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Exercise in the Fight Against Thrombosis: Friend or Foe?

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ABSTRACT

Thrombosis is a major cause of morbidity and mortality in Western countries and is associated with a range of chronic diseases such as cardiovascular disease, renal disease, diabetes, and various autoimmune conditions. Improved health care and approaches to the treatment of disease are leading to aging populations that will probably result in an increase in the incidence of thrombosis and associated manifestations over the next few decades. Adopting a physically active lifestyle through regular exercise has been proposed to lower the risk of developing thrombosis. Indeed, it has been demonstrated that exercise is beneficial for health, although there is inconsistent data from studies investigating the effect of exercise on the risk of thrombosis, with reports of both increased and decreased risk across a variety of cohorts. Studies in this area are difficult to critique due to the variety of confounders such as age, body composition, fitness level, underlying disease and treatment, as well as exercise intensity, frequency, duration, and energy expenditure. In younger individuals and those with chronic conditions such as cardiovascular and kidney disease, there is evidence that physical activity is beneficial for the lowering of thrombotic risk, whereas in older individuals the risk is more likely to be unchanged or increased. This review will explore whether exercise is a "friend" or "foe" in lowering the risk of thrombosis. It will also discuss whether elite athletes have a lower risk of thrombosis and whether exercise may help to reduce thrombotic risk in individuals with chronic disease.

KEYWORDS: Exercise, hemostasis, thrombosis, cardiovascular disease, kidney disease

It is probable that the incidence of thrombosis will increase in the next few decades, not only in industrialized nations but also in developing countries, due to aging populations and "westernization" of lifestyles. The incidence of venous thrombosis is ~0.1 to 0.3% of individuals per year and increases to ~1% in elderly individuals.[1–3] Physical activity and exercise have a variety of health benefits, including a reduction in the development of chronic diseases such as diabetes, osteoporosis, and cardiovascular disorders.[4,5] Furthermore, protection against the occurrence of coronary heart disease resulting from moderate to high levels of physical activity has been reported in a meta-analysis of 26 studies incorporating more than 500,000 individuals.[6]

Although increased physical activity and regular exercise may potentially lower the risk of venous thrombosis due to a reduction in stasis, it has also been demonstrated that hypercoagulability may result,

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Coagulopathies and Thrombosis: Usual and Unusual Causes and Associations, Part I; Guest Editors, Massimo Franchini, M.D., Giuseppe Lippi, M.D., and Emmanuel J. Favaloro, Ph.D., M.A.I.M.S.

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particularly after acute and strenuous exercise in untrained individuals. The specific effects of exercise on individual hemostatic parameters (e.g., platelet activity, blood coagulation, and fibrinolysis) have been reviewed by Lippi and Maffulli elsewhere in this issue of *Seminars in Thrombosis and Hemostasis*.[7] The aims of this review instead are to critique the scientific literature in relation to the effects of exercise on the risk of venous thrombosis in (1) the general population, (2) highly trained, or "elite," athletes, and (3) patients with chronic disease, such as cardiovascular disease (CVD) or kidney disorders.

EFFECTS OF REGULAR EXERCISE IN THE GENERAL POPULATION

There is inconsistent data from studies investigating exercise and the risk of venous thrombosis, with reports of both increased[8,9] and decreased[10–12] risk across a variety of subject groups. Studies are difficult to compare due to a variety of confounders, for example, age, gender, use of oral contraceptive pill, body mass index (BMI), fitness level, and underlying diseases. Moreover, exercise-related factors such as intensity, frequency, duration, and expenditure vary between studies. The type and time of exercise exertion are often not described, thus making it difficult to assess the precise impact of exercise on the risk of thrombosis.

