Venous Thromboembolism in Exploration Class Human Spaceflight

Sophie Levasseur*; Nina Purvis*; Sophia Trozzo; Seok Hoon Chung; Matthew Ades; Laura M. Drudi

INTRODUCTION: A recent finding of a deep venous thrombosis during spaceflight has prompted the need to clarify mechanisms and risks of venous thromboembolism (VTE). In turn, mitigation countermeasures, diagnostic modalities, and treatment options must be explored. The objective of this review was to synthesize current evidence on VTE in spaceflight.

METHODS: A literature review was performed from inception to April 2023 pertaining to VTE in the context of spaceflight or ground-based analogs with human participants. PubMed was searched for papers written in English using the terms "spaceflight" or "weightlessness" and "thrombotic" or "embolism" or "thromboembolism" in "venous" or "veins". Papers using cellular or animal models were excluded.

RESULTS: There were 63 papers captured; 7 original scientific studies, 3 narrative reviews, 2 systematic reviews, and 3 commentaries discussed VTE in spaceflight. Reference lists were screened. Important themes included: altered venous hemodynamics, increased fibrinogen and coagulation markers, hypoalbuminemia, and immune dysfunction. Additional risk factors may be seen in women, such as the use of oral contraceptives.

DISCUSSION: Venous stasis and decreased shear stress secondary to fluid shifts may induce inflammatory changes in the venous system, resulting in endothelial damage and upregulation of the coagulation cascade. Additionally, women in space are subject to physiological factors increasing their VTE risk, such as the use of oral contraceptives, inducing increased blood viscosity and hypoalbuminemia. Efforts should also be placed in optimizing sensitivity and specificity of imaging markers, payload, and training ability, notably the use of vector flow imaging, and improving point-of-testing biomarkers, such as albumin and p-selectin.

KEYWORDS: deep vein thrombosis, coagulation, microgravity, venous physiology.

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Until recently, the event of the formation of a venous thromboembolism (VTE) in astronauts was a risk not considered to be at the forefront of space medicine due to stringent medical selection and it having never occurred. Now, it is a topic of much interest after the reporting of the first VTE during spaceflight, specifically an internal jugular vein (IJV) thrombosis,[4] which occurred during a low Earth orbit (LEO) International Space Station (ISS) mission. Looking towards exploration class missions to the Moon and Mars, it is imperative that the risk of VTE is examined and countermeasures are employed along with in-flight diagnostic and treatment abilities being optimized. It is also imperative that astronauts are educated about this risk and red flags to look out for, as well as trained in diagnostic and treatment options available during a mission.

Exploration class spaceflight will introduce extreme environmental hazards that will affect astronaut physiology. Specifically, there are five challenges of long-duration spaceflight: higher levels of radiation, altered levels of gravity (including hyper-, micro-, and hypo-gravity environments), a long period of isolation, an enclosed and potentially hostile living environment, and the psychological stress associated with traveling a far distance from Earth.[50] Furthermore, during exploration spaceflight the

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effects of the extreme environment on medications, as well as communication delays, will further challenge any management of VTE.

VTE is a disease classification that includes clot presence in deep veins, usually in the extremities known as deep venous thrombosis (DVT), as well as clots that have embolized into the pulmonary vasculature, known as pulmonary embolism (PE). This pathology is caused by multiple precipitating factors which often interact synergistically, forming a thrombotic event if enough conditions are met. In terrestrial medicine, we consider Virchow's Triad, endothelial dysfunction, venous blood stasis, and hypercoagulability to be the physiological factors that, when imbalanced, contribute to VTE formation.[25] Multifactorial causes include modifiable and nonmodifiable risk factors, which can be seen in **Fig. 1**.

While arterial structure and function in the space environment has been well-studied due to its association with cardiovascular disease, there have been limited studies regarding the venous system in the space environment. Given the physiological differences between the two systems, it would be erroneous to translate the arterial findings to the venous system without caution, especially when assessing for VTE risk. Spaceflight may provide influences that change these balanced factors, including changes in venous blood flow, vessel wall injury, and hemostatic imbalance.

Due to the complex physiological changes in space that increase the risk of thromboembolic and associated events, it is necessary to identify and characterize pertinent risk factors that may warrant a modification of the astronaut medical selection and monitoring processes. This is especially important as humankind embarks on missions beyond LEO, where resources will be even more limited than current missions to the ISS. To date, we have simulation analogs and LEO and Apollo mission physiological data—but some level of uncertainty is to be accepted and planned for in terms of what might happen to the human body during these missions.

