Exercise and Air-Travel–Induced Alterations in Blood Hemostasis

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Abstract

Hemostasis is the ability of the body to control blood loss following vascular injury. The process is composed of a complex array of pathways made up of the coagulation and fibrinolytic systems that allow the fluid blood to clot after injury and then the subsequent breakdown of the clot, permitting repair of the injured tissue. Studies to date have shown exercise to be a stimulating factor in both the coagulation and fibrinolytic pathways. Additionally, air travel has been shown to be a risk factor for thrombosis. However, few studies have examined the combination of exercise and air travel on hemostasis, despite documented evidence of venous thrombotic episodes in the sports and endurance (marathon/triathlon) communities. This review summarizes and analyzes the literature with regard to (1) acute and chronic exercise, (2) air travel, and (3) exercise and air travel. In addition, the review examines confounding variables that may contribute to coagulation and strategies to prevent blood clot formation after exercise and during air travel.

Keywords

- coagulation
- fibrinolysis
- exercise
- air travel

Blood clot formation (thrombosis) is a significant event of which both athletes and other individuals who travel by air must be aware. Blood clots arising in veins can lead to a venous thromboembolism (VTE), either as a deep vein thrombosis (DVT), usually in the legs, or as a pulmonary embolism (PE) in the lungs. In the general population, DVTs arise in 1 out of 1,000 individuals.[1]

Individuals may carry various risk factors for VTE, such as being overweight or obese, a history of VTE, recent major surgery, or a hereditary disorder,[2] all of which enhance blood clot formation. Air travel increases the risks[3] and may be composed of cabin-related factors, particularly during long-haul flights, such as prolonged sitting, hypoxia, and dehydration. Together, these factors can increase the risk of VTE by two- to fourfold.[4] Since approximately 2 billion passengers fly worldwide each year, with approximately 300,000 per year taking long-haul flights of more than 5 hours,[5] the health risks posed by travel-related VTE are widespread.

Regular physical exercise is recommended to lower the risk of cardiovascular disease and avoid thrombotic events, including both DVT and PE.[6] However, intense, acute physical exercise can also activate coagulation by wearing away at the endothelium base layer, that is, during endurance exercise such as marathons,[7] triathlons,[8] and extensive resistance exercises.[9] During intense physical exercise, activity of the fibrinolytic system increases in tandem with the coagulation system to maintain hemostatic balance. However, even though this is the case in most circumstances, participants in some events such as ultramarathons have shown an imbalance where fibrinolytic activity returns to normal while coagulation activity remains elevated for almost 2 days after completion.[10]

Vigilance is required for individuals who exercise intensively, especially athletes who fly cross-country for competition, as they are the most likely to incur VTEs.[11] These risks can last for up to a month after the event and travel have occurred.[12] Although the effects of air travel in conjunction with physical exercise on hemostasis are not well understood, combining air travel and intense exercise may cause a coagulation–fibrinolytic imbalance that increases the risk of VTE. However, only a handful of studies have examined this question in any detail.

Issue Theme Hemostasis in Exercise and the Athlete; Guest Editors: Murray Adams, BSc(Hons), PhD, MAIMS, FFSc (RCPA), and James Fell, BEd, MPhil, PhD.

DOI https://doi.org/10.1055/s-0038-1670640.
ISSN 0094-6176.

This review begins with an overview of secondary blood coagulation and fibrinolysis, then examines research that looks at (1) the effect of exercise on blood coagulation and fibrinolysis, (2) the effect of air travel on blood coagulation and fibrinolysis, and (3) confounding variables that may contribute to coagulation and strategies to prevent blood clot formation after exercise and during air travel. Last, it turns to research regarding the combined effects of air travel and exercise on blood coagulation and fibrinolysis in competitive athletes.