Of interest, however, are two large studies published by van Stralen and colleagues that investigated the effect of regular exercise on thrombotic risk. The first investigated the effect of regular participation in sporting activity on the risk of venous thrombosis in 3608 thrombosis patients and 4252 control subjects and reported that participating in sports activities reduced the risk of venous thrombosis (odds ratio [OR], 0.64; 95% confidence interval [CI], 0.58 to 0.71) compared with that of not participating in sports activities.[11] In a more recent study of 5534 participants,[13] the relationship between exercise and thrombosis risk was investigated in the elderly ($\geq$65 years), and it was reported that in those who performed mild-intensity exercise such as walking, there was a non–statistically significant tendency for a decrease in risk compared with that of individuals who did not exercise. Conversely, strenuous exercise such as jogging was associated with an increased risk of venous thrombosis compared with that of either mild exercise or no exercise at all,[13] although the authors concluded that the overall benefits of exercise are likely to outweigh the potentially higher risk of venous thrombosis.

A further study suggests that physical fitness in an older athletic population does not protect against the prothrombotic effects of exercise and that the potential risks persist well into the recovery period.[14] These authors suggest that the older athletic population had an increased risk of cardiac events in view of increased age, and thus prophylactic platelet agents should be considered in this group after appropriate screening and risk stratification.[14] Furthermore, elderly individuals are also considered to be more susceptible to injuries from regular physical activity, especially associated with high rather than low levels of exercise,[15] potentially leading to immobilization, hypercoagulability, and increased thrombotic risk.[16,17]

THROMBOSIS IN THE ELITE ATHLETE

Elite athletes are often portrayed as the epitome of health due to their physical appearance and high level of physical fitness. In contrast with this perception, there is a more insidious side effect to the extreme training regimens usually required to achieve elite sporting status. As well as the potential risk of overuse injuries such as stress fractures[18] and tendinopathies[19] or neuroendocrine disorders such as overtraining syndrome,[20] the type, volume, and intensity of training undertaken by some elite athletes has also been recognized as a cause of "effort thrombosis" (Paget-Schroetter syndrome).[21] However, whether the training required by an elite athlete makes an individual more susceptible to thrombosis is not clear. In addition to training-induced risks, elite athletes often engage in practices that potentially increase the risk of venous thrombosis, such as extended air travel,[22] altitude exposure for training,[23–25] and the use of performance-enhancing supplements such as ephedra,[26] erythropoietin,[27] or anabolic steroids.[28] Furthermore, even minor musculotendinous injuries, which can often occur with exercise, have been attributed to an increased risk of venous thrombosis.[29] Whether these are associated with an increased risk of thrombosis in elite athletes has not been determined. To our knowledge, no study has attempted to determine whether the incidence of thrombosis is altered in elite athletes compared with that of the general population. However, consideration of changes to *Virchow's triad* in context of the demands placed on the elite athlete provides a reference point for discussion of possible outcomes from such a study.

Is the Risk of Thrombosis Greater in the Elite Athlete?

Changes to one or more of Virchow's triad (i.e., blood stasis, endothelial injury, or hypercoagulability) would be required for elite athletes to have a higher thrombotic risk. Athletes undertake activities that could be deemed as risk factors for each of these components. Although venous stasis would not generally be associated with athletic endeavors, there are two potential mechanisms by which the elite athlete may experience venous stasis. First, elite athletes increasingly undertake extended travel for training and competition, potentially exposing

them to an increased risk of travel-related thrombosis.[22,30] However, this may be compensated by mitigating characteristics typical of endurance-trained athletes such as increased plasma volume,[31] decreased blood viscosity,[32] and remodeled vascular structures,[33] perhaps providing little reason to assume that the risk for the athlete would be any greater than for the average person. In contrast, the nature of some sports may impose long periods of compression on specific blood vessels due to equipment or posture or may lead to inflammation or the overdevelopment of musculature that may impinge upon the vasculature, as occurs in Paget-Shroetter syndrome.[34] For example, prolonged periods of cycling has been linked with the development of endofibrosis of the external iliac artery and as a result may provide "soil for luminal thrombosis."[35]

