



Vascular Inflammation as a Therapeutic Target in COVID-19 “Long Haulers”: HIITing the Spot?

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BACKGROUND

In the wake of the first wave of the ongoing global pandemic, it has become imminently clear that coronavirus disease 2019 (COVID-19) has brought with it a whole new clinical syndrome: “long COVID” (1, 2). Hence, after recovery from the acute viral infection, a remarkably large proportion of patients, who initially coined themselves “long haulers” in social media-based patient communities for COVID-19 survivors suffer from persistent and often invalidating symptoms, including dyspnoea, chest pain, tachycardia, post-viral brain fog, exercise intolerance, and extreme fatigue to mention a few (3, 4). According to recent studies ~10% of all individuals infected with the causative acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and as many as nine out of 10 patients that have required hospitalization because of COVID-19 develop long COVID that persists for at least 4 months, according to the currently available data (4). Time will tell whether the symptoms associated with long COVID are transient or ever-lasting phenomena.

Long COVID will expectedly have a huge impact on the morbidity burden and quality of life in many COVID-19 survivors in the future, and when considering the extent of the global pandemic with currently more than 40 million verified cases, it will expectedly have substantial consequences, both in terms of economic cost and health care capacity throughout the world. It is thus widely recognized that there is an impending need for implementing evidence-based patient-tailored safe and effective rehabilitation schemes, but due to the paucity of data on this, the structure and specificity of such schemes remain obscure. While it is widely recognized that some exercise is better than none and more intense exercise is superior to less intense exercise, opinion papers and guidelines published over the past year have consistently refuted high-intensity interval training (HIIT) as an option for rehabilitation after COVID-19 (5–10). On the basis of the known pathophysiology of COVID-19 and the physiological effects of HIIT, we will however argue in favor of the opposite stand, that is, that HIIT should be considered as one of the rehabilitation interventions of choice for alleviating or even reversing the symptoms of long COVID.

COVID-19 IS (ALSO) A VASCULAR DISEASE

Even though COVID-19 is primarily a viral pneumonia, its multiorgan involvement, both in the acute phase and when considering the persistent systems in long COVID, stresses that this is far from the whole story. Over the past months, several studies have highlighted the presence of a substantial vascular component in the pathophysiology of the disease (11–14). Indeed, COVID-19 is associated with severe vascular inflammation, both in the

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pulmonary and extrapulmonary vasculature, both on the macro- and microvascular level (11). This involves diffuse endothelial damage with pyroptosis and apoptosis as well as a procoagulant change of the vascular endothelium. Consequently, both pulmonary and extrapulmonary thromboembolism are common complications, that may both determine the initial clinical presentation and the long-term consequences of COVID-19 in many patients (15).

The main mechanisms of the universal vascular component of COVID-19 may both involve the mode of entry of the virus into host cells and the immune response to the virus. The causative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invades host endothelial cells through endocytosis which is facilitated by the angiotensin converting enzyme 2 receptor and the transmembrane protease serine 2 which are expressed in practically all organs throughout the body (16).

In terms of the immune response, a type 3 hypersensitivity reaction has been reported to contribute to vascular inflammation in COVID 19, at least in some cases (17). This type of immune reaction takes place when an excess or slight excess of soluble antigens lead to the accumulation of immune complexes, which then precipitate inside the tissues, in particular blood vessels, where they may cause so-called “leukocytoclastic vasculitis,” which is a procoagulant condition that affects both the macro- and microvasculature.

