REVIEW

Marathon Maladies: Venous Thromboembolism Risk Associated with Marathon Running

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ABSTRACT

Marathon running exposes athletes to thrombogenic risk factors that increase blood clot risk in otherwise healthy athletes. Understanding the effect of these factors on coagulation and fibrinolysis can aid both the practitioner and athlete in primary and secondary prevention of venous thromboembolism. Accordingly, the purpose of the present review is to synthesize evidence surrounding athlete specific risk for venous thromboembolism. *Journal of Clinical Exercise Physiology*. 2016;5(1):1–5.

Keywords: endurance exercise, blood clot risk, mechanical prophylaxis

INTRODUCTION

Strenuous endurance exercise (e.g., marathon running) activates the coagulatory system by immediately increasing markers of coagulation such as thrombin-antithrombin complex (TAT), prothrombin fragment 1 and 2, and d-dimer (5,18,22). However, the fibrinolytic system (e.g., tissue plasminogen activator [t-PA] antigen and activity) is activated in coordination with the coagulatory system, such that changes in coagulation are paralleled by an activation of fibrinolysis to preserve hemostatic balance. A large body of evidence supports parallel activation of both coagulation and fibrinolysis following endurance exercise, including sustained downhill running (26), high-intensity exercise (21), and in older runners (30). While this collective evidence indicates that exercise-induced hemostatic activation is not detrimental for most individuals, factors incident to marathon training and competition may disproportionately activate the coagulatory system and increase venous thromboembolism (VTE) risk. Indeed, there is a growing body of published and anecdotal literature detailing reports of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) after prolonged, strenuous endurance events in otherwise healthy athletes (1,6,7,12,14,27,28,33). Given that marathon participation has increased 40% over the past decade with 550,637 finishers in 2014 (24), the increased risk of VTE associated with strenuous endurance events has implications for the increasing numbers of athletes who compete in endurance events.

Thus, the overall aim of the present review is to provide an evidence-based summary of the present state of the literature surrounding VTE risk in endurance athletes. Specific objectives are to appraise thrombogenic factors specific to endurance athletes, discuss possible interventions to mitigate VTE risk, and pose considerations for clinicians in their counseling of athletes for the prevention of VTE.

RISK FACTORS FOR VENOUS THROMBOEMBOLISM ASSOCIATED WITH MARATHON RUNNING

VTE is a leading cause of mortality and morbidity in clinical populations with approximately 1 case per 1,000 individuals

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and occurs as often as stroke (10), contributing to $7-10 billion in United States health care costs per year (8). Traditional health conditions or factors known to increase VTE risk are: increasing age, inherited thrombophilia, prolonged immobility, malignancy, major surgery (ie, general anesthesia for ≥30 min), physical trauma, prior VTE, and pregnancy (10). In the healthy athletic population, the overall incidence of athlete-related VTE is not well documented, though cases are relatively rare.

Rudolph Virchow was the first to propose VTE to be the result of at least 1 of 3 underlying etiologic factors (ie, venous stasis, vascular injury, and hypercoagulability); now known as *Virchow's triad* (15). While moderate aerobic exercise prevents the underlying physiological processes of clot formation (23), strenuous, sustained endurance activity may expose athletes to perturbations in the coagulation-fibrinolysis cascade that can increase risk for VTE. For example, an endurance athlete can experience all 3 components of Virchow's triad, including repetitive microtrauma, endothelial damage, and dehydration during competition; followed by periods of inactivity, immobility, and venous stasis while traveling to and from and/or recovering from the athletic event. Of note, parallel increases of coagulation and fibrinolysis after an endurance event occur irrespective of exercise modality (ie, running, swimming, cycling) (32). However, marathon runners experience markedly greater hemostatic activation than long-course triathletes (9), possibly due to foot-strike–induced mechanical trauma. Potential thrombogenic factors specific to marathon runners according to Virchow's triad are summarized in Figure 1 and reviewed below.

Venous Stasis

Of the several published and anecdotal case reports detailing VTE in athletes, travel is a frequent commonality (14-17). Endurance events such as a marathon or running relay (e.g., Ragnar Relay) often require travel to and from the event, with long periods of immobilization or inactivity, juxtaposed with prolonged, strenuous exercise. It has been shown that travel by any mode (ie, car, bus, train, or plane) at least 4 h in duration increases risk of DVT twofold (13). However, until recently, the combination of travel and endurance exercise and its effect on hemostatic balance was unknown.