In this review, the effects of the spaceflight environment on the formation of VTE are considered. Mitigation countermeasures are also discussed, and the possible diagnostic and treatment solutions are amalgamated from the evidence.

METHODS

A literature review was performed from inception to April 2023 pertaining to VTE in the context of spaceflight or ground-based analogs with human participants. The PubMed database was searched for papers written in the English language using the MeSH terms: [(spaceflight) OR (microgravity) OR (weightlessness)] AND [(venous) OR (veins)] AND

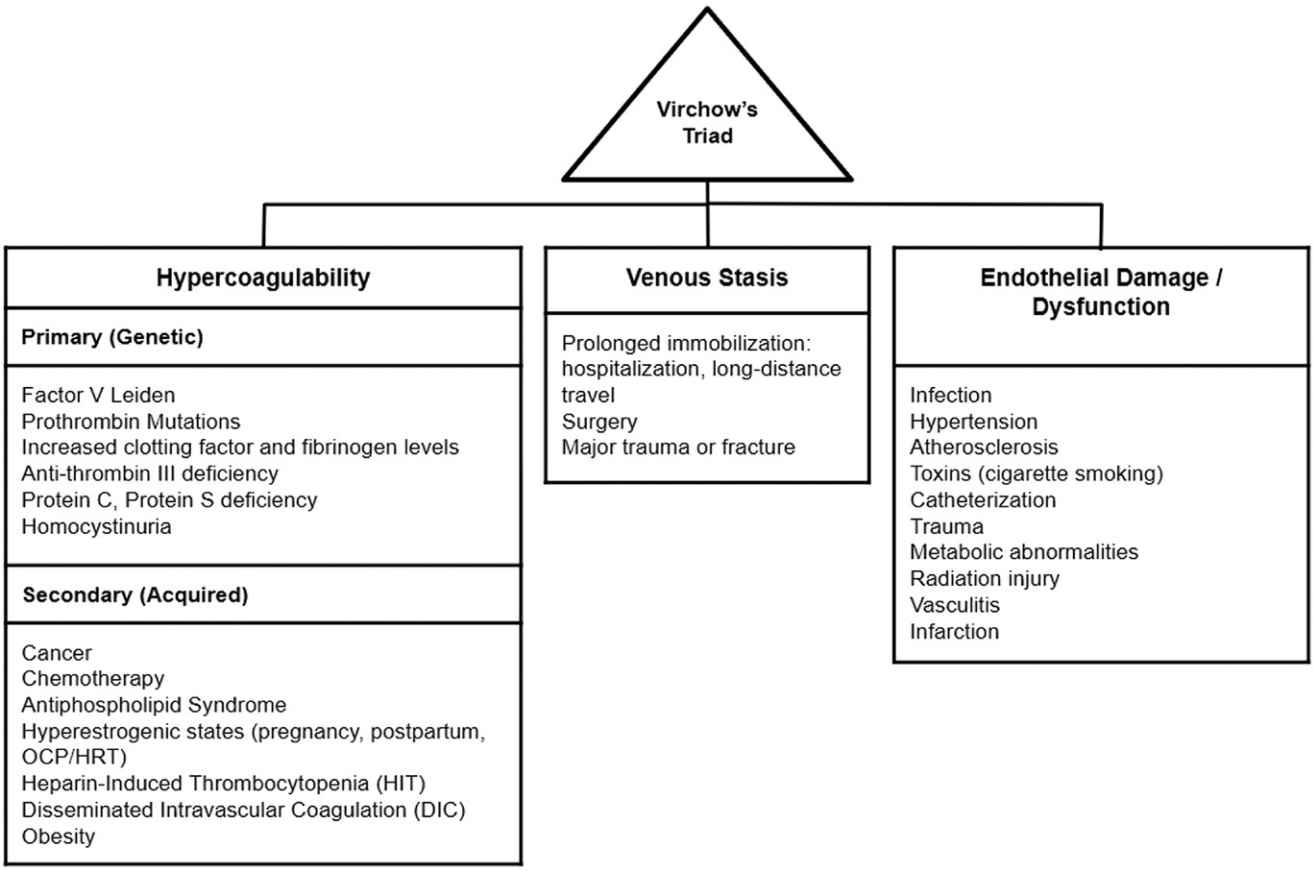

Fig. 1. Risk factors for venous thromboembolism (VTE) formation in the context of Virchow's Triad.

[(thrombotic) OR (embolism) OR (thromboembolism)]. The data was collected and analyzed descriptively.