Overview

Blood coagulation involves a series of integrated protein reactions. The classical concept of the coagulation "cascade" is largely outdated, but it is conceptually useful when considering laboratory tests of hemostasis.[13] Two independent but linked pathways can lead to clot formation in vitro: the tissue factor pathway (classically referred to as the extrinsic pathway) is activated by injury to the vasculature and exposure of tissue factors, while the contact factor pathway (classically referred to as the intrinsic pathway) is initiated through the exposure of blood to the endothelial surface. In vivo, the tissue factor pathway is more important in generating thrombin, and within the concept of the cell-based model of coagulation, which is based on coagulation overlapping over three phases: (1) initiation, (2) amplification, and (3) propogation.[13] An important component of coagulation is the activation of factor X, which converts prothrombin to thrombin. Thrombin's main function is the conversion of soluble fibrinogen to insoluble fibrin. It also promotes coagulation by activating proteins involved in the coagulation (factors V, VIII, XI) as well as the activation of platelets, which also play a central role in stable clot formation.[13]

The process of fibrinolysis normally keeps blood in the fluid state and free from clot formation. During active clot formation following injury, fibrinolysis acts to prevent excessive thrombus formation. The fibrinolytic system acts via the protease plasmin to further control fibrin formation through degradation and production of small fragments, including D-dimers: plasmin is activated by the urokinase plasminogen activator or tissue plasminogen activator (tPA), which are in turn regulated by the plasminogen activator inhibitor I (PAI-1).[14]

Effects of Endurance and Resistance Exercise Training on Hemostasis

Exercise is a powerful stimulant that produces physiological adaptation at the molecular, cell, and tissue levels. However, these adaptations are dependent on the interactions of exercise intensity and volume, rest intervals, muscle-mass involvement, specific muscle actions, and motor units recruited. The many benefits obtained from regular, sustained physical exercise are unquestionable, especially for the cardiovascular system.[15] Indeed, regular exercise has been specifically shown to yield a less thrombotic state.[16] Moreover, both DVT and PE have been documented in several athletes, especially marathon runners,[17,18] and at least a small percentage of otherwise healthy, avid exercisers may face an elevated risk of VTE following vigorous exercise.

Acute Exercise and Hemostasis

Several studies have shown that strenuous exercise simultaneously activates coagulation and fibrinolysis. However, results vary due to the wide range of types, intensities, and durations of exercise investigated.[19] Study populations also differ greatly, including factors such as the age and sex of participants, their experience in the type of training under study, and the blood homeostatic variables analyzed—all of which may affect the results and outcomes. Nonetheless, acute exercise has been shown to produce a hypercoagulable state across populations and with a wide variety of exercise types and intensities. For example, the activated partial thromboplastin time (aPTT), a marker of the contact pathway of in vitro coagulation, was consistently decreased after maximal-effort endurance exercise,[20,21] marathons,[22] and a heavy resistance training session,[9] while the prothrombin time (PT), a marker of the tissue-factor pathway of in vitro coagulation, demonstrated at most a very slight change[21] or even no change at all.[22,23] It has been suggested that this decrease in aPTT can be attributed to an increase in factor VIII.[24] Factor VIII exists in vitro in complex with von Willebrand factor (VWF), a platelet adhesive protein. Factor VIII:C represents the procoagulant activity of the complex. Both FVIII and VWF have been shown to increase after physical exercise.[25–29] Other coagulation factors (factors IX, X, XI, and XII) seem to show a slight or no change after exercise.[25,26,30]

Thrombin formation, a major activator of blood coagulation, can be measured by examining thrombin–antithrombin complexes (TAT) and/or prothrombin fragments I + II (PTF 1 + 2). TAT and PTF 1 + 2 levels increase post exercise following maximum-effort endurance exercise,[31] marathons,[32] triathlons,[8,33,34] ultramarathons,[10] as well as following intense resistance-training sessions.[9] Yet the rise in thrombin generation seems to be affected by the intensity[35] and/or duration[36] of the exercise. The rise of these variables is usually only transient. However, if the exercise is very intense or of long enough duration, PTF1 + 2 and TAT can remain elevated up to a day postexercise.[10,32]

Fibrinogen is a protein that provides the foundation of a blood clot. Although its main function is in the final phase of blood coagulation, it also promotes platelet aggregation and is a major determinant of blood viscosity.[37] Thrombin acts on fibrinogen, converting it to fibrin. Results of studies thrin examine the role of fibrinogen during acute exercise are inconsistent. In particular, there is no consensus in the literature about what occurs after exercise. Some invesigations show no changes in the concinentration of fibrinogen, some demonstrate an increase,[34] while others show a decrease.[40] Ovinerall, a more careful consideration of normal hemodynamics as hemoconcinentration occurs during intense exercise may be needed.[41]

It is known that acute exercise initiates the fibrinolytic system.[9,34,42] Fibrinolysis is performed by the enzyme plasmin via tPA, which is released by vascular endothelium cells and cleaves plasminogen into the active enzyme plasmin.