Another immune mechanism, which is probably important regardless of whether a type 3 reaction takes place, is the highly proinflammatory cytokine response to SARS-CoV-2, which is prominent both in milder and very severe cases, and which some have designated a “cytokine storm” (18, 19). This involves vast elevations in the classical pro-inflammatory cytokines, TNF- α and IL-1 β , which have prominent effects on the endothelium. Hence, TNF- α facilitates the development of a procoagulant endothelium by increasing the expression of endothelial cellular adhesion molecules and genes critical for coagulation, such as tissue factor and decreased thrombomodulin, resulting in a pro-thrombotic state (20, 21). Moreover, TNF- α suppresses endothelial nitric oxide synthase and cyclooxygenase 1, which further compounds endothelial dysfunction (22). Furthermore, IL-1 β , which is a downstream cytokine of TNF- α in the initial cytokine cascade triggered by an invading pathogen, is a potent trigger of vascular inflammation, among other things by enhancing monocyte and leukocyte infiltration in the vascular wall. This has most convincingly been demonstrated in studies of infants with non-functional IL-1 receptor antagonist (IL-1ra) function and thus uninhibited IL-1 β signal transduction, which leads to severe universal vasculitis (23, 24).

In the following sections we will argue that because the multiorgan involvement of COVID-19 may largely reflect universal vascular inflammation, HIIT is an alluring contender for alleviating and perhaps preventing long COVID.

THE ANTI-INFLAMMATORY EFFECT OF EXERCISE

Physical exercise is a fundamental physiological stressor that is capable of inducing ubiquitous adaptations in nearly all

cells, in nearly all tissues and organs (25). This involves the skeletal muscle “secretome” of myokines that are released from contracting skeletal muscle, and which exerts various functions through autocrine, paracrine, and endocrine functions, including marked immunomodulatory effects (Figure 1) (26). To this end, the low-grade inflammation, which is a common manifestation of aging has been demonstrated to be reversed by exercise of both moderate to strenuous intensity in randomized controlled trials in the elderly (27). Of note, IL-6 is the first detectable myokine released into the bloodstream during exercise. This is triggered by contraction-induced glycogen depletion in skeletal muscle and its concentration in blood increases exponentially depending on the intensity and duration of exercise (25). Therefore, exercise modalities involving large muscle groups produce the greatest IL-6 response. HIIT regimens or marathons can result in IL-6 increase of 100-fold, although increases of 2–10-fold are more common in exercise regimes of more moderate intensity or duration (28).