We were the first group to examine the effect of prolonged exercise and air travel on thrombotic risk factors (3,18). We examined 41 time-qualified runners participating in the 2010 Boston Marathon who either flew >4 h (travel) or drove <2 h (control) to the race. Blood samples to assess coagulation (TAT, d-dimer, p-selectin, and microparticles) and fibrinolysis (t-PA activity) were obtained the day before, immediately after the marathon, and the day after the marathon following the flight home. Immediately following the marathon, markers of coagulation and fibrinolysis were elevated in both the travel and control group, indicating hemostatic activation. However, marathon-induced increases in coagulatory factors were greater in the travel group than the control group. These coagulatory factor increases were not matched in parallel with fibrinolytic factors, indicating a hemostatic shift towards a more procoagulatory state in athletes who traveled >4 h and ran a marathon. Among individuals who flew >4 h, coagulation factor TAT increased to an almost twofold higher extent after the race in the travel group than in controls (5.0 ± 4.0 to 12.9 ± 15.6 mg•L^{-1} versus 4.0 ± 1.2 to 6.1 ± 1.2 mg•L^{-1}; $P = .02$). The increase in TAT in the travel group was greater in older runners, indicating that age appears to moderate the coagulatory response to endurance exercise in combination with air travel >4 h.

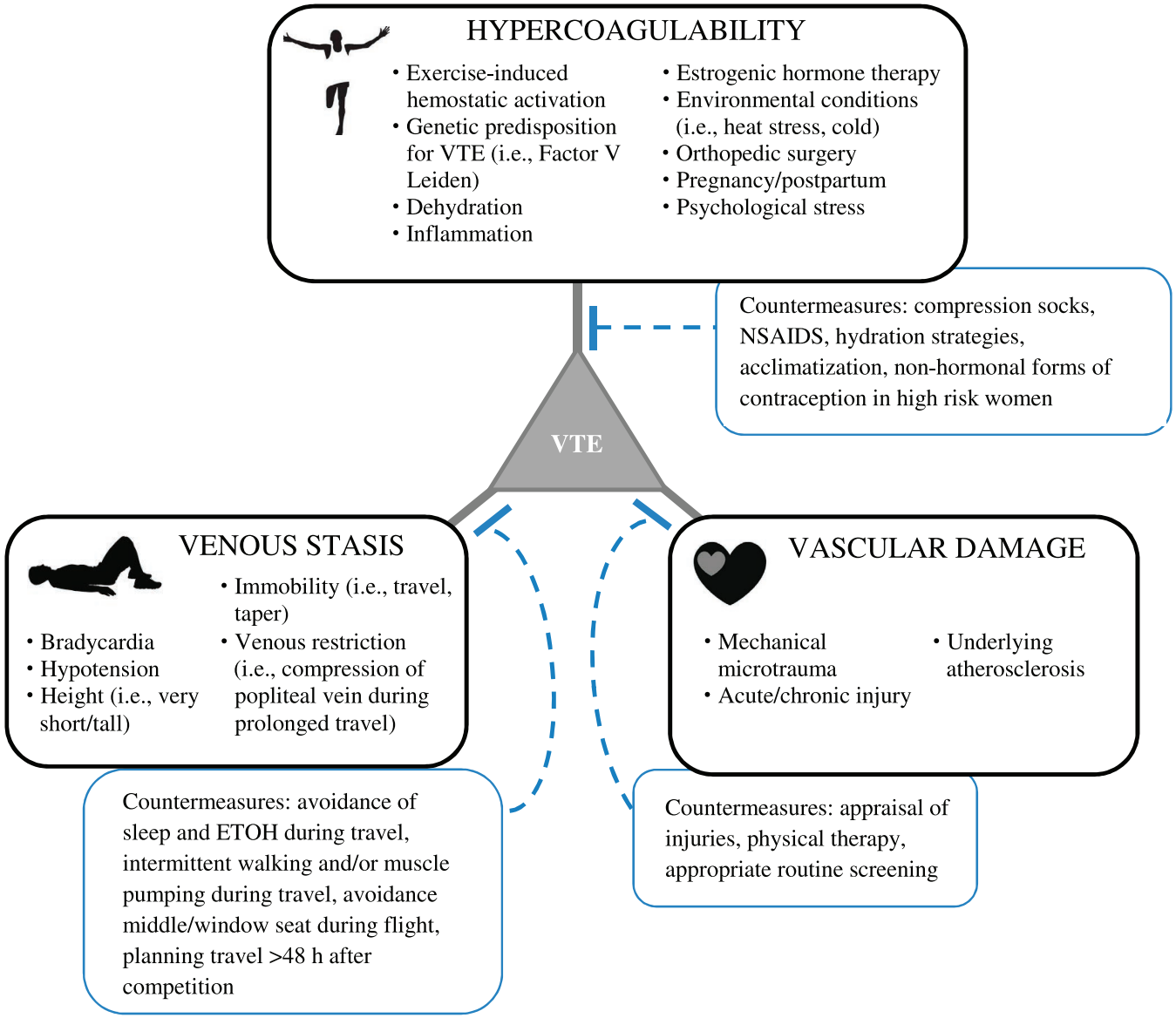
Similarly, exercise-induced increases in coagulatory factor d-dimer, a clinical biomarker of DVT, were also significantly greater immediately after the marathon in the travel group of athletes (142 ± 83 to 387 ± 196 ng•mL^{-1} versus 85 ± 26 to 233 ± 95 ng•mL^{-1}; $P = .02$). In fact, 6 of the travel subjects (versus no controls) had d-dimer values that exceeded the clinical threshold for preliminary diagnosis of DVT (ie, >500 ng•mL^{-1}). These data provided the first evidence that the combination of marathon running and air travel >4 h disrupts the hemostatic balance and favors a coagulatory response, which also appears to be exacerbated with increasing age.