Elevation of tPA antigen and activity has been documented following many types of exercise modes, including marathons,[32,43] ultramarathons,[10] triathlons,[33] cycling,[28,44] and resistance training sessions.[9,45] The degree of activation seems to be intensity dependent.[45] Activation can occur through many factors, including vascular shear stress caused by increased laminar blood flow,[46] catecholamines,[47] and thrombin.[48] In a few cases, tPA levels did not increase; however, those cases belonged to a diseased population.[49,50]

The main regulator of tPA is PAI-1. Many exercise studies have found that, unlike tPA, PAI-1 activity and antigen levels are inconsistent. Some studies have demonstrated a significant change in PAI-1 levels during aerobic endurance exercise,[28,41,51] as well as during anaerobic resistance exercise.[9,45] However, another study found no changes in PAI-1 levels following an endurance protocol.[32] These inconsistent results may be attributable to the training status of the individual and the type of exercise that was performed.[51]

D-dimers, a marker of in vivo hyperfibrinolysis, are split products formed from the breakdown of fibrin. Increases in D-dimer concentrations have been shown to occur during many different types of strenuous exercises, including maximum endurance exercise,[51] marathon,[43,52] ultramarathon,[10,53] and resistance training.[9] Although D-dimers are also elevated during DVT and PE, they are not conclusive indicators of these disorders, as they can also be increased during pregnancy, lung and connective tissue disease, and malignancy.[54,55]

Blood Coagulation and Air Travel

An estimated 150,000 cases of DVT occur annually due to air travel.[56] Since nearly 2 billion individuals fly each year,[5] VTE remains a relatively rare event.[57] However, it should be noted that data on the occurrence of VTEs are taken only from individuals who present symptoms and report them to a medical institution. Individuals with VTE are often asymptomatic, and those who are symptomatic may not go to a medical institution for treatment.[58] Conversely, 20% of the patients who reported VTE had recently travelled by air.[59] This latter frequency is important because the risks of VTE increase with the length and number of flights over a given time but decrease as postflight time passes.[60] VTE usually occurs within 2 weeks after air travel; however, risks remain until around 4 weeks postflight.[13]

Some passengers are more susceptible to VTE than others. The three main cabin-related risk factors include extended sitting (long periods of immobility), hypoxia, and low cabin humidity. Passenger-related risk factors can also increase the odds of clot formation during a flight, thus playing a role in the development of VTE. Major passenger-related risk factors include being overweight or obese (body mass index $\geq$ 30 kg/m^2), having a history of VTE, recent major surgery, or exercise that causes muscle damage.[3] Additionally, a hereditary disorder such as factor V Leiden or an elevated factor VIII can increase risk of VTE by up to 50-fold (►**Table 1**).[61]

Environmental factors inside the aircraft, especially when coupled with reduced access to *ad lib.* fluid intake, can lead to dehydration and hemoconcentration. A synergistic effect of the three main risk factors of extended sitting in restricted spaces, decreased air pressure, and low humidity may contribute to the formation of VTE, but taken independently they likely do not explain clot formation during air travel.[62]

Table 1 Risk factors for venous thromboembolism

Passenger related[3]	Inherited or acquired[61]
Traveling long distances to and from a sports competition (by plane, bus, or car)	Prothrombin 20210 mutation
Dehydration (during and after a strenuous sporting event)	Factor V Leiden mutation
Significant trauma	Elevated factor VIII
Immobilization (brace or cast)	Protein C deficiency
Bone fracture or major surgery	Protein S deficiency
Birth control pills and patch, pregnancy, hormone replacement therapy	Antithrombin III deficiency
Family history of DVT or PE	Hyperhomocysteinemia
BMI > .8-1r4Bromla77.38.5(a)65.4(T)301.55(d)2-2.8677Tm02(61)Tj8.50087203	