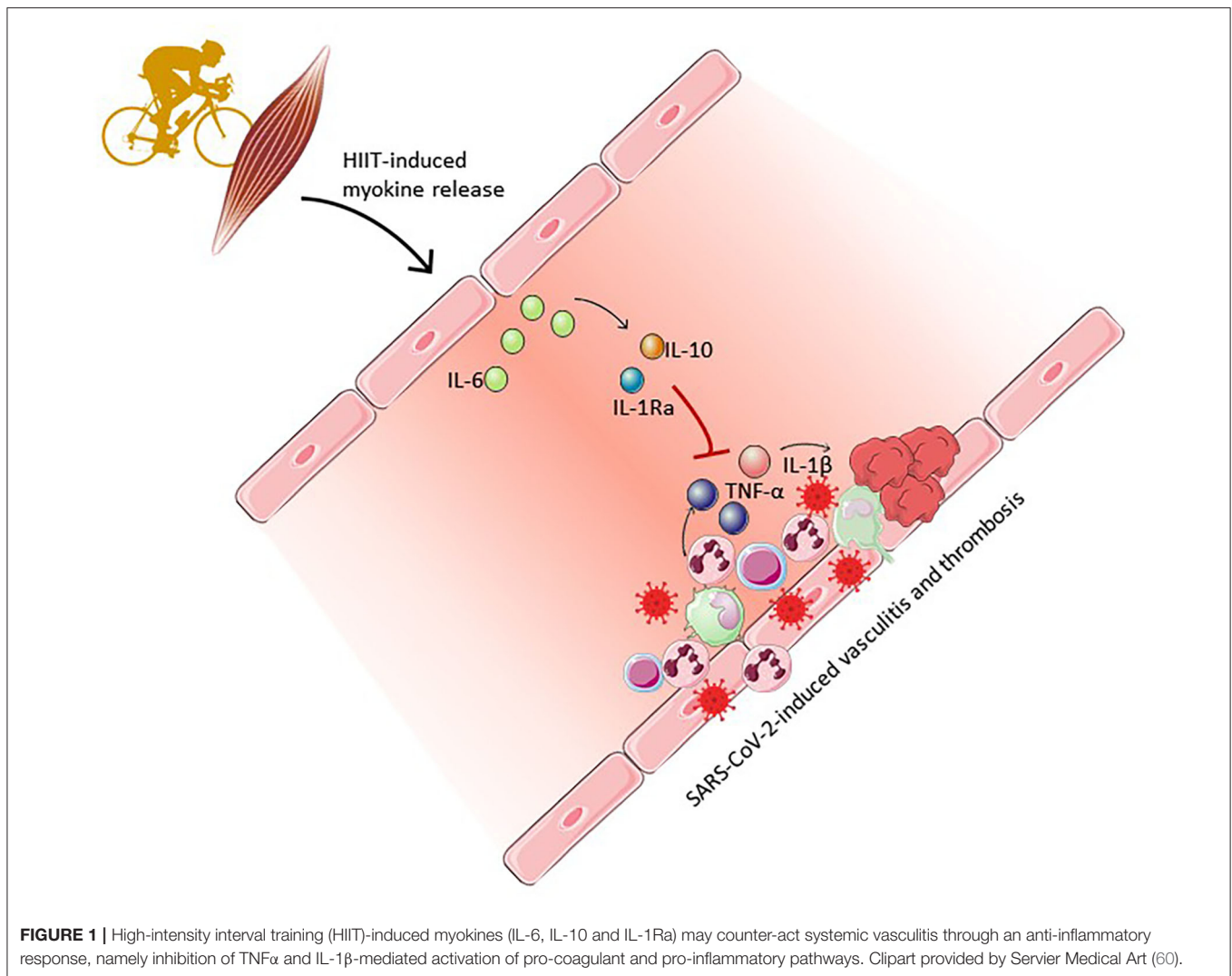
Once released, recent studies indicate that IL-6 directly stimulates cardiac exercise adaptations (29) and also affects the vasculature by mobilizing natural killer and dendritic cells to the blood stream (30), which are critically involved in viral clearance. The principal immunomodulatory function of IL-6 released during exercise is however to stimulate the release of IL-10 and IL-1ra by monocytes (31), while also reducing the expression of genes encoding several pro-inflammatory cytokines, including TNF- α and IL-1 β . IL-10 also directly inhibits the synthesis of TNF- α (32) while IL-1ra inhibits IL-1 β signaling. Additionally, IL-10 negatively interferes with tissue factor expression, thus exerting an anti-coagulant effect in the vasculature (Figure 1) (33).

By increasing viral clearance, while also aberrating TNF- α and IL-1 β signaling, and alleviating the associated procoagulant state, exercise may thus reduce vascular inflammation in COVID-19.

HIIT: IS IT EFFECTIVE AND/OR SAFE IN COVID-19?

Given that the anti-inflammatory effects of exercise depends critically on the intensity of exercise, intense modalities that involve large muscle groups, such as HIIT protocols, have the potential to produce marked anti-inflammatory effects in target tissues in a time-efficient fashion (28, 34, 35).

HIIT has become increasingly popular in various rehabilitation schemes in patients with lung diseases, mostly because patients with respiratory symptoms are often unable to engage in classical continuous exercise regimens at an intensity sufficient to induce a training adaptation, but during HIIT relatively high intensities are often tolerated (36). Another advantage of HIIT, which is also a benefit in the scientific study of exercise adaptations, is its highly standardized and reproducible nature and that it evokes measurable physiological adaptations much faster than continuous training, i.e., within 2 weeks in healthy volunteers (36). Hence, although an acute HIIT bout elicits apparently similar plasma IL-6 as an iso-energetic continuous exercise bout, the higher intensities and total workloads that may be tolerated during HIIT in



various disease states compounds the exercise-induced anti-inflammatory effects (37, 38). Hence, HIIT has been shown to reduce disease-related TNF- α in an animal model of diabetes (39), and furthermore has specific suggested effects related to vascular inflammation, including reduced chemokine chemotaxis and enhanced endothelial repair reported in reviews and meta-analyses conducted on diverse populations of both normal overweight and obese individuals (40–42). This may both reflect the imminent effects of the high-intensity intervals on the IL-6 response as well as on the vasculature *per se*, i.e., due to the pronounced changes in vascular shear stress between intervals (43).