RESULTS

This search yielded 63 results. Only papers published or translated to English were considered. Of those, seven were original scientific studies: two head-down tilt analog studies,[16,61] one parabolic flight study,[32] and four spaceflight studies,[22,51,63] with one corresponding to the original IJV thrombosis finding.[38] Three narrative or viewpoint reviews,[18,19,35] two systematic reviews,[17,23] and three commentaries[4,11,33] were relevant to VTE in spaceflight. A summary of the initial search by category can be found in **Fig. 2**. The original scientific studies included were comprised of ground-based analog studies and spaceflight studies. Studies from animal or cell models were excluded. From this initial query, references were screened for other relevant publications not included in the original search. Mathematical models relevant to the topic of VTE were considered. The relevant papers were classed into broad categories which outline topics critical to the discussion of venous thromboembolism during spaceflight: venous stasis, hypercoagulability, endothelial dysfunction, the immune system, sex-based physiology, and biomarkers.

One paper described a VTE occurrence during spaceflight in a female astronaut and a partially occlusive thrombus in a second female astronaut.[4] There were 12 studies (incorporating both analog and in-flight studies) that demonstrated altered venous hemodynamics: 1 showed decreased venous emptying,[13] 2 reported decreased venous linear velocity,[44,47] 2 showed decreased venous flow rates,[37,48] 1 reported decreased venous compliance,[7] 1 showed decreased femoral vein cross-sectional area,[1] and 5 demonstrated increased IJV pressure and cross-sectional area, 3 of those being in-flight studies[2,20,38] and 2 being analog studies.[32,39] No studies explored in-flight coagulation; however, three studies reported increased fibrinogen[29,30,57] and one reported hypoalbuminemia.[63] Three analog studies did not demonstrate an activation of the coagulation system,[3,16,61] three reported increased proinflammatory cytokines or decreased cytotoxic T-lymphocyte function,[6,9,12] and one study reported the presence of endothelial microparticles.[47] Others focused on mathematical models, VTE risk in women, and countermeasures.

DISCUSSION

To gain a holistic understanding of VTE risk in space, factors affecting Virchow's Triad in the spaceflight environment must be considered. A summary of the findings of this literature review in the context of these alterations is illustrated in **Fig. 3**.

Venous Stasis

It is well established that in LEO, astronauts experience a cephalic fluid shift as a result of the removal of the hydrostatic gradient created by gravity due to freefall or the altered gravitational field. There is also absence of the musculo-venous pump without the use of antigravity muscle groups in the lower body. Veins in the upper body have fewer valves than in the lower body,[43] further decreasing the efficacy of the musculo-venous pump. A previous comprehensive review, serving as a summary of the impact of spaceflight on Virchow's Triad until 2021, identified several important papers exemplifying the complexity of previous results.[23] Changes in blood flow have been recognized during spaceflight and in microgravity analogs such as parabolic flight. Increased jugular vein pressure was seen during parabolic flight, as well as progressively increasing cross-sectional area with decreasing gravitational levels.[32,39] During spaceflight, increased jugular vein cross-sectional area and pressure were seen, with an +178% increase in cross-sectional area at Day 15 of spaceflight and +225% at Month 5 compared to preflight values.[2,20,38] Increases in cross-sectional area have also been reported for the portal vein, as well as the femoral vein, although with contradicting results in ground-based head-down tilt and head-down bed rest (HDBR) studies.[2] Leg venous compliance was decreased in a −6° HDBR, and an increase in leg venous resistance demonstrated decreased venous flow.[7] Additionally, Arbeille and colleagues[1] reported a decrease in femoral vein cross-sectional area in their HDBR study, indicating the need for further clarification of venous hemodynamics

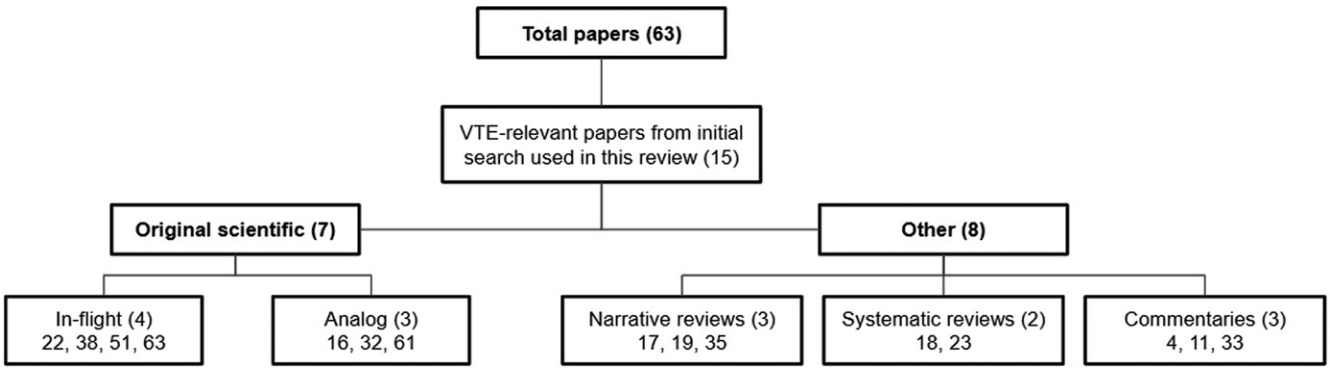

Fig. 2. Initial search query results by category.