Sitting for an extended time (even < 3 hours) is associated with reduced velocity of venous blood flow in the lower extremities[63] and an increase in blood viscosity,[64] a known risk factor for VTE.[65] The hemostatic effects of prolonged sitting or immobilization in healthy individuals were first reported during World War II, when those taking shelter during bombardments developed VTEs.[66] More recently, Beasley et al reported on a PE in an individual from sitting at his computer for more than 12 hours.[67]

The decreased air pressure and hypoxia typical of commercial airline cabins can also limit fibrinolytic activity and lead to venous stasis.[68] At the air pressure maintained for transcontinental U.S. flights, arterial oxygen saturation is 93% in healthy individuals.[69] Hypoxia has been shown to induce a hypercoagulable state in rats[70] and in cell cultures has been shown to decrease fibrinolytic activity and induce free radical generation, which may in turn lead to clot formation.[71] However, Crosby et al[72] found no evidence for thrombin generation during exposure to 8 hours of isocapnic hypoxia compared with 8 hours of normobaric normoxia under study conditions. Toff et al[69] exposed 73 volunteers alternately to hypobaric hypoxia and normobaric normoxia but found no difference between the changes in markers of thrombin generation (TAT) during hypobaric or normobaric exposures. These findings were confirmed by Schobersberger and colleagues.[73] Markers of fibrinolysis typically remained unchanged during hypoxia in most studies,[69,72,74] although Schobersberger et al found a decrease in t-PA after 10 hours of hypoxia.[73] This difference in results may have arisen because some of these studies were performed in simulated aspects of flight that did not encompass all the stresses presented by air travel. Moreover, results in cell culture

or rat models do not always translate into similar results in humans.

The atmosphere inside commercial airliners is typically around 1% relative humidity, which can cause increased perspiration rates. However, multiple studies that have examined low cabin relative humidity did not lead to increased water loss therefore leading to dehydration and increased blood viscosity.[64,75,76]

Research

Sitting on long, cross-country flights when dehydration causes the blood to thicken inhibits circulation and often causes blood to pool in the legs where platelets may gather and form a clot. That risk can be elevated after a sporting or athletic event. A study evaluating coagulation in healthy, low-risk individuals after an 8-hour flight showed an increase in coagulation factors VII and VIII but no increases in thrombin generation as measured by TAT.[73] However, Boccalon et al[77] found no shortening of aPTT due to a long-haul flight ($>$ 4 hours). Previous studies also had inconsistent results in thrombin activity after a flight, showing increases in thrombin generation after an 8 hours of flying compared with controls sitting in cinema theater for the same amount of time; decreases after a long-haul flight;[77] and no changes in formation of thrombin generation markers.[73] A 5-hour transcontinental flight did not independently increase PF 1 + 2 or TAT, and no changes were seen with fibrinolytic markers, tPA or PAI-1 immediately after flight or 1 day postflight.[78] Other investigators have likewise found that air travel had either no effect or a potential decrease on tPA concentrations.[73,77] However, Schobersberger et al[73] found a decrease in fibrinolytic activity demonstrated by elevated PAI-1/tPA levels. These discordant findings could be due to the difference in flight times (3 hours less than in Kupchak et al[78]) and a broader range of ages in the study population, either of which may have led to increased PAI-1 and decreased tPA.[73]

Although Kupchak et al[78] and Schobersberger et al[73] saw no rise in D-dimer immediately after flying 5 and 8 hours of flights, Jacobson et al determined that approximately 8.2% of all passengers had elevated D-dimer levels during long-distance flights. Their result was not limited to economy-class passengers.[79]

Combined Effects of Air Travel and Exercise on Blood Hemostasis

In the late 19th century, Rudolph Virchow began to characterize the risk of VTE, breaking the broad diagnosis into three main categories: hypercoagulability, endothelial vessel damage, and circulatory stasis. Athletes, especially endurance and combative sports athletes, may have at least one risk factor in each category that may in turn lead to significant risk for a VTE (►**Fig. 1**).[80] These individuals are more likely to have bruises and damaged muscle tissue, which can trigger clotting due to injury in the endothelium vessel wall. They may also be at greater risk due to decreased resting blood flow rate, which encourages clotting. Adding constant travel by air to such risk factors can place a tremendous stress on the athlete's blood coagulation system.