In addition to this potential for impingement of blood vessels is the likelihood of endothelial injury. Athletes are susceptible to a variety of vascular injuries[36] potentially caused by trauma from physical contact,[37] minor injuries such as muscular strains,[29] and repetitious or strenuous loading of the muscles and joints,[10,38,39] all of which have the potential to propagate endothelial injury and thrombosis. Van Stralen and colleagues have provided some of the best evidence linking sports participation to venous thrombosis.[10,29] For example, in a population-based, case-controlled investigation into the risk of sports activity on developing idiopathic upper-extremity venous thrombosis, it was demonstrated that sports activities involving strenuous arm exercise increased the risk of thrombosis in the right arm (the likely dominant arm) by twofold.[10] More recently, minor injuries such as muscle or ligament ruptures, sprains, and contusions were associated with a threefold greater relative risk of venous thrombosis.[29] This was particularly evident for leg injuries (OR adjusted for age and sex, 5.1; 95% CI, 3.9 to 6.7), specifically the sural muscle (OR adjusted for age and sex, 22.5; 95% CI, 8.3 to 61.5).[29] This latter study adds to research by Ehsan et al[38] who reported cases of effort-induced venous thrombosis in endurance athletes but did not provide information regarding previous injuries or other risk factors.

Hypercoagulability is possibly the most uncertain in terms of identifying whether the elite athlete is at any different risk of thrombosis than that of the general population. Elite athletes may engage in many actions that have the potential to influence blood coagulability. Altitude training or hypoxic exposure,[24,40] dehydration from prolonged exercise or to make competition weight,[41] overtraining,[42] and misuse/abuse of ergogenic substances[26] have all been identified as being associated with hypercoagulability. Furthermore, simply participating in exercise, both acute and chronic, has been demonstrated to influence coagulation and fibrinolysis status.[43,44] However, it remains unclear if exercise contributes to blood hypercoagulability in the elite athlete more than in the general population.

Chronic Exercise and Hemostasis

Chronic participation in sport or endurance training has been associated with an overall decrease in the risk of venous thrombosis[10,11] and a reduction in various markers of coagulation.[45] Whereas there appears to be a dose-response effect leading to a negative correlation between hemostasis markers and amount of regular exercise,[11,46] such a relationship has not been entirely consistent.[32,47] Furthermore, in the few studies to investigate hemostasis parameters in elite athletes, there has been no evidence of reduced resting levels of hemostatic markers.[48,49]

Acute Exercise and Hemostasis

The potential for increased platelet reactivity, coagulation, and fibrinolysis after acute exercise creates a conundrum regarding the overall risk of thrombosis during and after exercise in the athlete. For the elite athlete, the influence of exercise intensity may be of greater importance as he or she will often be required to engage in high-intensity exercise in training and competition. However, the existing research is complicated, as findings have at times been conflicting due to factors such as blood sampling and analysis methods, participant health status, and the duration, intensity, and type of exercise employed. An elegant review[44] proposed that whereas light to moderate exercise is of likely benefit, enhanced platelet reactivity and coagulation in response to vigorous exercise may increase the risk of thrombosis. Given that vigorous exercise is an integral component of training and competition for most athletes, this may suggest a heightened risk of thrombosis for this population.

Based on current research, possibly the greatest prothrombotic risk factor for the well-trained athlete is specific to those that engage in repetitive upper-body exercise that has the potential to impact upon the subclavian-axillary vein. The findings of Ellis et al[50] that "effort" was the most prevalent cause of upper-limb deep vein thrombosis, in conjunction with the work of van-Stralen et al[10] associating upper-extremity sports activity with venous thrombosis in the arm, add support to such a suggestion. However, this is not to say that the elite athlete has an overall increased risk of thrombosis. Whereas factors such as hypoxic training, air travel, doping, or misuse of nutritional supplements and acute, chronic, and pathologic (overtraining) training may all potentially contribute to an increase risk of thrombosis, there is no strong evidence to suggest that these factors clearly predispose the elite athlete to thrombosis. Possibly the strongest argument that the elite athlete may be more susceptible to thrombosis is the relationship between

injury and thrombosis.[29] Whereas there is only limited evidence to indicate that elite athletes are more susceptible to injury than are lower-level athletes or the general population, studies such as that of Kujala et al[51] and van Stralen et al[10,13] suggest that certain types of sports participation may increase the risk of specific injuries and the potential for thrombogenesis.