In addition, bradycardia and hypotension as a result of training are not uncommon characteristics of endurance athletes (29). Hypothetically, low circulatory blood flow at rest may increase risk of VTE, particularly in combination with long periods of tapering, low activity, and prolonged travel (ie, venous stasis); though this has yet to be examined to the best of our knowledge (11). Extreme height (ie, shorter or taller than average) may influence hemostatic balance. Interestingly, men >71 in (180 cm) experience an approximately twofold increased risk of VTE compared with men <68 in (173 cm) (4). It is unclear if this phenomenon is due to differences in venous surface area, number of venous valves, or hydrostatic pressure among height quartiles (16). Theoretically, shorter athletes may experience greater compression of the popliteal vein during travel due to fixed seat dimensions, while taller athletes may experience similar venous restriction due to cramped leg space. The potential interaction among travel, height/limb length, and endurance exercise on hemostatic activation certainly warrants investigation.

Hypercoagulability

Endurance athletes may be exposed to thrombogenic factors that influence hypercoagulability in response to training, competition, and environment. Incidence of a genetic hypercoagulability disorder, such as Factor V Leiden thrombophilia is found in 20% to 25% of patients with VTE and is a significant risk factor (17,35). For example, individuals who are homozygous for the Factor V Leiden, *F5* 1961 G>A [Arg>Gln rs6025/560] risk allele (ie, A) possess an 80-fold greater risk for VTE, while heterozygosity confers a sevenfold risk. Moreover, estrogen-based oral contraceptives are considered a risk factor for the development of a clot during air travel (6,8), as they increase the risk of VTE five-fold (2). Interestingly, contraceptives are commonly used by athletes and military personnel for menstrual suppression during competition/missions, perhaps increasing their risk for VTE

FIGURE 1. Marathon specific risk factors for venous thromboembolism according to Virchow's triad and potential countermeasures to mitigate risk.



(3,19). Dehydration and inflammation post-competition also present as significant, but modifiable, risks.

Vascular Damage

Sustained, prolonged exercise results in microtrauma to the endothelium due to increased blood flow and laminar shear stress exerted upon the vascular wall. Prolonged shear stress induces platelet release, aggregation, and pro-inflammatory markers (ie, leukocytes, high sensitivity c-reactive protein), which in turn activate the clotting cascade. Inflammatory processes recruit adhesion molecules (ie, p-selectin) and immunoglobin-like molecules (ie, soluble vascular cell adhesion protein 1; sVCAM-1) to encourage tethering, rolling, and adhesion of leukocytes to the vascular wall, which further promote inflammation and increased risk of VTE (13). We have previously shown that p-selectin nearly doubles after a marathon and that increasing age is associated with greater post-exercise levels of this thrombotic risk marker (19).