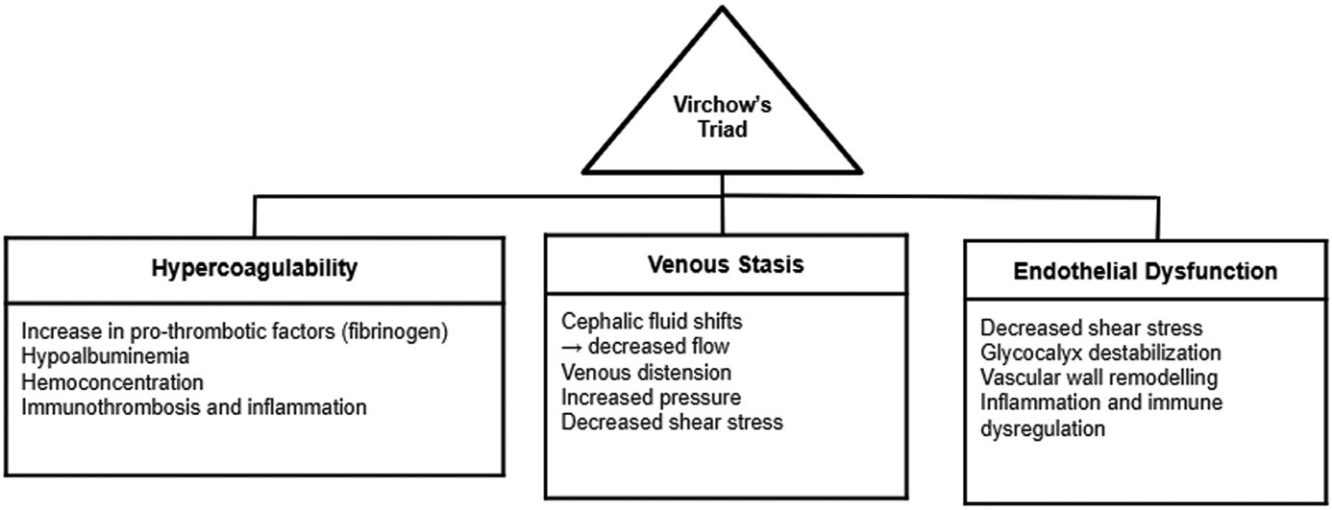

Fig. 3. Factors affecting Virchow's Triad in the spaceflight environment.

during spaceflight. Ground-based analog studies have reported decreased cerebral outflow, suggesting decreased flow rates with distension.[1,37,48] There was no evidence of compensatory mechanisms for these increases in volume, including no increase in flow velocity, supporting that headwards fluid shifts result in passive venous pooling.[1] There was no evidence of physiological compensatory mechanisms. Decreased venous emptying has been reported,[13] along with decreased linear blood velocity in a week-long dry immersion study.[44,47] This picture of reduced flow states, combined with distention and increased pressure within the cephalic venous system, can trigger cell-signaling cascades promoting thrombus formation.[23] This is extremely important in the upper body venous systems where an increase in pressure above normal limits may impact organs at a structural and functional level, such as increasing intracranial pressure via the cephalic system and jugular vein and potentially causing cerebrovascular dysregulation.[62]

A retrospective analysis of the 2019 internal jugular vein thrombotic event by Marshall-Goebel and colleagues showed reversal of internal jugular vein flow.[38] However, there exists no clear mechanism explaining this phenomenon; in order for this to occur, cerebral resistance, or intracranial pressure, would have to drop significantly for venous blood to reverse given the gravity-dependence of cerebral drainage.[19] In fact, intracranial pressure seems to increase in the upright position in astronauts and is elevated over 24 h compared to terrestrial findings.[31] This lack of elucidation, in addition to the limitation imposed by current imaging techniques, points away from the possibility of retrograde flow but does not exclude the presence of flow reduction or stagnation. The above-mentioned fluid shifts have further consequences on intravascular volume, which may also contribute to a hypercoagulable state.