According to AirHealth.org, 85% of air-travel thrombosis victims are endurance athletes such as marathoners.[81] Superimposing air travel on an athlete who has recently engaged in intense exercise may shift the hemostatic balance in athletes'

relationship between age and post-marathon TAT in the travel group but not in the control group. The interaction between long-haul air travel and endurance exercise seems to have a greater effect on coagulation with increasing age. In another analysis by the same authors, assessment of coagulation markers revealed that microparticle activity not only increased with exercise but also increased further the day after flying home.[86]

An online registry (www.airhealth.org) details numerous reports of athletes who developed DVT after plane flight. Marathoners, ultramarathoners, and triathlon athletes need to be especially vigilant about thrombotic risk factors, including dehydration, muscle damage, and injury leading to inflammation, long-distance air travel, and contraceptive use.[87,88] There are also several published case reports of such athletes developing DVT and PE after athletic events and travel. Tao and Davenport[84] reported both a female triathlete presenting with DVT and PE after completing a half-Ironman triathlon and then driving for 5 hours and a male triathlete who developed a DVT after a flight from Minneapolis to San Francisco.[89]

A study of marathoners that examined TAT, tPA, and D-dimer in women (taking oral contraceptives vs. not) found no differences in either group postexercise and after flying approximately 5.6 hours the next day.[90] A separate study that examined individuals who flew 5 hours on the day after they had performed a full-body, muscle-damaging workout[78] found that thrombin generation markers TAT, PTF-1, and PTF-2 all increased significantly after the full-body workout and immediately after 5 hours of air travel compared with baseline. Their TAT levels remained elevated 29 hours after postflight. Fibrinolytic activity, also assessed during the study, showed an increase after the full-body workout and remained increased immediately after the 5-hour flight, as shown by PAI-1 and D-dimer levels. D-dimer levels were further increased 29 hours postflight, signifying prolonged effects of flying. Transcontinental flight alone did not activate the coagulation and fibrinolytic systems, yet maintained a hypercoagulable state following the exercise protocol, with TAT, PAI-1, and D-dimers remaining elevated into recovery.[78]

Athlete-Specific Risk Factors for Clots

In recent years, a growing number of VTE cases have occurred in the athletic population. It is estimated that half a million people are affected by VTE in the United States each year, and it is relatively common in this active population.[80] The best way for an athlete or individuals who exercise to reduce the likelihood of a VTE is to understand the risks. Unfortunately, in this population, there is a general lack of awareness about what can cause VTEs and what factors may predispose the athlete to a VTE (►**Fig. 1**, ►**Table 2**).[80,91] Professional athletes are not unique in developing VTEs, as they are prone to several thrombotic conditions, which can include both inherited or acquired conditions such as tissue trauma from during games, hemoconcentration from dehydration, circulatory stasis secondary to bradycardia (high cardiopulmonary fitness), and long periods of stasis from either travel or immobilization during injury.[80,91]

Table 2 Anatomical conditions that may lead to increased clotting[80]

• Presence of a congenital abnormality of the anatomy of the veins
• May–Thurner syndrome (narrowing of the major left pelvic vein)
• Narrowing or absence of the inferior vena cava (the main vein in the abdomen)
• Cervical rib causing thoracic outlet obstruction

Professional sports are an especially common factor in VTEs due the frequent long-distance travel required, usually by air. This sports-related requirement arises from the fact that games are played across the United States and Canada, in all four time zones. Increasingly, professional players from the United States/Canada travel internationally: to Australia (Major League Baseball [MLB]), China (National Baseball Association [NBA]), Great Britain (NBA and National Football League [NFL]), and Sweden (National Hockey League [NHL]).[92] Furthermore, the intense exercise that these athletes have performed shortly before boarding a long-haul flight places them in a hypercoagulable state.[78,85] Injuries or, in contact sports such as ice hockey and football, hard hits can also cause internal traumas, both large and small. Most of the NHL players diagnosed with blood clots since 2011 had either hereditary disorders that increased their risk or some kind of trauma while playing.[93,94] Similarly, the NFL has seen several cases from the hitting inherent in the sport, which causes impact trauma.[94] During the 2015 NBA season, a prominent All-Star was diagnosed with a PE that subsequently led to his retirement.[95] Another NBA player on the Brooklyn Nets was also diagnosed with a PE later that year.[96] MLB players can be similarly affected, as a handful of these athletes (mostly pitchers) have suffered from upper arm VTEs due mostly to biomechanical demands and changes in blood-flow mechanics due to the pitcher's throwing motion.[94,97,98] It is likely that such data translate to athletes living in other countries who also travel long distances.