The interactions between elite sports participation and hemostatic variables are complex. Furthermore, much of the literature discussed focuses mainly on endurance exercise as relatively little is known about the effects of resistance training on parameters of hemostasis.[52,53] To address this issue, there is an immediate need for case-controlled studies aimed at identifying whether the risk of thrombosis is in fact higher in elite athletes.

EXERCISE AND CARDIOVASCULAR DISEASE

Although regular exercise arguably provides protection against thrombosis in healthy individuals, these benefits may not necessarily be replicated in chronic disease. In cardiovascular and renal diseases, for example, changes in endothelial and other tissue functions may alter the hemostatic response to exercise. In addition, there is the possibility that prescribed medications may affect hemostatic function either indirectly through improving cardiovascular or endothelial cell function or by directly affecting one or more hemostatic parameters.

Effect of a Single Bout of Exercise in Cardiovascular Disease

Several studies have examined the effects of a single bout of exercise on thrombosis in CVD patients with most[54–57] but not all[58] reporting similar responses to exercise between CVD patients and healthy controls. Across these studies there is a trend for exercise to significantly increase fibrinolytic activity, through increases in tissue plasminogen activator (tPA) antigen and activity, as well as decreases in plasminogen activator inhibitor-1 (PAI-1) activity, in both patients and controls immediately after exercise. The effect of a single bout of exercise has also been examined in heart-failure patients. Platelet activation markers were increased in response to a maximal graded exercise test in patients with mild to moderate stable systolic or diastolic heart failure though interestingly were not different from levels in aged-matched healthy controls,[54] suggesting that acute exercise does not provide protection against platelet activation in these patients.

To our knowledge, there is one study that has reported differences in the hemostatic response to exercise between CVD patients and healthy controls. In a small yet elegantly designed study, Mustonen et al[58] used a matched pair design to investigate the effect of a single bout of exercise in a group of 15 patients with peripheral arterial occlusive disease and 15 healthy controls who were matched for age, sex, medication use, smoking habit, and fitness. Subjects performed a graded exercise test on a treadmill until a point of unbearable claudication. The healthy controls performed the same test and ceased exercise once their heart rate reached the same level as that reached by their matched patients. After exercise, thrombin-antithrombin complexes were increased in the patients but not the controls reflecting increased thrombin generation and hypercoagulability in this group.

A single study has examined the effect of a bout of resistance (strength) training on hemostasis in CVD.[55] In an uncontrolled study, low- to moderate-risk males ($n = 14$; 58 ± 9 years; BMI 26.7 ± 4.0 kg.m^{-2}) from an outpatient cardiac rehabilitation program performed one set of 10 repetitions of eight different resistance-training exercises using major muscle groups to volitional fatigue. There was a significant increase in tPA antigen and decrease in PAI-1 activity immediately after the resistance exercise. At 1 hour after exercise, PAI-1 activity remained significantly decreased, however tPA antigen had returned to baseline levels, suggesting that resistance training also provides a protective effect against risk of thrombosis by increasing fibrinolytic activity.

Results of studies investigating the effect of a single bout of exercise on hemostatic function in CVD consistently suggest that exercise increases fibrinolytic activity and in a manner similar to that observed in a healthy population. It should be noted, however, that these studies typically used medically stable patients and did not control for medication status. Although medications such as angiotensin-converting enzyme (ACE) inhibitors are important for the regulation of blood pressure in CVD, they have been reported to have procoagulant effects through increased expression of PAI-1[59] and thus may partially contribute to the prothrombotic state in CVD.