Hypercoagulability

The cephalad fluid shift and consequent increase in central blood volume during spaceflight result in intravascular volume contraction. This occurs via compensatory mechanisms such as increased urine output and decreased thirst. In turn, relative concentrations of platelets, fibrinogen, and red blood cells increase, which may drive coagulability.[28,35] Synthesis of such components affecting coagulability also seems to be increased; increased fibrinogen synthesis was reported postflight following a 16-d Space Shuttle mission compared to preflight measurements.[57] In a similar vein, fibrinogen measurements following a 10–11-d spaceflight mission were significantly increased compared to preflight measurements, with a nonsignificant trend toward shortened thrombin time, pointing toward potential hypercoagulability.[29] However, there were no changes in coagulability or fibrinolysis markers such as D-dimer nor any observed changes in International Normalized Ratio and plasminogen activity. The absence of in-flight measurements for the above-mentioned studies limits our knowledge of the role of coagulability during spaceflight. Another spaceflight study performed a blood analysis preflight, on the day of return, and 1 wk after return to Earth, which demonstrated increased fibrinogen alpha-chain levels in flight, the day of the return, and postflight.[30] Similarly to the Kuzichkin study, no other coagulation markers, including coagulation factors, prothrombin, plasminogen activity, and other fibrinogen chains were elevated.

On the other hand, ground-based analog studies have had more conflicting results. While increased aggregation and fibrinogen concentration have been reported, platelet activation was reduced and there were no clinically significant changes in coagulation.[3,61] Similarly, during another 60-d HDBR study, there was no evidence of coagulation system activation nor of fibrinolysis suppression, further complicating our understanding of the role of hemostasis in long-duration spaceflight.[16] Further investigation of blood volume reductions and hemoconcentration is warranted.

Launch day and landing day are both physically demanding and are associated with increased levels of fibrinogen synthesis alongside other signs of acute phase response.[35] However, it is uncertain whether these acute changes are linked to clinically significant coagulation activation. It is also important to

consider that the physical demands of landing may have enough force to dislodge a thrombus, increasing the risk of a venous thromboembolism adverse event. It can be seen that we do not yet have a clear understanding of coagulation dynamics in space. One underlying factor is that there are no studies investigating in-flight coagulation parameters such as velocity index, peak thrombin, and time-to-peak.[23] Gaining an understanding of these parameters would clarify the effect of re-entry into the gravitational environment on coagulation. Furthermore, to holistically understand coagulability in space, endothelial dysfunction must also be considered. Hypercoagulability is intimately linked with endothelial dysfunction as coagulation factors are released from the endothelium, such as tissue plasminogen activator, further complicating the independent analysis of hypercoagulability in space.[17]

Endothelial Dysfunction

It is well known that endothelial dysfunction plays a vital role in the formation of thrombotic events. Additionally, several mechanisms contributing to endothelial dysfunction may be present or exacerbated in spaceflight conditions. Lowered shear stress, such as in reduced or low flow situations, has been associated with thrombosis via upregulated proinflammatory changes and prothrombotic markers, overriding the protective mechanisms, such as fibrinolysis, usually present with wall shear stress.[36,49] Additionally, this increase in inflammatory components upregulates the Von Willibrand factor and other coagulation factors, activating the coagulation cascade while promoting arterial atherogenic events.[8] It is currently unclear how weightlessness affects endothelial shear stress in both venous and arterial systems. However, fluid shifts in spaceflight likely lead to lowered shear stress given low flow states. Despite this, no causal relationship between reduced venous flow and the coagulation cascade in spaceflight has been concretized.

The extent of endothelial damage as a result of these inflammatory changes is also not well understood. Both direct inflammation markers and endothelial dysfunction markers have been found to be elevated in VTE.[17] However, a causal link has yet to be elucidated. On Earth, increases in venous pressure have been shown to result in wall inflammation and remodeling, causing endothelial dysfunction.[35] It has not yet been demonstrated that during spaceflight the increase in venous pressures secondary to cephalad fluid shifts also results in the same inflammatory and remodeling process. There have been reports of endothelial microparticles suggesting endothelial damage after enforced physical activity in dry immersion studies, which has limited applicability to the spaceflight climate, inciting the need for further research.[47]

The endothelial glycocalyx is an important mechanotransducer that signals endothelial cells to produce vasoactive substances in response to shear stress. Additionally, it is a vital component of endothelial platelet aggregation, reduces inflammation, and maintains fluid homeostasis. Certain stressors can result in destabilization of the glycocalyx, negatively impacting the integrity of the endothelium. In turn, many biochemical substances stabilize the glycocalyx, such as albumin.[63] Hypoalbuminemia is a phenomenon previously identified in the spaceflight environment, supporting the presence of endothelial dysfunction and thus VTE risk. Additionally, decreased albumin increases blood viscosity, another established VTE risk factor, by altering phospholipid biochemistry and in consequence red blood cell elasticity. Interestingly, the astronaut who developed a VTE during the 2019 mission had hypoalbuminemia and the highest blood viscosity among the astronauts participating in the retrospective study. These changes signal the need to further investigate trends in albumin during spaceflight and assess its use as a biomarker.

