

Coronavirus (COVID-19), Coagulation, and Exercise: Interactions That May Influence Health Outcomes

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Abstract

The proinflammatory cytokine storm associated with coronavirus disease 2019 (COVID-19) negatively affects the hematological system, leading to coagulation activation and endothelial dysfunction and thereby increasing the risk of venous and arterial thrombosis. Coagulopathy has been reported as associated with mortality in people with COVID-19 and is partially reflected by enhanced D-dimer levels. Poor vascular health, which is associated with the cardiometabolic health conditions frequently reported in people with severer forms of COVID-19, might exacerbate the risk of coagulopathy and mortality. Sedentary lifestyles might also contribute to the development of coagulopathy, and physical activity participation has been inherently lowered due to at-home regulations established to slow the spread of this highly infectious disease. It is possible that COVID-19, coagulation, and reduced physical activity may contribute to generate a “perfect storm,” where each fuels the other and potentially increases mortality risk. Several pharmaceutical agents are being explored to treat COVID-19, but potential negative consequences are associated with their use. Exercise is known to mitigate many of the identified side effects from the pharmaceutical agents being trialled but has not yet been considered as part of management for COVID-19. From the limited available evidence in people with cardiometabolic health

Keywords

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conditions, low- to moderate-intensity exercise might have the potential to positively influence biochemical markers of coagulopathy, whereas high-intensity exercise is likely to increase thrombotic risk. Therefore, low- to moderate-intensity exercise could be an adjuvant therapy for people with mild-to-moderate COVID-19 and reduce the risk of developing severe symptoms of illness that are associated with enhanced mortality.

Since the first reported case of coronavirus disease 2019 (COVID-19) in 2019,¹ as caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a global pandemic has ensued and infection rates have increased exponentially.² At the time of writing, this highly contagious virus had infected more than 6 million people globally, resulted in more than 400,000 deaths,³ and has been forecast to cost the global economy more than two trillion U.S. dollars in 2020 alone.⁴ People with COVID-19 can present with mild symptoms, which may progress to severe disease and affect multiple organs beyond the lungs, including the hematological systems.^{5–10} Such COVID-19-related effects can contribute to an increased risk of venous and arterial thrombosis.^{11,12} Although there remains an urgent need for clinical biomarkers to predict disease severity,¹³ hematological impacts including increased D-dimer, fibrinogen, von Willebrand factor, and factor VIII (FVIII) levels have been associated with the occurrence of coagulopathy in COVID-19.¹⁴ Many pharmacological agents have been proposed for treating COVID-19,^{15,16} although exercise has yet to be considered as part of treatment options. Therefore, this review explores how exercise could be prescribed to influence coagulopathy and how it might interact with pharmaceutical medications being used in people with COVID-19.

COVID-19 and Hemostasis

Hemostasis is the physiological process that maintains the balance between excessive bleeding and clotting to achieve normal blood circulation.^{11,17–19} To maintain normal circulation, a dynamic equilibrium between activators and inhibitors of hemostasis occurs, including (1) the vascular system, (2) blood platelets, (3) the coagulation system, (4) the physiological inhibitors of coagulation, and (5) the fibrinolytic system.^{11,20,21}

Blood platelets, typically the first responders when damage to the vascular endothelium occurs, are known to directly interact with different viruses.²² However, it remains unclear how platelets interact with SARS-CoV-2.²³ Hypoxia, a common clinical feature of COVID-19,^{1,24} increases thrombus under systemic or local hypoxic conditions.²⁵ Hypoxia-inducible transcription factors directly activate platelets but also increases the inflammatory response.^{26,27} In healthy individuals, fibrinolysis is regulated by tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1).^{20,28} COVID-19 prompts immune cells to release a cytokine storm that ramps up inflammation, platelet activation, endothelial dysfunction, hypoxia, and stasis of blood flow as a result of

prolonged immobility.^{24,29,30} The resulting coagulation abnormalities are recognized as “COVID-19–associated coagulopathy.”¹⁰

COVID-19 and Coagulopathy

It has been reported that up to 68% of people diagnosed with COVID-19 and needing intensive care have preexisting comorbidities known to affect the vascular system, including hypertension, cardiovascular disease, hypercholesterolemia, and diabetes.³¹ These conditions typically stem from, or contribute to, the metabolic syndrome, which is associated with increased amounts of visceral adipose tissue. This tissue is known to secrete several cytokines that are implicated in the inflammatory cascade, leading to a state of low-grade inflammation.³² Reports on clinical characteristics of COVID-19 intensive care patients include elevated cytokine levels such as interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein-1 α (MIP1A), and tumor necrosis factor- α (TNF α).¹ Activation of these cytokines can result in an inflammatory cascade, leading to coagulation activation and endothelial dysfunction.^{33,34}