Symptoms

Symptoms of VTEs can start during a flight, but they usually occur within 4 days after flying.[99–101] It should be noted that DVTs may be silent until a major blockage of blood occurs. Until then, the only evident symptoms could be cramps or swelling in the lower leg. PE symptoms may be more common, including chest pains or shortness of breath (►**Table 3**).

Prevention Strategies

Fortunately, there are several preventive measures that help reduce the risk of a VTE (►**Table 4**).[90,91,106] For some individuals, mechanical prophylaxis such as graduated compression stockings may help decrease the risk of travel-related VTE.[107] Compression stockings are often used in the medical community to reduce the incidence of DVT in surgical patients[108] who must be immobile for extended

Table 3 Symptoms of venous thromboembolism

Deep vein thrombosis[80,102,103]	Pulmonary embolism[80,104,105]
Swelling in one leg or arm Bruising or tenderness in lower leg or arm, or behind the knee or elbow	Sudden shortness of breath

periods. Full-body compression garments have also been shown to decrease levels of coagulation after an exercise event followed by air travel, so they too may lower the risk of a DVT.[78]

Individuals who have been immobilized due to injury during training or competition yet need to fly may also benefit from pharmaceutical prophylaxis.[57] In some cases, and under strict medical care, low-molecular-weight heparin (LMWH) may be given if the individual is known to have risks factors such as factor V Leiden.[109] The effective use of LMWH for the individuals at high risk has been confirmed by multiple studies.[110–112] Aspirin has also been shown to be beneficial, but to a lesser extent.[113]

Research

Only a few studies have examined prevention of DVT or PE in the research setting due to the exorbitant costs and monitoring requirements of a well-designed flight research protocol. Kupchak et al[78] demonstrated that individuals utilizing a full-body compression garment during and after a post–workout flight were able to limit blood coagulation. They had higher aPTT, lower TAT, and lower PAI-1 levels compared with controls who wore only loose clothing. In another study, marathon runners who wore compression socks before the start and throughout the duration of the marathon but not between finish and post-race blood draw (which encompassed a flight) had lower TAT and tPA levels compared with controls, both the day after the event and following their flight.[85]

A similar study by Taylor et al examined female marathon runners, comparing a control group consisting of women not taking oral contraceptives (controls) to those who were (OC).[90] The OC group was further divided into two subgroups: those running in compression stockings and those running in ordinary athletic socks. TAT, D-dimer, and tPA were taken premarathon, immediately postmarathon, and after a flight of at least 4 hours. The study found that TAT did not increase with exercise, although there was a trend of higher postexercise TAT levels among controls. TAT and t-PA levels did not differ between the contraceptive groups at any point, although the authors observed significantly higher D-dimer levels in the OC group wearing compression socks immediately postexercise but not postflight. Based on these results, they concluded that contraceptive use had no negative additive effect on hemostatic balance in women who flew more than 4 hours after running a marathon. Study limitations included use of data from two different years of the same marathon and absence of a control group wearing compression socks.[90]

Conclusion

Taken independently, both intense exercise and air travel pose a real, if small, risk for developing a VTE. The risk increases when intense exercise and air travel are combined, as they are after many athletic and professional sporting events. A hereditary disorder can raise risk still further, as can hormonal contraceptives used by women. Nonetheless, these individuals should not fear or withdraw from performing athletic activities. They only need to be aware of these dangers and take appropriate steps to mitigate their risk factors. Further research should be focused on coagulation and fibrinolysis around exercise and sporting competitions, such as football games and extreme ultra-endurance events.

Conflict of Interest
The opinions and assertions expressed herein are those of the author and should not be construed as reflecting those of the Uniformed Services University, Department of the Army, Department of the Air Force, Department of the Navy, or the United States Department of Defense.

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