In addition to Virchow's Triad, it is important to consider the impact of the immune system on VTE formation. Increasing evidence supports that the immune system itself can promote the coagulation cascade in a phenomenon called immunothrombosis.[15]

Immunology

It is widely accepted that there exists a complex interaction between the immune system and the coagulation pathway; during local infection or inflammation, the innate immune system has been found to promote thrombus formation as a first-line defense for infection control, supporting host defense via immunothrombosis.[15] Furthermore, evidence exists that medications with anti-inflammatory properties such as statins may reduce the incidence and recurrence of VTE, supporting the interplay between the coagulation and immune systems.[26,27] Other studies have further explored this relationship, with varied conclusions. One review paper suggests a double role for inflammation as both a cause and effect of VTE. Patients with VTE exhibited high levels of proinflammatory cytokines Interleukin 6 (IL-6) and tumor necrosis factor alpha compared to a control group without VTE.[53] Proinflammatory cytokines promote the coagulation pathway by inducing the expression of tissue factor, mainly found on monocytes.[55] Interestingly, proinflammatory cytokine levels remained elevated in patients despite halting anticoagulation therapy. Further, high levels of IL-6 sustained after VTE have been correlated to post-disease complications.[53,54] Often referred to as the "messenger cytokine", IL-6 activates many proteins involved in the thrombosis pathway, such as fibrinogen.[60] Studies have been able to correlate IL-6 plasma levels to cases of VTE.[46] Further research is necessary to understand the complex role of proinflammatory cytokines on VTE development.

Another factor of inflammation promoting VTE development is the role of platelets in forming a thrombus, and potentially activating innate and adaptive immune cells. To prevent pathogens from spreading in circulation, platelets facilitate the innate immune response by interacting in aggregates primarily with monocytes and neutrophils. Specifically, platelet-monocyte aggregates have been correlated with VTE in older patients, suggesting a link between viral and bacterial infections and VTE development. Subsequently, platelets may facilitate the adaptive immune response by activating dendritic cells and promoting T-cell differentiation.[24]

Aside from platelets, leukocytes have also been functionally linked to the formation of VTE. Neutrophils are involved both in thrombus formation and resolution. In the early stages of thrombus formation, neutrophils are recruited in high quantities. They release neutrophil extracellular traps, which engage platelets to promote the coagulation pathway. Monocytes also work in tandem with neutrophils to promote thrombosis by aggregating to the vein wall.[55] Natural killer (NK) and NK-like T cells produce interferon-gamma, which helps to promote thrombus formation.[34] In studies conducted with VTE-induced mice, thrombus size was smaller in interferon-gamma-deficient mice compared to wild-type mice.[46]

It is known that the spaceflight environment impacts the immune system. Spaceflight-mediated immune dysregulation introduces functional deficits to many leukocytes, including NK cells, macrophages, monocytes, T cells, and B cells. Notably, reduced gravity in spaceflight decreases the cytotoxic function of T lymphocytes and NK cells.[6,12] Additionally, spaceflight-mediated immune dysregulation introduces latent viral reactivation, which puts astronauts at high risk for developing infections.[9] As previously discussed, inflammatory activity as a result of viral infections is a risk factor for VTE development. Astronauts on a mission with a 6-mo duration or longer also show increased plasma levels of proinflammatory cytokines.[9] Increased levels of proinflammatory cytokines in astronauts on long-duration spaceflight missions may promote thrombosis and subsequently increase the risk of VTE development in astronauts. Despite the probable relationship between spaceflight-mediated immune dysregulation and VTE risk in astronauts, few studies have been conducted to assess their correlation.[41,42,45]

Sex Differences

Both women and men undergo headwards fluid shift and the associated compensation mechanisms to reduce blood pressure, including a reduction in plasma volume by baroreceptors to maintain a euvolemic state and counteract the increased upper extremity volumes. During bed-rest studies, women have been shown to have reduced total peripheral resistance and suffer worse orthostatic intolerance upon reintroduction to gravity.[40,58]