Elevated levels of proinflammatory cytokines might partially explain the large number of COVID-19 infected individuals presenting with coagulopathy,³⁵ in particular elevated D-dimers,^{1,29,30} fibrinogen degradation products (FDPs),³⁵ and abnormal activated partial thromboplastin time.^{1,29} Elevations in these coagulopathy parameters and impaired fibrinolysis are significantly related to poor prognosis in COVID-19.^{28,30,35} For example, Zhou et al³⁶ reported that 68% of patients presenting with COVID-19 had increased activation of coagulation as indicated by elevated D-dimer concentration at presentation (>500 ng/mL). Most importantly, Zhou et al³⁶ reported that D-dimer concentrations > 1,000 ng/mL were associated with an eightfold increased odds of fatal outcome, suggesting coagulopathy to be a predictor of mortality risk in individuals with COVID-19.³⁵

D-dimer is a widely used clinical biomarker of endogenous fibrin clot formation^{37–42} and a well-recognized laboratory marker of hypercoagulability (coagulation activation).^{43–45} Elevated D-dimer levels in people with COVID-19 are associated with a higher risk of intensive care unit admission or death.⁴⁶ The mortality risk associated with higher levels of D-dimer is particularly evident in older people and those with cardiometabolic comorbidities.³⁰ In addition to elevated D-dimer levels, Tang et al³⁵ reported significantly higher levels of FDPs and

prolonged prothrombin time (PT) in COVID-19 nonsurvivors compared with those who survived. Therefore, it can be suggested that these conventional parameters of coagulation are significantly associated with overall prognosis.

Physical Activity and Risk for Coagulopathy

A common behavioral feature, and risk factor, for the comorbidities associated with COVID-19 is insufficient physical activity.⁴⁷ A diagnosis of COVID-19, whether mild or severe symptoms occur, is likely to reduce physical activity even further in those required to isolate in the home environment or be bedbound in a hospital setting.⁴⁸ While under instructions to self-isolate indoors to slow the outbreak of COVID-19, data obtained by smartwatches have demonstrated that weekly physical activity has decreased by 9% to 48%.^{49,50} This reduction in physical activity is frequently associated with venous thromboembolism,⁵¹ which typically consists of pulmonary embolism or deep vein thrombosis.^{52,53} These major clinical problems negatively alter blood coagulability and have potential life-threatening consequences, such as acute cardiac injury and/or sudden death.^{35,54} Therefore, it may be that COVID-19, coagulation, and reduced physical activity contribute to generate a “perfect storm,”⁵⁵ where each fuels the other and potentially increases mortality risk. Physical activity can induce many health benefits^{56,57} and can positively modify coagulation markers in healthy populations.^{58,59} High cardiorespiratory fitness has been suggested to offer some protection against the deleterious effects of COVID-19⁶⁰ and consequently it is important to safely participate in physical activity during this pandemic.⁶¹ Therefore, early intervention through physical activity or exercise might mitigate negative health consequences and reduce mortality risk in people with mild or moderate COVID-19. However, at this point, it is not clear if, or how, physical activity or exercise can be used as part of the overall treatment process for coagulopathy associated with COVID-19.

Exercise and Hemostasis

Exercise (planned physical activity completed specifically for the purpose of improving health and fitness) has been demonstrated to have considerable effects on hemostasis by positively modifying markers of coagulation and fibrinolytic response in apparently healthy populations.^{58,59,62} Low- to moderate-intensity exercise is likely to reduce the risk of coagulopathy; however, acute bouts of high-intensity exercise may act as a potential trigger for increased thrombotic risk due to an increase in venous blood flow, blood viscosity, and laminar shear stress, activating the coagulation system.^{63,64} Nonetheless, the influence of acute bouts of exercise on coagulation and fibrinolysis have often produced conflicting data due to various factors including varying study protocols and exercise modes.^{62,65–69} It is evident that exercise intensity plays an influential role in shifting the equilibrium between coagulation and fibrinolysis, with strenuous (high-intensity) exercise consistently demonstrated to increase hemostatic activation as opposed to low- to moderate-intensity exercise.^{63,64,70–73}

For apparently healthy individuals, exercise completed at a higher intensity appears to increase clot degradation, probably in response to coagulation activity. This is evidenced by an increase in overall fibrinolytic activity when cycling at 70% VO_2 max compared with 40% VO_2 max⁷⁴ but also an approximately 50% increase in t-PA activity when cycling at 80% VO_2 max compared with 50% VO_2 max.⁶² Furthermore, Menzel and Hilberg⁷⁵ observed increased thrombin–antithrombin complexes when cycling at 100% but not at 80% individual anaerobic threshold. These findings indicate that exercise intensity is an important contributor to thrombin generation through activation of both the coagulation and fibrinolytic systems, albeit in a healthy population,⁷⁶ and it is clear that to minimize the risk of coagulopathy, moderate- to high-intensity exercise should be avoided by untrained, inappropriately trained, or sedentary individuals.^{77–79} Despite this, there remains an opportunity to explore the use of exercise as an adjuvant therapeutic tool in the management and prevention of COVID-19-associated coagulopathy.