COMPRESSION SOCKS AND OTHER STRATEGIES TO MITIGATE VENOUS THROMBOEMBOLISM RISK IN MARATHON RUNNERS

Because of the infrequent and atypical presentation, cases of VTE in athletes are often misdiagnosed initially, and recommendations for athlete specific screening and prevention are equivocal. That being said, awareness of VTE in endurance athletes has garnered significant attention over the past few years, and consequently running associations and events are increasingly urging athletes to wear compression socks during

flight and/or competition to mitigate risk of VTE (24,25). Although these informal (albeit common sense) recommendations are grounded in evidence derived from clinical populations, the efficacy of compression socks to attenuate marathon-induced hemostatic activation has only recently been tested. Our group recently examined the safety and efficacy of compression socks worn during a marathon on hemostatic activation immediately following the 2013 Hartford Marathon (34). Using a similar study design as previously described (18), venous blood samples were obtained before, immediately after, and the day after a marathon for the assessment of coagulatory factors (ie, TAT and d-dimer), a fibrinolytic factor (ie, t-PA activity), and hematocrit. Subjects in the sock group (n = 10) were compression sock naïve and received their socks (2XU Compression Performance Run Sock; 19-25 mmHg at the ankle) at the marathon expo and were instructed to wear them to the race start and throughout the duration of the marathon. Subjects in the control group (n = 10) were instructed to wear their typical athletic socks, but refrain from compression sock use during training, during the marathon, or the day after the marathon.

Consistent with findings from previous studies, we observed parallel increases in markers of coagulation and fibrinolysis immediately following strenuous exercise as evidenced by exercise-induced increases in d-dimer, TAT, and t-PA activity. Average t-PA activity across all 3 time points was lower in the compression sock group compared to the control group (11.0 ± 1.0 ng•mL^{-1} versus 9.07 ± 1.0 ng•mL^{-1}; P = .04). Similarly, average TAT across all 3 time points tended to be lower in the compression sock group compared to the control group (3.4 ± 0.2 mcg•L^{-1} versus 2.8 ± 0.2 mcg•L^{-1}; P = .07). Because runners were not wearing compression socks at baseline, and there were no differences in hemostatic markers at baseline between groups, the sock effect on t-PA activity and TAT was driven largely by the effect of socks on immediate and 24 h post-marathon hemostatic markers. Therefore, our results suggest that overall hemostatic activation following a marathon was lower with compression socks, with no significant interactions at any individual time point. Because compression socks are increasingly popular with athletes due to their supposed enhancement of exercise performance and recovery, these results were reassuring in that compression socks appeared safe for overall use in runners. Although interesting, we caution that our interpretations are based on a small investigation, and larger studies are required to establish the efficacy of compression socks to mitigate VTE risk in athletes. As prolonged travel (>4 h) activates the coagulatory system and many marathoners travel long distances to their events, the use of compression socks may be effective for preserving hemostasis in athletes who are considered high risk for VTE.

Other common sense recommendations (Figure 1) to consider may be the use of nonsteroidal anti-inflammatories (NSAIDs) or prophylactic baby aspirin (25), isometric exercises to engage the skeletal muscle pump and prevent venous stasis, proper hydration strategies (2,3,20), and/or abstaining from sleeping pills or excessive alcohol use during extended travel to and/or from an endurance event. Although the aforementioned interventions have yet to be tested in combination with endurance exercise, they carry little to no risk. It is prudent, however, that prophylactic pharmacologic interventions such as NSAIDs or baby aspirin be implemented only after careful appraisal of risk by a clinician.

CLINICAL IMPLICATIONS

Exercise-induced hemostatic activation, with proportional augmentation of both coagulation and fibrinolysis is a normal response to exercise. However, certain thrombogenic factors may shift hemostatic balance to a procoagulatory state and increase risk of VTE in otherwise healthy athletes. Understanding the nature and impact of these individual and combined factors will ultimately aid both the practitioner and athlete in primary and secondary prevention of VTE associated with prolonged endurance exercise and travel to and from the event. Although further research is needed, common sense preventive measures such as compression socks are readily available. They are an inexpensive intervention to counteract stasis and hypercoagulability and appear safe for use. Athletes should be aware of manufacturer specifications and proper sizing techniques. For example, endurance athletes typically have larger calves and socks should be sized according to calf circumference (as opposed to shoe size) to avoid misuse (31). Proper appraisal of potential risk factors should be individualized to the athlete, training cycle, and event. Appropriate interventions can then be considered that both preserve performance and lower VTE risk, which is critically important given the time and effort associated with training and competition.

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