Female physiology in space and the related VTE risk may also be complicated by the use of oral contraceptives (OCPs), since on Earth its use doubles the risk of VTE.[59] The space environment likely increases this risk, alongside any thrombophilia or other associated conditions. Data so far is limited and contradictory. A retrospective study demonstrated no difference in VTE risk in female astronauts post-mission according to OCP use, as well as no differences in hematological measures and biochemical variables.[22] However, this study did not control preflight and postflight data timing and had a very small sample size, which further hinders an accurate screenshot of in-flight risk. As previously mentioned, high blood viscosity and low albumin levels were two biochemical factors present in the astronaut who sustained a VTE, who was also on a third-generation combined OCP (COC) containing Drospirenone. These COCs have been demonstrated to reduce albumin synthesis and secretion, leading to deficiency in maintenance of the vascular endothelium.[63] In the same study, COC use was also found to be associated with increased inflammatory markers and higher transferrin levels. This highlights the importance of investigating the safety of COC use during spaceflight and of determining the safest generation to be employed by female astronauts.

According to Ronca and colleagues, the average age of female astronauts for long-duration missions has increased since missions earlier than 2014,[52] which is an important factor to consider as middle-aged women in the 40–50-yr age group have a doubled VTE risk compared to women less than 30 yr of age.[59] The risk of age, compounded with the effects of COC and the unknown risk of spaceflight, may be a cause of concern for this astronaut population. It would be beneficial to further characterize the risk of female astronauts taking OCPs and further understand the interactions between the two factors to better prevent future thromboembolic events.

Diagnostic Ability and Biomarkers

Ultrasound is the modality of medical imaging used for medical care and physiology studies aboard the ISS. During exploration class missions, this is likely to be a mainstay, with other, larger payload modalities unlikely to be taken to Mars with current mission projections. However, ultrasound studies have some inherent limitations that cannot be overlooked. Firstly, specialized techniques are required to identify thrombi on ultrasound, which also requires expertise. Additionally, ISS ultrasound studies have often evaluated select venous portions.[19] This differs from terrestrial clinical work-up for VTE wherein a large area is analyzed for pathology. Thus, we cannot exclude the possibility of missed thrombi; more extensive training is required to ensure such events are not missed in the future.

Duplex ultrasound is a valuable tool in screening and diagnosing VTE; it is also realistic in terms of payload and astronaut skill burden.[11] However, due to respiratory and cardiac cycles in addition to its asymmetrical walls, internal jugular vein blood flow patterns are nonuniform, yielding complex patterns on Doppler. These patterns, which include flow separation and recirculation such as eddies, are erroneously identified as retrograde flow.[19,56] Thus, in-flight diagnostic specificity for the measurement of cerebral venous flow patterns may be ameliorated by the utilization of newer technologies such as vector-flow imaging. These findings highlight the lack of concrete imaging markers in addition to biochemical markers, as mentioned in the previous section.

On Earth, biomarkers alone are not sufficient for the diagnosis of VTE. The use of D-dimer, although used in preclinical risk assessments, is limited and warrants further imaging when positive due to its lack of specificity. Further terrestrial research is required to facilitate the diagnosis of VTE by identifying potential biomarkers, which could further assist in diagnosis during spaceflight, where other imaging resources are limited. Topical reviews have reported several studies with

high levels of P-selectin, a cell adhesion molecule, in patients with VTE.[5,21] Despite its superior diagnostic performance compared to D-dimer, especially when combined with the Wells score, it has not yet been adopted in global medical practice. Endothelial microparticles have also been reported to be elevated in the presence of inflammation and VTE with limited evidence, thus it cannot yet be ascertained as a novel biomarker.[21] Low serum albumin is an independent risk factor for VTE, and thus should be further investigated as a biomarker.[63] One qualitative systematic review looked in detail to identify venous endothelial dysfunction biomarkers relevant to VTE formation in astronauts.[17] Distinction between arterial and venous systems as well as between local and systemic inflammation was lacking. Possible biomarkers were identified but not enough evidence was seen to formally recommend screening in astronauts. Relevant biomarkers may include D-dimer, tissue plasminogen activator inhibitor-1, tissue factor, plasmin-alpha2-antiplasmin, Factor VIII, von Willebrand Factor, and soluble thrombomodulin.

There is now an occupational surveillance program for VTE formation during human spaceflight, utilizing ultrasonic evaluation, which may highlight any further incidences of VTE aboard the ISS and missions beyond.[51] There is also the prospect of personalized medicine and the use of omics in monitoring and tailoring countermeasures. Could we predict increased risk through a blended model of the standardized risk model as well as an individual astronaut's genetic profile? And through this, would it be possible to tailor treatments and countermeasures accordingly to properly allocate resources?