Separate to acute responses to exercise, individuals who are regularly physically active possess a “thromboprotective element,” whereas individuals who are not regularly active or those with a preexisting medical condition have attenuated fibrinolytic responses in combination with exaggerated changes in procoagulant and platelet variables.^{65,80–83} When investigating coagulation and fibrinolytic responses in relation to exercise in physically inactive individuals and those with varying medical conditions (i.e., peripheral arterial disease, metabolic syndrome, hemiparetic strokes, and hypertension), exercise intensity varied between 50% and 70% VO_2 max.^{62,84–87} Exercise performed at 50% VO_2 max increased fibrinolytic activity in both active and inactive apparently healthy males, but larger increases in t-PA were observed only in physically inactive males.⁶² In sedentary males with metabolic syndrome, exercise at 70% VO_2 max reduced fibrinolytic activity and these individuals remained hypofibrinolytic compared with non-obese sedentary males.⁸⁶ In middle-aged females with previous myocardial infarction, Eriksson-Berg et al⁶⁸ demonstrated increased fibrinolytic activity following exercise at 50% maximal work capacity, whereas markers of coagulation activation remained undisturbed. Low- to moderate-intensity exercise in people with varying medical conditions increases fibrinolytic activity, as evidenced by elevated t-PA concentrations, which may persist up to 1 hour postexercise.^{84,85,87} Therefore, even for individuals with existing cardiometabolic health conditions associated with worse COVID-19 outcomes, lower intensity exercise may have thromboprotective effects.⁶³ It is then possible that low- to moderate-intensity exercise may increase acute fibrinolytic activity and reduce COVID-19-associated blood clot formation. However, to date, no studies have investigated how exercise might impact the hemostatic profile within this population.

COVID-19, Pharmaceutical Agents, and Exercise

No universal pharmaceutical treatment for COVID-19 is as yet available, although multiple therapeutic strategies are

being attempted and trialled.^{15,16,88–91} These relate to pharmaceutical agents that (1) block viral entry to host cells through the prevention of attachment or fusion, or removal of virus by immune cells, or the use of hyperimmune plasma, (2) block viral replication and survival in host cells through viral protease inhibition or viral nucleic acid and protein synthesis inhibition, (3) dampen the exaggerated immune response through corticosteroids, cytokine blockade, or intravenous immunoglobulin, and/or (4) inhibit the abnormal prothrombotic response by anticoagulants.^{88,92}

Due to the broad range of pharmaceutical agents being trialed for COVID-19, and the apparent impact of the virus on hematological parameters that are associated with poor prognosis and mortality,¹³ it is critical to examine the possible pharmaceutical agent interactions with exercise. ► **Table 1** indicates the broad class of pharmaceutical agents being trialed for COVID-19,^{15,16} potential consequences associated with their use, and implications for exercise.

Anti-inflammatory agents have been used to minimize systemic inflammation and augment hemostasis. However, some anti-inflammatory agents inhibit the receptor for IL-6,⁹³ which has both pro- and anti-inflammatory effects,⁹⁴ depending on the tissue that expresses the cytokine. Therefore, anti-inflammatory agents might also impair the recovery process.

Anticoagulants have been suggested for use in COVID-19 to mitigate the risk of venous and arterial thromboembolism.^{15,16,95} Anticoagulants such as heparin promote angiogenesis but dilate blood vessels, meaning that exercise-induced hypotension is a potential outcome. Exercise, particularly at higher intensities, is also known to promote angiogenesis and vasodilation, partly to regulate temperature.⁹⁶ Therefore, caution with exercise prescription is required to mitigate the increased risk of bleeding while using anticoagulation agents in patients with enhanced bleeding risk and to prevent injury and further complications.