Of all the potential exercise interventions that may be prescribed in COVID-19, HIIT is nonetheless the most controversial. Several aspects of HIIT have been highlighted to disfavor it in this context, including presumed immunosuppressive effects that could increase viral susceptibility and decrease viral clearance (5, 44) and the potential risk of sudden cardiac arrest due to COVID-19-induced residual

cardiovascular pathology (45). Due to the latter, the American College of Sports Medicine (ACSM) and experts endorsed by the section of Sports Cardiology & Exercise of the European Association of Preventive Cardiology (EAPC) have recommend that even athletes accustomed to high exercise intensities should resume to exercise only after a complete cardiovascular evaluation and in a gradual manner following a COVID-19 infection (6–10).

Concerns relating to viral susceptibility and clearance are directly contradicted by the known effects of exercise on immune function, including the effects on NK and dendritic cells described above (30). Accordingly, others have also stressed the potential of HIIT as a means to enhance immune surveillance and regulation while also exerting anti- rather than pro-inflammatory effects in COVID-19 survivors (46, 47).

In terms of the concerns of increasing the risk of adverse cardiovascular outcomes by HIIT in COVID-19 survivors, other reports suggest otherwise (48). Hence, a recent, admittedly small retrospective study of 28 discharged

COVID-19 survivors reported that rehabilitation triggered by HIIT, with endurance training at the maximum tolerated exercise load was both safe and feasible (49). To this end HIIT has successfully been implemented as a rehabilitation strategy in other “high risk” populations, as demonstrated in larger studies on patients at risk or with prevalent ischaemic heart disease, heart failure, chronic obstructive pulmonary disease, cystic fibrosis, and asthma with effects on parameters such as cardiorespiratory fitness (VO₂ peak) and exercise capacity with few reports of severe adverse events, even in patients with left ventricular assist devices (36, 41, 50–59). The rate of cardiovascular complications has been reported of 1 per 23,182 h of high-intensity exercise (51) and later studies have confirmed that HIIT is safe in patients with cardiovascular disease (53). As of now, no studies have thus provided any documentation to indicate that high intensity exercise regimes such as HIIT are not safe in COVID-19 survivors.

CONCLUSION

While the major focus in handling the burgeoning COVID-19 pandemic has hitherto been on reducing the spread of disease and mortality rates, the startlingly high prevalence and severity

of long COVID in survivors heralds an aftermath of similar proportions. This may put health care systems throughout the world on the spot in the years to come, and clinical studies that seek to identify and implement effective rehabilitation strategies are thus of utmost importance. We thus believe that the following questions should be addressed by such studies in the very near future: “When should HIIT be initiated in COVID-19 patients?” “Which specific HIIT protocol should be instigated in COVID-19 patients?” and “What are the effects on HIIT-based rehabilitation on cardio-pulmonary function, symptom burden, and quality of life in patients with long COVID?”. HIIT may comprise a valuable component of the rehabilitation intervention in this context, given that its anti-inflammatory effects may target the prominent disease-specific vascular inflammation that is likely a substantial pathogenetic component of the “long haul” of COVID-19.

AUTHOR CONTRIBUTIONS

RC and RB conceived and wrote the initial draft of the manuscript. All authors provided critical input at all stages, and were involved in drafting and editing subsequent versions of the manuscript, read, and approved the final version of the manuscript.

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