventions. Hobbs et al. (54) used a 2 x 2 three-month factorial trial of cilostazol (a phosphodiesterase III inhibitor which allows patients to exercise longer before pain onset) and supervised aerobic exercise in 34 patients with intermittent claudication to assess their combined impact on thrombosis. Disappointingly, there were no main or interaction effects of exercise on TAT, F1+2, (thrombin generation), PAI-1 antigen, or tPA antigen (fibrinolysis) at three or six months. This is despite the fact that, at six months, there were main effects of exercise and cilostazol on the amount of exercise people could do before experiencing claudication, and despite an additive interaction effect of the two interventions. More work of this kind is needed to define the role of exercise in-

terventions in the context of current clinical treatments in people at risk for thrombotic CVD events.

Summary and future research

The above summary of recent research studies has highlighted a number of areas where new and exciting research opportunities lie, with several key questions that remain to be answered:

- 1) When engaging in maximal exercise, what is the optimal volume and intensity of warm-up exercise that will reduce negative exercise-induced changes in the thrombotic state, especially during the recovery period?
- 2) Is there a role for active cool downs in this process?
- 3) What are the implications of medications on exercise-induced thrombosis? In addition to the studies presented above, previous studies suggest that aspirin resistance is enhanced by acute maximal exercise in patients with or at high risk for CVD (55, 56), and that this resistance is associated with increased platelet aggregation (56).
- 4) Acutely, is there a 'band' of sub-maximal intensity where platelet reactivity is triggered, but where this is offset by a positive fibrinolytic/coagulation balance? In a similar manner, is there a critical volume component to triggering a prothrombotic state? If so, can this be used to better define appropriate exercise programs for individuals? Furthermore, how would chronically exercising at this optimal level influence the long term changes in thrombosis?
- 5) Given that physical inactivity is not the only risk factor for CVD events, what are the relative contributions of exercise and other risk factors, both independently and synergistically, on thrombus formation?
- 6) What is the impact of resistance training in comparison to aerobic exercise on the prothrombotic state? Whilst there is evidence that they may exert similar effects, there are too few studies to be truly convinced that this is the case.

Finally, whilst most of the previous work in the field has focused on thrombotic changes through alterations in platelet activity, coagulation, and fibrinolysis (8, 9), we know that thrombus formation involves more complex processes than those studies to date. Over 150 years ago, Randolph Virchow is credited as describing the underlying factors associated with thrombus formation as being, a) haemodynamic changes, b) endothelial changes, and c) haemostatic changes (57). To our knowledge, only one study to date has assessed the impact of all three components of Virchow's triad in response to exercise. In a study of 72 patients with CVD, submaximal exercise induced significant changes in haemodynamics, haemostatics, and endothelial function (58). Whilst this provides a starting point to assess the impacts of exercise on Virchow's triad, much more work is needed.

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