Table 1 Classes of pharmaceutical agents being trialed for COVID-19, intended action, potential side effects associated with their use, and considerations for exercise

Pharmaceutical class	Intended action	Potential side effects/ interactions	Consideration for exercise
Anticoagulants	Suppression of synthesis/function of various clotting factors to prevent the formation of blood clots	Hemorrhage Thrombocytopenia Hypersensitivity reactions Adverse interactions with other drugs that bind to plasma proteins or are metabolized by the liver	↑ Blood fluidity & blood flow, ↑ oxygen delivery. Excessive bleeding. Exercise induced hypotension
Antiviral agents	Blocks viral entry to host cells <ul style="list-style-type: none"> • Serine protease inhibitors Blocks viral replication in host cells Inhibits angiotensin-converting enzyme 2	Joint and/or muscle pain Headaches, dizziness, nausea Cough, nasal congestion, fever, body aches, malaise, and, in severe cases, death	J-shaped hypothesis for exercise dose and infection risk. ↓ Proprioception due to neuropathy & ↓ muscle control due to myopathy and muscle weakness.
Corticosteroids	Regulates gene expression to suppress inflammation and immune responses	Can ↑ risk and severity of infections, as well as masking infections May cause elevated blood glucose levels, fluid retention, or elevated blood pressure Long-term use may suppress the immune system May ↑ gastrointestinal symptoms Can ↓ bone density, cause osteoporosis, and ↑ risk of fractures Affects metabolism fat deposition Impaired ability to sleep Mood changes (>30 mg/day) Eye problems Atherosclerosis and aseptic necrosis (long-term use and high doses) Withdrawal can cause fatigue, joint pain, muscle stiffness and tenderness, or fever	> 2 wk use ↓ ability of the body to respond to physical stress. Muscle weakness in people who may already be strength compromised. Potential for impaired physiological response to exercise due to adrenal gland dysfunction. Potential for impaired neural signaling, muscle damage, and muscle weakness.
Nonsteroidal anti-inflammatory	Inhibits COX-1 or COX-2 enzymes, thus stopping prostaglandin production Blocks toll-like receptors involved in cytokine production	Gastrointestinal irritation, fluid retention, and elevated blood pressure ↑ Risk heart attack and stroke, dizziness, light-headedness, tiredness, headache, ringing in the ears	During prolonged exercise, they may strain the kidneys and ↓ the ability of the muscle to recover. ↑/Exacerbate risk of injury as it masks musculoskeletal pain. ↑ Blood pressure response with exercise, particularly with higher intensities. ↓ Capacity for skeletal muscle oxygen transfer ↓ energy availability.
Disease-modifying antirheumatoid drugs	Antimalarial <ul style="list-style-type: none"> • Destruction of parasite 	May be immunosuppressive, myelosuppressive, cause cardiac toxicity, or severe low blood glucose levels	Myelosuppressive side effects could impair exercise capacity. Reliance on aerobic energy metabolism. Additional thermoregulation required.

Notes: ↑ increased; ↓ reduced/decreased. Intended action and potential side effects information obtained from the Australian Medicines Handbook (<https://amhonline.amh.net.au/auth>). This table is a general review only and is not specific to individual drugs. For a more empiric or investigational use of individualized agents with antithrombotic properties in COVID-19, please see the review by Bikdeli et al.¹⁵

Antiviral agents previously used to treat influenza have been reported to be effective for treating COVID-19.⁹⁷ When these have been used in combination with immune system pharmaceuticals (i.e., antimalarial and protease inhibitors), symptoms have been alleviated, along with reduced viral shedding and hospital stay.⁹⁸ Recognized side effects of antiviral agents include fatigue, dizziness, and poor mental health.^{89,99–101} Antimalarial agents have some common side effects with antiviral drugs, including dizziness and mental health issues along with other exercise prescription considerations such as muscle weakness,^{102,103} cardiac arrhythmia,¹⁰⁴ and heart failure.⁸⁹ Protease inhibitors also have the potential to induce cardiac arrhythmia^{105,106} and reduce metabolic control.^{107,108} Therefore, the use of exercise as an adjuvant therapy might be appropriate given the positive effects of exercise on all of the potential adverse reactions to the pharmaceutical agents (i.e., enhanced mood/mental health,^{109,110} cardiovascular and metabolic health^{57,111}), along with the strong potential of low- to moderate-intensity exercise to directly affect the coagulation process. However, the setting and mode for exercise delivery needs to be carefully selected, thus avoiding the potential consequences of exacerbating symptoms of dizziness and the potential for falling and further injury.¹¹²

Conclusion

The association of abnormal coagulation with severe pneumonia and death in people with COVID-19^{1,35} has led to reports on thromboembolic complications.³⁴ This seems to be more apparent in people who also have cardiometabolic health conditions. Particularly in people who have mild or moderate symptoms of COVID-19, and perhaps those with more severe COVID-19, low- to moderate-intensity exercise could be regarded as adjuvant therapy to assist with minimizing the potential adverse reactions of the infection and any treatment-related issues. Furthermore, low- to moderate-intensity exercise might be important to contribute to reducing the risk of developing more severe forms of COVID-19 and further reducing the risk of coagulopathy that seems to be associated with mortality. Yet, enhanced social distancing (i.e., at least 2 m) while practicing outdoor sport and exercise would be mandatory since airborne virus propagation is considerably higher during physical exercise.¹¹³

Conflict of Interest

None.

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