Treatment and Countermeasures

The only case of VTE in an astronaut received treatment following multidisciplinary input with enoxaparin ($1.5\,mg \cdot kg^{-1}$ once daily for 33 d, followed by $1\,mg \cdot kg^{-1}$ once daily to extend therapy until apixaban could be transported to the ISS). Apixaban, protamine, and prothrombin complex were supplied to the spacecraft at the earliest opportunity. Apixaban at 5 mg twice daily was started 42 d after the diagnosis of the VTE, and the dose was reduced to 2.5 mg twice daily 3 mo after diagnosis. Subsequent sonographic surveillance demonstrated progressive reduction of the thrombus in the left internal jugular vein.[11] Another internal jugular vein mass, identified as a partially occlusive thrombus, was also found in a second astronaut; however, this was not treated during the spaceflight mission as it was not identified until during a subsequent retrospective imaging analysis.[38]

The use of oral agents, namely direct oral anticoagulants, has been preferred over alternatives[33] due to the complexity of administering injections in weightlessness and the availability of reversal antidotes. To date, therapeutic interventions for spaceflight-associated thrombosis have not been formally investigated.[35] The complex balance required between managing thrombotic risk and bleeding risk probes the need for the development of formal anticoagulation guidelines.

Preventative countermeasures, such as lower body negative pressure, may yield promising results as it can restore venous flow and maintain compensatory baroreflexes by simulating gravitational stress.[18] However, limited research exists on the optimal dose and delivery of lower body negative pressure. Further research is needed to evaluate the use and efficiency of lower body negative pressure during spaceflight.

Commercial Spaceflight

Commercial spaceflight is not new, having been a reality for decades. However, it is becoming more popular and accessible with the advent of several new companies joining the ranks of space tourism and scientific payload endeavors. With the widening of participation in spaceflight of individuals who may not have been selected based on stringent medical standards, the risk of VTE may be even larger in these space-touring populations.

The risk of VTE is well established in commercial air passengers, and so this risk will translate to commercial spaceflight for space tourism. Just as in commercial air passenger flying, VTE is a risk for passengers sitting for an extended amount of time. This is primarily caused by prolonged immobilization and dehydration, which is exacerbated if the individual (~20% of the general public) is genetically predisposed for increased clotting.[10] A clear link between air travel and increased risk of DVT is yet to be established, but it remains an important consideration if traveling for prolonged periods of time in a confined space (e.g., commercial aircraft or a suborbital flight)

Testing for thrombophilia risk factors, either hereditary or acquired, is currently not part of certain astronaut selection processes and has not been formally recommended for commercial astronaut selection.[35] Congenital findings that increase cardioembolic accident risks, such as patent foramen ovale, are also not part of the selection criteria.[14] The astronaut medical screening should be reassessed to better encompass risk factors posing a threat to astronaut health. To do so, further research is required to clarify the threats posed by such factors.

CONCLUSIONS

Although potential risk factors such as OCP and COC use and environmental hazards for VTE in altered gravity fields have herein been identified, causal mechanisms have not been confirmed and one cannot simply extrapolate risk factors for VTE on Earth, or even in LEO, to exploration-class missions. Moreover, risk factors may superimpose if a crewmember were to develop a malignancy or experience a traumatic injury reducing their mobility and requiring invasive intervention. More research studies are needed to clarify the role of vessel distension, flow disturbances, and endothelial dysfunction during spaceflight on VTE formation during spaceflight. Baseline normal values for biomarkers are needed pre-mission with changes monitored on-mission and then upon return. Studies have shown a lack of reliable imaging and biomarkers in assessing VTE risk, even terrestrially, but surveillance ultrasound is used in orbital spaceflight and we can measure biomarkers on the ISS to further research. The use of oral anticoagulation in one astronaut has been demonstrated in unanticipated conditions.

Treatment with direct oral anticoagulants has the advantage of reversal agents. A futuristic but real possibility is that of 3D-printing medications for Mars missions. Nonpharmacological therapy could include focused ultrasound to degrade the clot, utilizing ultrasound as image-guidance. Limited studies have explored sex-based discrepancies. Countermeasures may include exercise-based or even intermittent pneumatic compression devices for the upper limbs.

With the advent of the era of long-duration, exploration-class missions, including commercial spaceflight, it is critical to further elucidate the mechanisms to quantify spaceflight-associated VTE risk, mechanisms, surveillance, diagnosis, and management, prioritizing preparedness for upcoming missions and enabling safe exploration for all.

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