Effect of Chronic Exercise on Hemostasis in Cardiovascular Disease

Whereas the effect of a single bout of exercise on hemostatic function in CVD has been well described, the effects of regular (chronic) exercise on hemostatic parameters in these patients are not as clear, with several studies reporting disparate results.[60–63] For example, it has been reported that habitual physical activity has no effect on either flow-mediated dilation of the brachial artery or plasma von Willebrand factor (VWF) concentration in patients with hypertension,[60] whereas a more recent study[61] reported significantly lower prothrombin fragment $1 + 2$ concentrations in hypertensive patients that undertook regular exercise than that of participants

who did not, reflecting reduced thrombin generation with exercise.

Two small studies used an interventional design to determine the effect of an exercise-training intervention on hemostatic balance in CVD.[62,63] The effect of a 6-week phase II cardiac rehabilitation program on markers of hemodynamic and fibrinolytic function was investigated in a small group ($n = 14$) of patients.[62] Although markers of hemodynamic function (resting heart rate and systolic blood pressure) were improved after intervention, there were no significant changes in either the activity or RNA expression of tPA or PAI-1. A similar study investigated the effect of a 6-month training program on hemostasis parameters in a small group ($n = 16$) of male heart-failure patients and reported no effect of the training protocol on PAI-1, thrombin activatable fibrinolysis inhibitor (TAFI), urinary plasminogen activator (u-PA), or tPA, either at rest or immediately after exercise.[63]

Chronic Exercise and Endothelial Function

Several studies have used interventional designs to determine the effect of exercise training on endothelial function in CVD.[64–68] A recent uncontrolled study[65] investigated the effect of a 20-week aerobic training protocol on arterial stiffness in a small group ($n = 9$) of older hypertensive patients. The authors used high-resolution ultrasound to determine arterial distensibility and the β stiffness index of the carotid and brachial arteries. These parameters were measured prior to, immediately after, and 24 hours after an acute maximal treadmill exercise session, at baseline and after a 20-week aerobic training protocol. They reported no change in either measurement as a result of either acute or chronic exercise and attributed the lack of change in arterial stiffness after the chronic training to the possibly larger aging effect attributable to the presence of hypertension. In contrast, Hambrecht et al[67] investigated the effect of 6 months of endurance exercise training on total peripheral resistance (TPR) at rest and during exercise in heart-failure patients and reported that not only did the exercise reduce TPR in the training group, but also it prevented significant increases that were observed in the nonexercising controls.

Two studies have investigated the effect of exercise training on forearm blood flow in chronic heart failure (CHF).[64,68] Significant changes in forearm blood flow and decreases in forearm vascular resistance were reported in 12 patients with CHF after an 8-week combined endurance and resistance training protocol.[68] More recently, we observed similar improvements in forearm blood flow at rest and in response to submaximal exercise and limb ischemia in a group of 19 CHF patients after a 3-month circuit resistance training intervention.[64] Changes in forearm blood flow with resistance training were accompanied by increases in skeletal muscle capillary density in a subpopulation of patients who volunteered to undergo skeletal muscle biopsies from the vastus lateralis prior to and after the exercise training program,[69] which may explain the increase observed in skeletal muscle blood flow.[64]

EXERCISE AND KIDNEY DISEASE

Cardiovascular morbidities such as left ventricular hypertrophy and arterial disease are commonly associated with end-stage kidney disease (ESKD).[70] In addition to the characteristic lesions of atherosclerosis, dialysis patients also experience thickening and fibrosis of the arterial wall in response to pressure and volume overload, loss of elastic fibers, and medial fibrosis.[71] Such arterial remodeling, along with medial calcification, causes arteries to stiffen, exacerbating left ventricular dysfunction.[72] In these patients, more than 60% of deaths have been attributed to coronary artery disease compared with 40% of cardiac deaths in the general population.[73] While the cardiovascular alterations that occur in ESKD are well described, the precise mechanisms responsible have yet to be elucidated. Potential mechanisms are beyond the scope of this article and are reviewed elsewhere.[74] Regardless of the cause of the cardiovascular pathologies and increased arterial stiffness in ESKD, there is evidence that altered hemostatic balance in kidney disease patients[75–77] is dependent on disease progression,[77] coagulation activation,[78] and CVD incidence.[76] Although the effects of exercise on hemostatic function have not been reported in chronic kidney disease (CKD) patients, oxidative stress[79] and inflammation[80] are reduced as a result of chronic exercise training, providing evidence that regular exercise may in turn have favorable effects on hemostasis in this population.

Recent studies have reported reductions in arterial stiffness[81,82] and pulse wave velocity (PWV)[82] in hemodialysis patients as a result of aerobic exercise training. In an uncontrolled study of 11 hemodialysis (HD) patients,[81] a significant improvement in augmentation index after 3 months of supervised exercise training outside of dialysis was reported. More recently, aortic PWV was significantly decreased after 3 months of intradialytic (ID) exercise using a crossover study design in 19 HD patients.[82] However, a similar study in our laboratory that has just concluded (unpublished observations) has failed to demonstrate any similar effect of aerobic training on either augmentation or PWV. In our study, baseline PWV in participants was similar to data in healthy individuals,[71] in contrast with baseline PWV previously reported in ESKD patients.[71] Furthermore, the volume of exercise undertaken by our patients was also lower than that in the previous study.[83] It is therefore possible that the benefits of exercise to arterial

health in ESKD may be dependent on the severity of kidney disease and/or to a critical training load.

A single study has examined the effect of exercise training on oxidative stress in CKD patients.[84] Patients ($n = 26$) with moderate CKD were separated into a training group that performed low-intensity aqua aerobic exercise twice a week for 12 weeks ($n = 17$) and a nontraining control group ($n = 9$). At the end of the training period, the plasma concentration of reduced glutathione was increased and serum lipid peroxidation was decreased, indicating improved antioxidant defense mechanisms. In contrast, the concentration of reduced glutathione was decreased and lipid peroxidation was increased in the control group, although results did not reach the level of statistical significance. These results indicate that this type of exercise training may not only reduce oxidative stress but also prevent continued increases that may be linked to progression of cardiovascular dysfunction.

Several studies have investigated the effect of exercise on inflammatory markers in CKD. An observational study[85] investigated the relationship between inflammatory markers and physical activity in hemodialysis patients ($n = 47$). No significant associations were reported between weekly physical activity level and any of the inflammatory markers measured, suggesting that physical activity may not influence inflammation in this population. To date, only a single study has investigated the effect of an exercise intervention on inflammation in CKD.[86] Inflammatory markers were measured in a group of nondialyzed CKD patients ($n = 26$) after 12 weeks of resistance training. In contrast with the previous study,[85] serum C-reactive protein (CRP) and interleukin-6 levels were reduced in patients who had undergone training compared with that in those randomized to the control group, indicating that the resistance-training protocol reduced inflammation. Given the close relationship of inflammation with blood coagulation in the pathogenesis of vascular disease,[87] it would seem reasonable to suggest that controlling inflammation in patients with kidney disorders may also help to lower the risk of thrombosis.

CONCLUSION

Studies to date that have investigated the relative benefits of exercise on hemostasis have been limited by a large number of variables. It is clear that large, prospective trials that account for the myriad of these potential confounders are required to determine the precise effects that different levels of exercise have on the risk of thrombosis in both the general population and in disease states. There is evidence that in younger individuals and those with chronic diseases such as cardiovascular and kidney disease, exercise is a "friend" rather than "foe" and that physical activity is beneficial for lowering the thrombotic risk in these groups. The future may see exercise prescription tailored to the individual on the basis of age, physical fitness and disease state, and monitored regularly.

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